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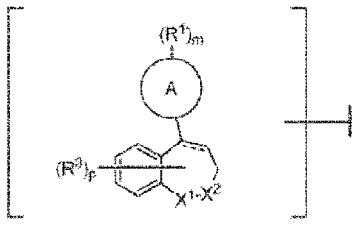
(54) Title: ESTROGEN RECEPTOR ALPHA DEGRADERS AND MEDICAL USE THEREOF

I-a

ERBM =



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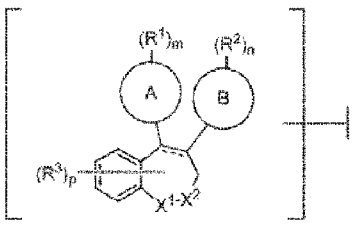

(57) Abstract: The application relates to bifunctional compounds which act as degraders of the estrogen receptor alpha (ERα) and are useful for treating disorders associated with ERα-mediated transcription regulation such as endometriosis and cancer. The compounds are bifunctional molecules comprising a cereblon-binding moiety LBM linked to a ligand ERBM that binds ERα and comprises a benzofused 7-membered ring.

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[Continued on next page]

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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ESTROGEN RECEPTOR ALPHA DEGRADERS AND MEDICAL USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/355,970 filed June 27, 2022; U.S. Provisional Application No. 63/398,064 filed August 15, 2022; and U.S. Provisional Application No. 63/429,805 filed December 2, 2022, the contents of each of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds and methods useful for the modulation of estrogen receptor alpha ("ERα") via ubiquitination and/or degradation by compounds according to the present invention. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] The Estrogen Receptors (ER) are members of the nuclear hormone receptor superfamily. Two classes of ER exist: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), encoded by the *ESR1* and the *ESR2* genes respectively. ERα and ERβ are ligand-activated transcription regulators activated by the hormone estrogen (e.g. 17β-estradiol). The ligand of ER, estrogen, is synthesized by the enzyme aromatase.

[0004] In the absence of estrogen, ERs are largely inactive and located in the cytosol of the cell. Upon estrogen binding, ERs migrate to the nucleus, form dimers and bind to specific genomic sequences called Estrogen Response Elements (ERE). ERs further recruit co-regulators to form a multi-protein complex that regulates the transcription of multiple target genes involved in the cellular proliferation and differentiation in target tissues.

[0005] Under physiological conditions, ERα expression is mainly restricted to reproductive tissues such as uterus, ovary, breast as well as bone and white adipose tissue. ERα is also expressed in more than 70% of breast cancer and is a major contributor to the pathophysiology of this cancer. Tumors harboring high levels of ERα are classified as ER-positive breast cancer. The etiological role of estrogen and ERα in breast cancer is well established and modulation of the ERα signaling pathway through endocrine therapy is a cornerstone of ER+ breast cancer treatment.

[0006] Currently, several strategies for inhibiting the estrogen/ ERα signaling pathway in breast cancer exist: 1- Aromatase Inhibitors (AI), that act upstream of the ERα signaling pathway by blocking estrogen production through inhibition of the aromatase enzyme and decreasing the levels of circulating estrogen; 2- Selective Estrogen Receptor Modulators (SERM) bind directly to ERα and competitively inhibit estrogen binding and thus antagonizing ERα activity; 3- Selective Estrogen Receptor Downregulators or Degradors (SERD) that both antagonize and degrade ERα. This process is mediated by induced-conformational changes and ERα protein degradation through the proteasome pathway; 4- Proteolysis-Targeting Chimeras (PROTAC) are heterobifunctional molecules that selectively recruit an E3 ubiquitin ligase to the ERα protein through induced proximity and mediate ubiquitination and proteasomal degradation of ERα.

[0007] Ubiquitin-Proteasome Pathway (UPP) is a critical pathway that regulates key regulator proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, it leads to pathogenesis of a variety of diseases. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases.

[0008] There are over 600 E3 ubiquitin ligases which facilitate the ubiquitination of different proteins in vivo, which can be divided into four families: HECT-domain E3s, U-box E3s, monomeric RING E3s and multi-subunit E3s. See generally Li et al. (PLOS One, 2008, 3, 1487) titled "Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle's dynamics and signaling."; Bemdsen et al. (Nat. Struct. Mol. Biol., 2014, 21, 301-307) titled "New insights into ubiquitin E3 ligase mechanism"; Deshaies et al. (Ann. Rev. Biochem., 2009, 78, 399-434) titled "RING domain E3 ubiquitin ligases."; Spratt et al. (Biochem. 2014, 458, 421-437) titled "RBR E3 ubiquitin ligases: new structures, new insights, new questions."; and Wang et al. (Nat. Rev. Cancer., 2014, 14, 233-347) titled "Roles of F-box proteins in cancer."

[0009] UPP plays a key role in the degradation of short-lived and regulatory proteins important in a variety of basic cellular processes, including regulation of the cell cycle, modulation of cell surface receptors and ion channels, and antigen presentation. The pathway has been implicated in several forms of malignancy, in the pathogenesis of several genetic diseases (including cystic fibrosis, Angelman's syndrome, and Liddle syndrome), in immune surveillance/viral pathogenesis, and in the pathology of muscle wasting. Many diseases are associated with an abnormal UPP and negatively affect cell cycle and division, the cellular response to stress and to

extracellular modulators, morphogenesis of neuronal networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

[0010] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0011] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein binding ligand and an E3 ubiquitin ligase ligand induce proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, l7(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0012] De-novo and acquired resistance to endocrine therapies can arise through distinct mechanisms such as ERα coregulators overexpression or post-translational modification of ERα and its coregulators upon activation of intercellular signaling pathways. All contribute to hypersensitivity of ERα to low circulating estrogen levels. Additionally genomic alterations such as point mutations in the *ESR1* gene or chromosomal translocation can result in the ability to bind to DNA in the absence of ligand and confer hormone independence in ERα mutated cancer cells. Since most of the endocrine therapy resistance mechanisms identified rely on ERα-dependent mechanisms, strategies aimed at downregulating ERα (both wild-type and mutant) through targeted protein degradation may overcome resistance and provide better treatment options.

[0013] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as breast cancer. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated

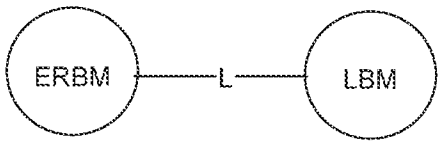
proteins such as estrogen receptor alpha ("ERα") hold promise as therapeutic agents. Accordingly, there remains a need to find bifunctional compounds that are ERα degraders useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0014] The present application relates novel bifunctional compounds, which function to recruit ERα to E3 Ubiquitin Ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of ERα, which is then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of ERα. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., breast cancer.

[0015] The present application further relates to targeted degradation of ERα through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds ERα.

[0016] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as degraders of ERα. Such compounds have the general formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0017] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders, or conditions, associated with regulation of signaling pathways implicating ERα. Such diseases, disorders, or conditions include those described herein.

[0018] Compounds provided by this invention are also useful for the study of ERα enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new ERα inhibitors or ERα degraders or other regulators of ERα-mediated transcription in vitro or in vivo.

[0019] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of formula **I-a**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

[0020] In some embodiments, the present disclosure provides a method of treating an ERα-mediated disorder comprising administering to a patient in need thereof a compound of formula **I-a**, or composition comprising said compound.

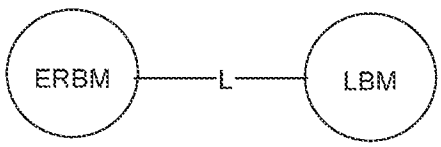
[0021] In some embodiments, the present disclosure provides a process for providing a compound of formula **I-a**, or synthetic intermediates thereof.

[0022] In some embodiments, the present disclosure provides a process for providing pharmaceutical compositions comprising compounds of formula **I-a**.

DETAILED DESCRIPTION

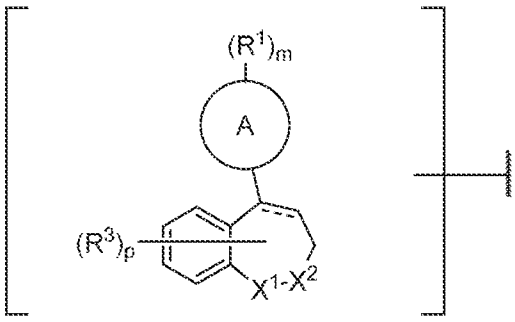
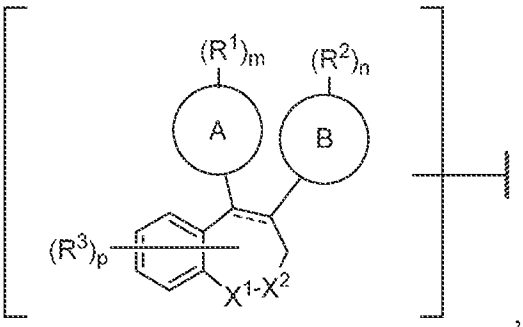
1. General Description of Certain Embodiments of the Disclosure

[0023] Compounds of the present disclosure, and pharmaceutical compositions thereof, are useful as degraders of ERα. In some embodiments, the present disclosure provides a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

ERBM is selected from  and  , wherein ⊣ indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and ≈ indicates a single or double bond;

each of X^1 and X^2 is independently $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, –S(O)–, $–S(O)_2–$, or $–N(R^{A2})–$;

each instance of R^1, R^2, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C;

each instance of R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A is independently oxo, deuterium, halogen, –CN, $–NO_2$, –OR, $–SF_5$, –SR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –S(O)(NCN)R, –S(NCN)R, –C(O)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, –P(O)(R)OR, or $–B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated

bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C is independently oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)C(NR)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$, –$P(O)R_2$, –P(O)(R)OR, -$B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a bivalent moiety that connects ERBM to LBM;

LBM is a ligase binding moiety;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p is 0, 1, 2, 3, or 4;

provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

2. Compounds and Definitions

[0024] Compounds of the present disclosure include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0025] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" or "cycloaliphatic"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle") refers to a monocyclic C_3–C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0026] The term "alkyl", unless otherwise indicated, as used herein, refers to a monovalent aliphatic hydrocarbon radical having a straight chain, branched chain, monocyclic moiety, or polycyclic moiety or combinations thereof, wherein the radical is optionally substituted at one or more carbons of the straight chain, branched chain, monocyclic moiety, or polycyclic moiety or combinations thereof with one or more substituents at each carbon, wherein the one or more substituents are independently C_1–C_{10} alkyl. Examples of "alkyl" groups include methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

[0027] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0028] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[0029] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0030] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0031] The suffix "ylenyl," as used herein, refers to a bi-valent radical (*i.e.*, a radical with two attachment points) of the moiety to which "ylenyl" is appended. For example, the term "heterocyclylenyl," as used herein, refers to a heterocycle with two points of attachment to the rest of the molecule. One or both points of attachment could be through carbon atoms or heteroatoms. In another example, the term "phenylenyl," as used herein, refers to a divalent form of an optionally substituted phenyl group by itself or in part of another group, and the term "cycloalkylenyl," as used herein, refers to a divalent form of an optionally substituted cycloalkyl group by itself or part of another group.

[0032] As used herein, the term "C_{1-8} (or C_{1-6}, or C_{1-4}) bivalent saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0033] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from

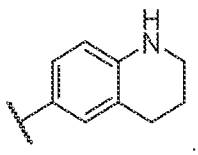
1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0034] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0035] The term "halogen" means F, Cl, Br, or I.

[0036] The term "aryl," used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but is not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents.

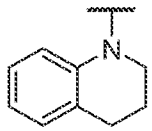
[0037] The terms "heteroaryl" or "heteroaromatic", unless otherwise defined, as used herein refers to a monocyclic aromatic 5-6 membered ring containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur, or an 8-10 membered polycyclic ring system containing one or more heteroatoms, wherein at least one ring in the polycyclic ring system is aromatic, and the point of attachment of the polycyclic ring system is through a ring atom on an aromatic ring. A heteroaryl ring may be linked to adjacent radicals though carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, thiophene, pyrrole, thiazole, oxazole, isothiazole, isoxazole, imidazole, pyrazole, triazole, pyridine, pyrimidine, indole, etc. For example, unless otherwise defined, 1,2,3,4-tetrahydroquinoline is a heteroaryl ring if its point of attachment is through the benzo ring, e.g.:



[0038] The terms "heterocyclyl" or "heterocyclic group", unless otherwise defined, refer to a saturated or partially unsaturated 3-10 membered monocyclic or 7-14 membered polycyclic ring system, including bridged or fused rings, and whose ring system includes one to four heteroatoms,

such as nitrogen, oxygen, and sulfur. A heterocyclyl ring may be linked to adjacent radicals through carbon or nitrogen.

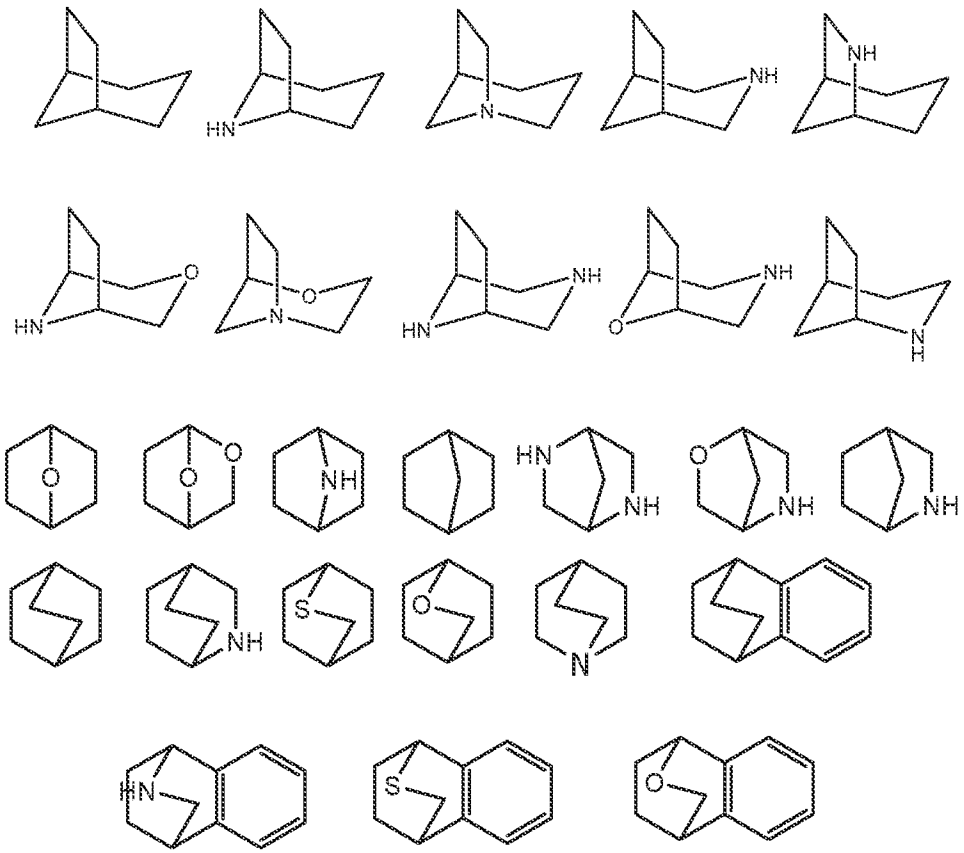
[0039] The term "partially unsaturated" in the context of rings, unless otherwise defined, refers to a monocyclic ring, or a component ring within a polycyclic (e.g. bicyclic, tricyclic, etc.) ring system, wherein the component ring contains at least one degree of unsaturation in addition to those provided by the ring itself, but is not aromatic. Examples of partially unsaturated rings include, but are not limited to, 3,4-dihydro-2H-pyran, 3-pyrroline, 2-thiazoline, etc. Where a partially unsaturated ring is part of a polycyclic ring system, the other component rings in the polycyclic ring system may be saturated, partially unsaturated, or aromatic, but the point of attachment of the polycyclic ring system is on a partially unsaturated component ring. For example, unless otherwise defined, 1,2,3,4-tetrahydroquinoline is a partially unsaturated ring if its point of attachment is through the piperidino ring, e.g.:



[0040] The term "saturated" in the context of rings, unless otherwise defined, refers to a 3-10 membered monocyclic ring, or a 7-14 membered polycyclic (e.g. bicyclic, tricyclic, etc.) ring system, wherein the monocyclic ring or the component ring that is the point of attachment for the polycyclic ring system contains no additional degrees of unsaturation in addition to that provided by the ring itself. Examples of monocyclic saturated rings include, but are not limited to, azetidine, oxetane, cyclohexane, etc. Where a saturated ring is part of a polycyclic ring system, the other component rings in the polycyclic ring system may be saturated, partially unsaturated, or aromatic, but the point of attachment of the polycyclic ring system is on a saturated component ring. For example, unless otherwise defined, 2-azaspiro[3.4]oct-6-ene is a saturated ring if its point of attachment is through the azetidino ring, e.g.:

[0041] The terms "alkylene", "arylene", "cycloalkylene", "heteroarylene", "heterocycloalkylene", and the other similar terms with the suffix "-ylene" as used herein refers to a divalently bonded version of the group that the suffix modifies. For example, "alkylene" is a divalent alkyl group connecting the groups to which it is attached.

[0042] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:



[0043] As described herein, compounds of the disclosure may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable

substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0044] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)(OR^\circ)R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0045] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^{\bullet}$, $-(haloR^{\bullet})$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-O(haloR^{\bullet})$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^{\bullet}$, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0046] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0047] Suitable substituents on the aliphatic group of R^* include halogen, $-R^{\bullet}$, -(haloR$^{\bullet}$), $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0048] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an

unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0049] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(haloR$^{\bullet}$), –OH, $-OR^{\bullet}$, –O(haloR$^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0050] The term "isomer" as used herein refers to a compound having the identical chemical formula but different structural or optical configurations. The term "stereoisomer" as used herein refers to and includes isomeric molecules that have the same molecular formula but differ in positioning of atoms and/or functional groups in the space. All stereoisomers of the present compounds (*e.g.*, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this disclosure. Therefore, unless otherwise stated, single stereochemical isomers as well as mixtures of enantiomeric, diastereomeric, and geometric (or conformational) isomers of the present compounds are within the scope of the disclosure.

[0051] The term "tautomer" as used herein refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another. It is understood that tautomers encompass valence tautomers and proton tautomers (also known as prototropic tautomers). Valence tautomers include interconversions by reorganization of some of the bonding electrons. Proton tautomers include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Unless otherwise stated, all tautomers of the compounds of the disclosure are within the scope of the disclosure.

[0052] The term "isotopic substitution" as used herein refers to the substitution of an atom with its isotope. The term "isotope" as used herein refers to an atom having the same atomic number as that of atoms dominant in nature but having a mass number (neutron number) different from the mass number of the atoms dominant in nature. It is understood that a compound with an isotopic substitution refers to a compound in which at least one atom contained therein is substituted with

its isotope. Atoms that can be substituted with its isotope include, but are not limited to, hydrogen, carbon, and oxygen. Examples of the isotope of a hydrogen atom include ^{2}H (also represented as D) and ^{3}H. Examples of the isotope of a carbon atom include ^{13}C and ^{14}C. Examples of the isotope of an oxygen atom include ^{18}O. Unless otherwise stated, all isotopic substitution of the compounds of the disclosure are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present disclosure. In certain embodiments, for example, a warhead moiety, R^{W}, of a provided compound comprises one or more deuterium atoms.

[0053] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Exemplary pharmaceutically acceptable salts are found, *e.g.*, in Berge, *et al.* (*J. Pharm. Sci.* 1977, 66(1), 1; and Gould, P.L., *Int. J. Pharmaceutics* 1986, 33, 201-217; (each hereby incorporated by reference in its entirety).

[0054] Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0055] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^{+}(C_{1-4}alkyl)_{4}$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts

include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0056] Pharmaceutically acceptable salts are also intended to encompass hemi-salts, wherein the ratio of compound:acid is respectively 2:1. Exemplary hemi-salts are those salts derived from acids comprising two carboxylic acid groups, such as malic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, glutaric acid, oxalic acid, adipic acid and citric acid. Other exemplary hemi-salts are those salts derived from diprotic mineral acids such as sulfuric acid. Exemplary preferred hemi-salts include, but are not limited to, hemimaleate, hemifumarate, and hemisuccinate.

[0057] As used herein the term "about" is used herein to mean approximately, roughly, around, or in the region of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20 percent up or down (higher or lower).

[0058] An "effective amount", "sufficient amount" or "therapeutically effective amount" as used herein is an amount of a compound that is sufficient to effect beneficial or desired results, including clinical results. As such, the effective amount may be sufficient, *e.g.*, to reduce or ameliorate the severity and/or duration of afflictions related to ERα signaling, or one or more symptoms thereof, prevent the advancement of conditions or symptoms related to afflictions related to ERα signaling, or enhance or otherwise improve the prophylactic or therapeutic effect(s) of another therapy. An effective amount also includes the amount of the compound that avoids or substantially attenuates undesirable side effects.

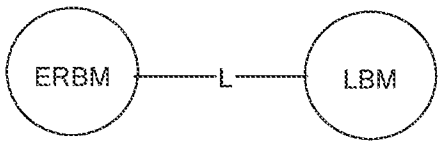
[0059] As used herein and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results may include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminution of extent of disease or affliction, a stabilized (*i.e.*, not worsening) state of disease or affliction, preventing spread of disease or affliction, delay or slowing of disease or affliction progression, amelioration or palliation of the disease or affliction state and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. In some embodiments, treatment may be administered after one or more symptoms have developed. In other

embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0060] The phrase "in need thereof" refers to the need for symptomatic or asymptomatic relief from conditions related to ERα singaling or that may otherwise be relieved by the compounds and/or compositions of the disclosure.

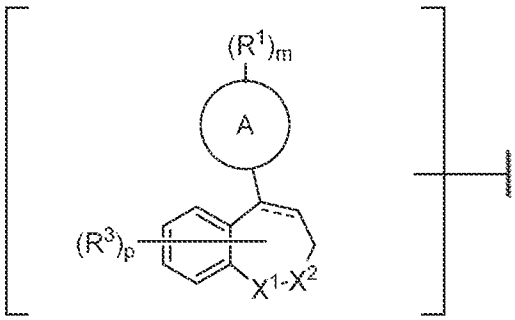
3. Description of Exemplary Embodiments

[0061] As described above, in some embodiments, the present disclosure provides a compound of formula **I-a**:

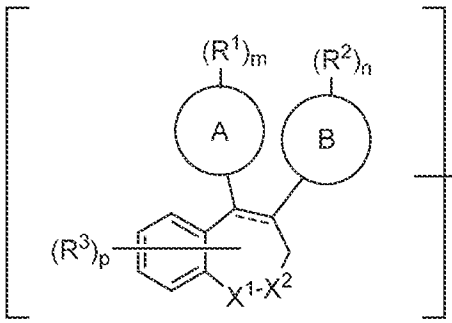


I-a

or a pharmaceutically acceptable salt thereof, wherein:

ERBM is selected from 

and



, wherein ⊣ indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and ≈ indicates a single or double bond;

each of X^1 and X^2 is independently $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, –S(O)–,

$-S(O)_2-$, or $-N(R^{A2})-$;

each instance of R^1, R^2, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C;

each instance of R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-S(O)(NCN)R$, $-S(NCN)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, or $-B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C is independently oxo, deuterium, halogen, $-CN$, $-NO_2$, $-OR$, $-SF_5$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, $-P(O)(R)OR$, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a bivalent moiety that connects ERBM to LBM;

LBM is a ligase binding moiety;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p is 0, 1, 2, 3, or 4;

provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

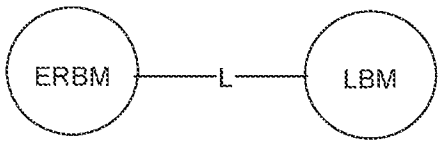
[0062] In some embodiments, LBM is an E3 ligase ligand. Such E3 ligase ligands are well known to one of ordinary skill in the art and include those described in M. Toure, C. M. Crews, *Angew. Chem. Int. Ed.* **2016**, 55, 1966; T. Uehara *et al. Nature Chemical Biology* **2017**, 13, 675; WO 2017/176708, US 2017/0281784 (LBM corresponds to the Cereblon-Binding Warhead); WO 2017/161119, US 2021/0177825 (LBM corresponds to the cereblon E3 Ubiquitin Ligase binding moiety CLM); WO 2017/176957, WO 2017/176958, WO 2017/180417, US 2019/0119289, US 2019/0169195, US 2019/0127387, US 2021/0002289 (LBM corresponds to B); WO 2015/160845,

WO 2016/197032, WO 2019/199816, US 2015/0291562, US 2016/0058872, US 2018/0228907, US 2020/0155689, US 2020/0155690, US 2022/0089570 (LBM corresponds to ULM); WO 2016/105518, US 2018/0009779, WO 2017/007612, 2018/0134684 (LBM corresponds to Degron); WO 2013/106643, US 2014/0356322 (LBM corresponds to ULM); WO 2002/020740, US 2002/0068063 (LBM corresponds to A); WO 2016/118666, US 2016/0214972 (LBM corresponds to ULM); WO 2016/149668, US 2016/0272639 (LBM corresponds to ULM); WO 2016/169989, US 2018/0118733 (LBM corresponds to IAP binder); WO 2016/197114, US 2018/0147202 (LBM corresponds to ULM); WO 2017/011371, US 2017/0008904 (LBM corresponds to ULM); WO 2017/011590, US 2017/0037004 (LBM corresponds to ULM); WO 2017/079267, US 2017/0121321 (LBM corresponds to ULM); WO 2017/117473, US 2020/0216454 (LBM corresponds to Degron); WO 2017/117474, US 2019/0016703 (LBM corresponds to Degron); WO 2017/197036, US 2019/0076540 (LBM corresponds to Degron); WO 2017/197046, US 2019/0076542 (LBM corresponds to Degron); WO 2017/197051, US 2019/0076539 (LBM corresponds to Degron); WO 2017/197055, US 2019/0076541 (LBM corresponds to Degron); WO 2017/197056 (LBM corresponds to Degron), WO 2022/081928 (LBM corresponds to Degron); WO 2019/060742, US 2021/0238193 (LBM corresponds to UBM); WO 2019/140380, US 2021/0002296 (LBM corresponds to UBM); WO 2020/010177, US 2020/0010468 (LBM corresponds to CRBN ligand); WO 2020/010227 (LBM corresponds to UBM); and WO 2021/011634 (LBM corresponds to UBM), the entirety of each of which is herein incorporated by reference.

[0063] In some embodiments, L is a bivalent moiety that connects ERBM to LBM. Such L moieties are well known to one of ordinary skill in the art and include those described in M. Toure, C. M. Crews, *Angew. Chem. Int. Ed.* **2016**, 55, 1966; T. Uehara *et al. Nature Chemical Biology* **2017**, 13, 675; WO 2017/176708, US 2017/0281784 (L corresponds to the connector C); WO 2017/161119, US 2021/0177825 (L corresponds to the linker L); WO 2017/176957, WO 2017/176958, WO 2017/180417, US 2019/0119289, US 2019/0169195, US 2019/0127387, US 2021/0002289 (L corresponds to L); WO 2015/160845, WO 2016/197032, WO 2019/199816, US 2015/0291562, US 2016/0058872, US 2018/0228907, US 2020/0155689, US 2020/0155690, US 2022/0089570 (L corresponds to the chemical linker L); WO 2016/105518, US 2018/0009779, WO 2017/007612, 2018/0134684 (L corresponds to Linker); WO 2013/106643, US 2014/0356322 (L corresponds to linker group L); WO 2016/118666, US 2016/0214972 (L corresponds to L); WO 2016/149668, US 2016/0272639 (L corresponds to Linker); WO 2016/169989, US 2018/0118733 (L corresponds to L); WO 2016/197114, US 2018/0147202 (L corresponds to L); WO

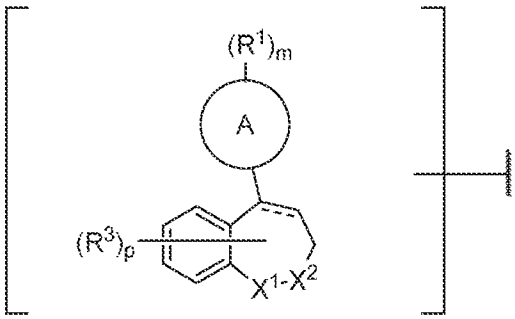
2017/011371, US 2017/0008904 (L corresponds to L); WO 2017/011590, US 2017/0037004 (L corresponds to L); WO 2017/079267, US 2017/0121321 (L corresponds to L); WO 2017/117473, US 2020/0216454 (L corresponds to Linker); WO 2017/117474, US 2019/0016703 (L corresponds to Linker); WO 2017/197036, US 2019/0076540 (L corresponds to Linker); WO 2017/197046, US 2019/0076542 (L corresponds to Linker); WO 2017/197051, US 2019/0076539 (L corresponds to Linker); WO 2017/197055, US 2019/0076541 (L corresponds to Linker); WO 2017/197056 (LBM corresponds to Degron); WO 2022/081928 (L corresponds to Linker and/or Spacer); WO 2019/060742, US 2021/0238193 (L corresponds to L); WO 2019/140380, US 2021/0002296 (L corresponds to L); WO 2020/010227 (L corresponds to L); and WO 2021/011634 (L corresponds to L); the entirety of each of which is herein incorporated by reference.

[0064] In some embodiments, the present disclosure provides a compound of formula **I-b**:

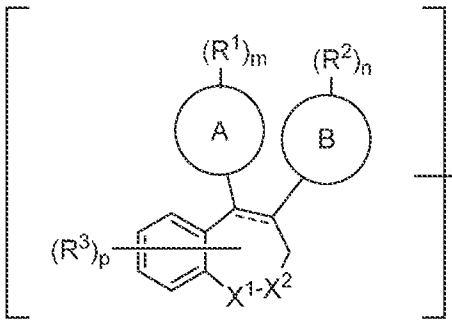


I-b

or a pharmaceutically acceptable salt thereof, wherein:

ERBM is selected from 

and



, wherein ⊣ indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and ≈ indicates a single or double bond;

each of X^1 and X^2 is independently $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, $–O–$, $–S–$, $–S(O)–$, $–S(O)_2–$, or $–N(R^{A2})–$;

each instance of R^1, R^2, R^4, R^5, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C;

each instance of R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A is independently oxo, deuterium, halogen, $–CN$, $–NO_2$, $–OR$, $–SF_5$, $–SR$, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, $–S(O)R$, $–S(O)NR_2$, $–S(O)(NR)R$, $–S(O)(NCN)R$, $–S(NCN)R$, $–C(O)R$, $–C(O)OR$, $–C(O)NR_2$, $–C(O)N(R)OR$, $–OC(O)R$, $–OC(O)NR_2$, $–N(R)C(O)OR$, $–N(R)C(O)R$, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, $–P(O)(R)OR$, or $–B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain, phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

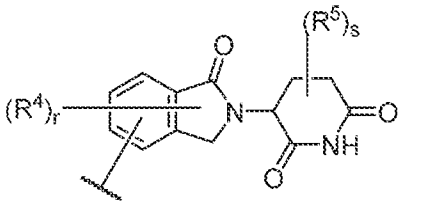
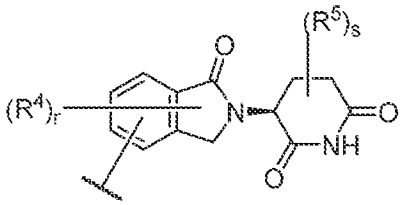
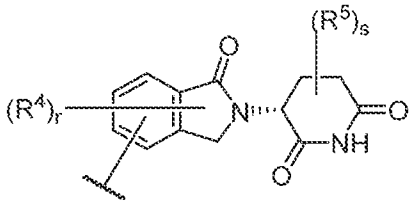
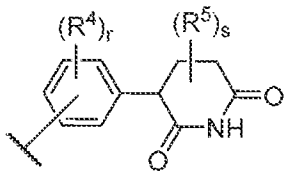
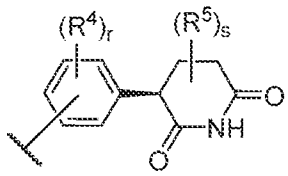
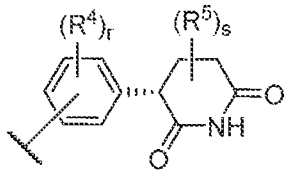
each instance of R^C is independently oxo, deuterium, halogen, $–CN$, $–NO_2$, $–OR$, $–SF_5$, $–SR$, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, $–S(O)R$, $–S(O)NR_2$, $–S(O)(NR)R$, $–C(O)R$, $–C(O)OR$, $–C(O)NR_2$, $–C(O)N(R)OR$, $–OC(O)R$, $–OC(O)NR_2$, $–N(R)C(O)OR$, $–N(R)C(O)R$, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, $–P(O)(R)OR$, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a bivalent moiety that connects ERBM to LBM;

LBM is selected from  ,  ,  ,  ,  , and  ;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

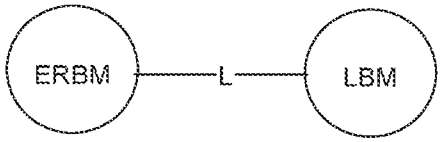
p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

s is 0, 1, 2, 3, or 4;

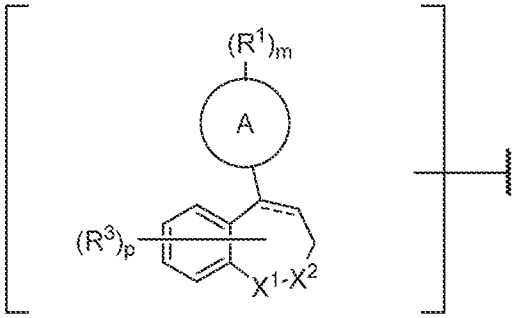
provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

[0065] In some embodiments, the present disclosure provides a compound of formula **I-c**:

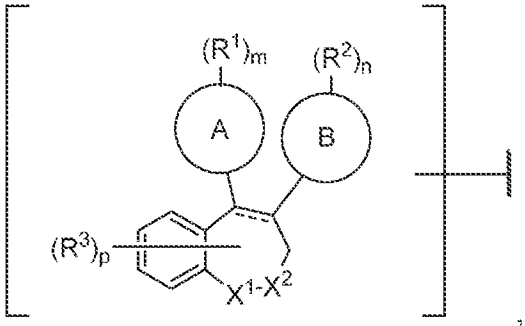


I-c

or a pharmaceutically acceptable salt thereof, wherein:

ERBM is selected from 

and



, wherein ⊣ indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and ⩫ indicates a single or double bond;

each of X^1 and X^2 is independently $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, –S(O)–, $–S(O)_2–$, or $–N(R^{A2})–$;

each instance of R^1, R^2, R^4, R^5, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C;

each instance of R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A is independently oxo, deuterium, halogen, –CN, $–NO_2$, –OR, $–SF_5$, –SR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –S(O)(NCN)R, –S(NCN)R, –C(O)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, –P(O)(R)OR, or $–B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

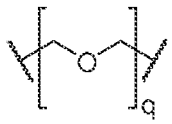
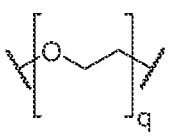
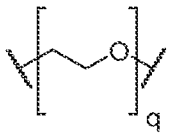
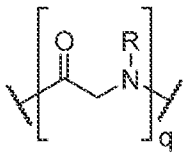
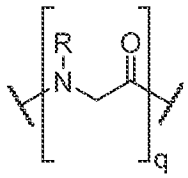
each instance of R^C is independently oxo, deuterium, halogen, –CN, $–NO_2$, –OR, $–SF_5$, –SR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, –P(O)(R)OR, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-

6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

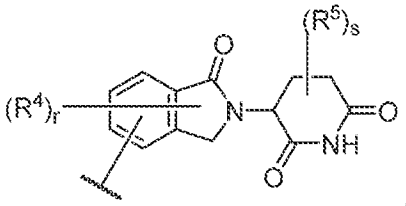
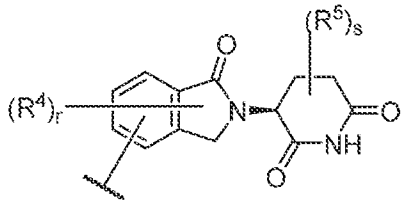
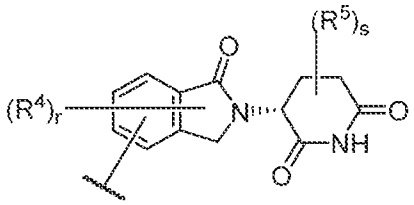
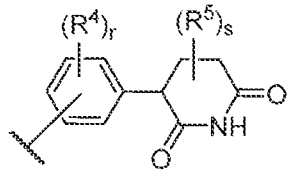
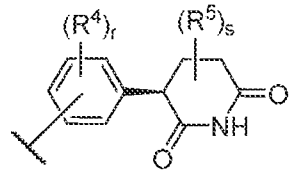
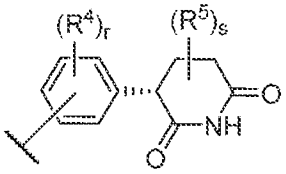
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, $–C(R)_2–$, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, $–S(O)–$, $–S(O)_2–$, $–NRS(O)_2–$, $–S(O)_2NR–$, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,  ,  ,  , or  , wherein:

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2

heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

LBM is selected from  ,  ,  ,  ,  , and  ;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

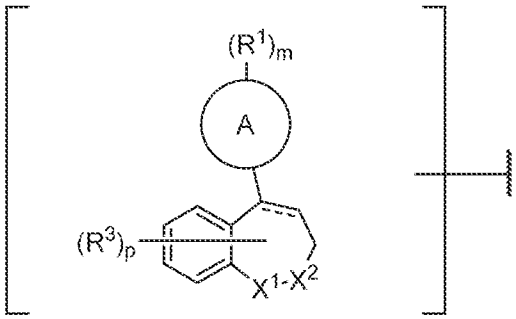
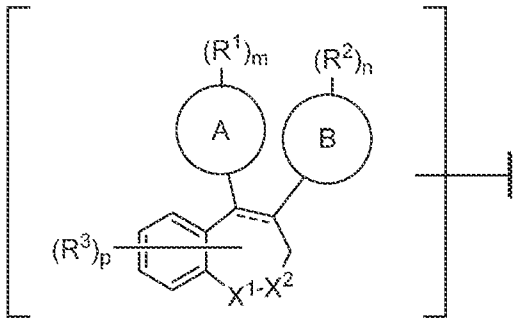
each of q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

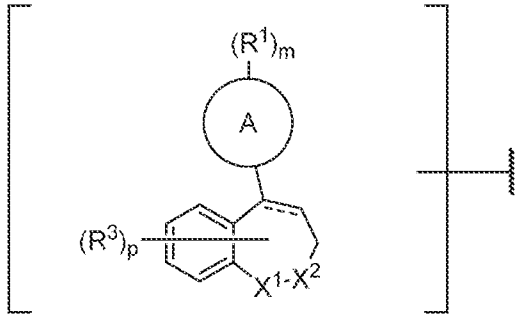
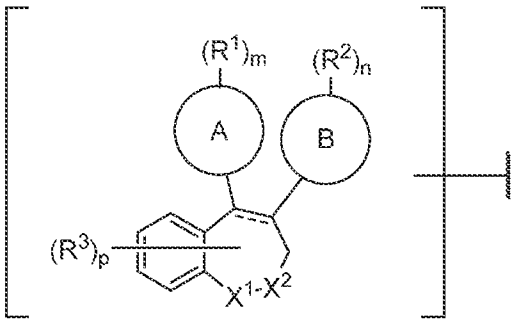
r is 0, 1, 2, 3, or 4; and

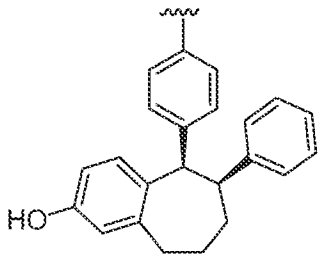
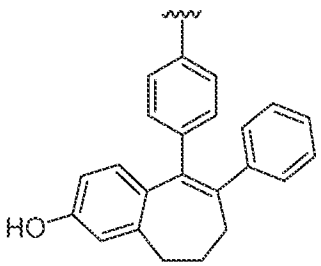
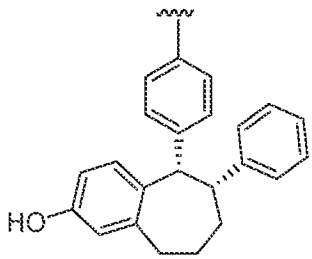
s is 0, 1, 2, 3, or 4;

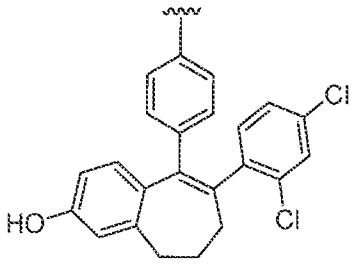
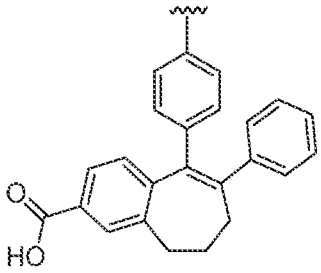
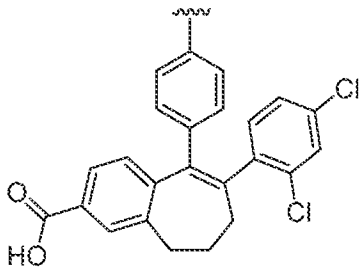
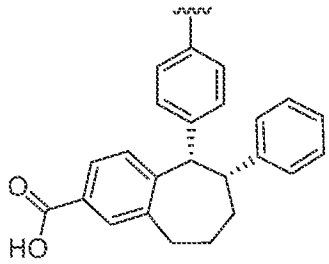
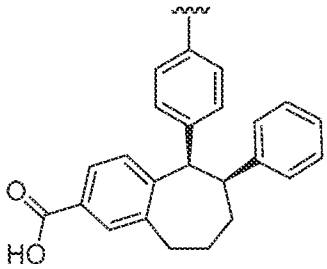
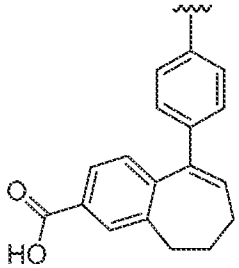
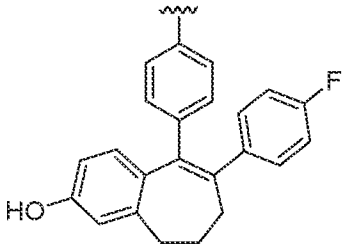
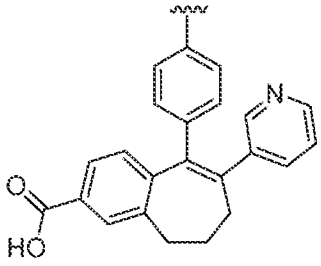
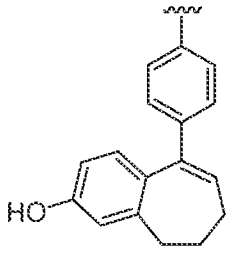
provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

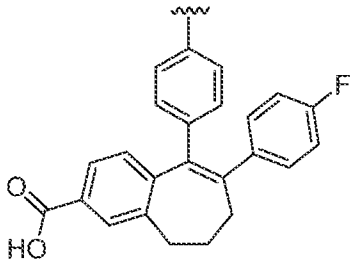
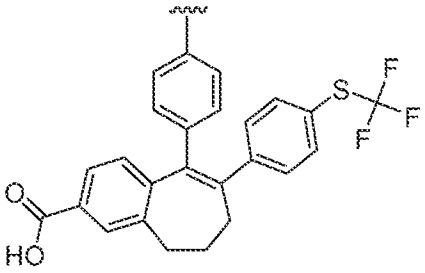
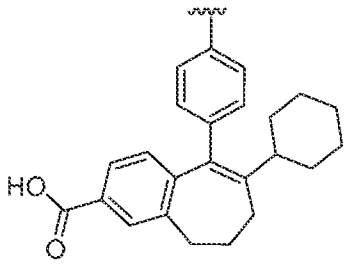
[0066] As defined generally above, ERBM is an ERα binding moiety capable of binding to ERα.

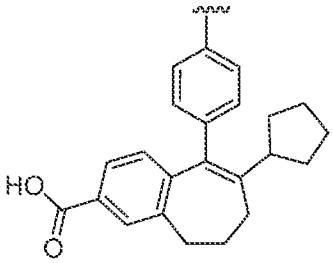
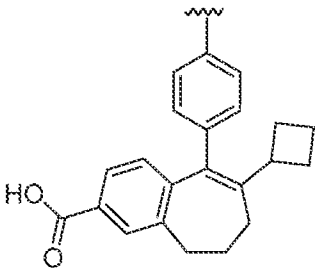
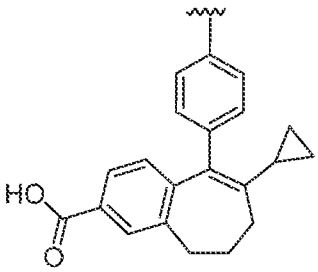
[0067] As defined generally above, ERBM is selected from  and  , wherein indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and indicates a single or double bond.

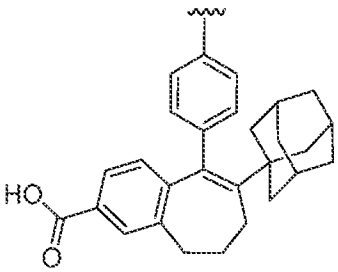
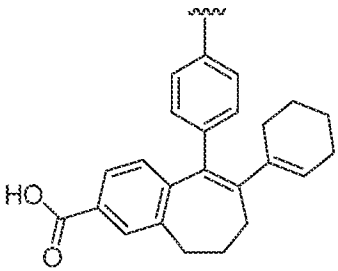
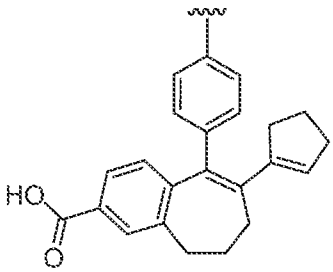
[0068] In some embodiments, ERBM is  . In some embodiments, ERBM is  .

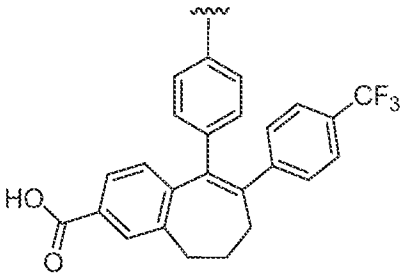
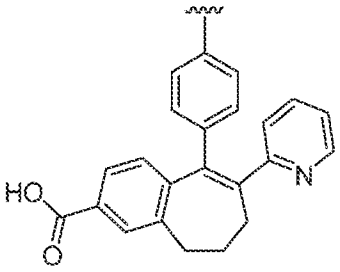
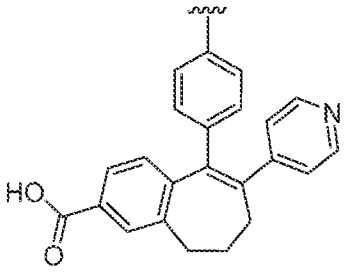
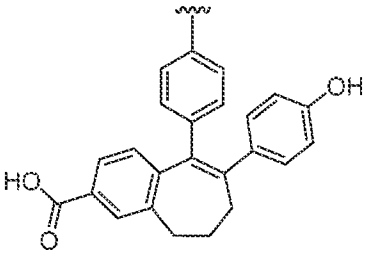
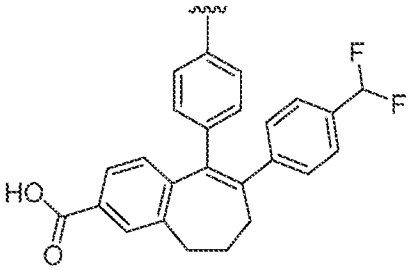
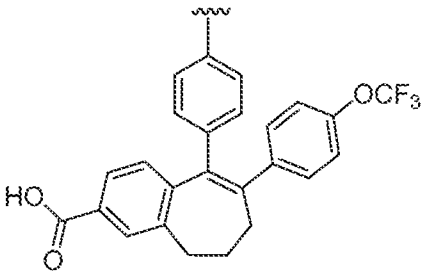
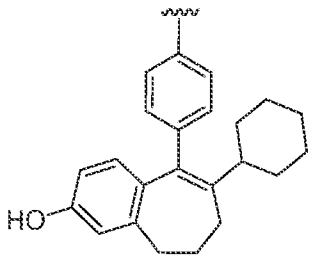
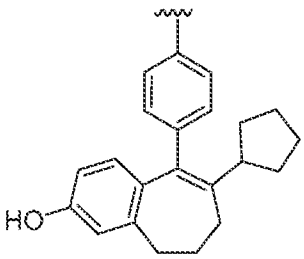
[0069] In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  .

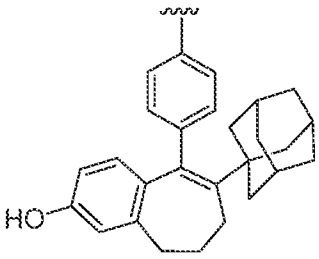
In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some

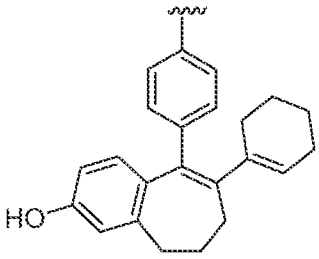
embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  .

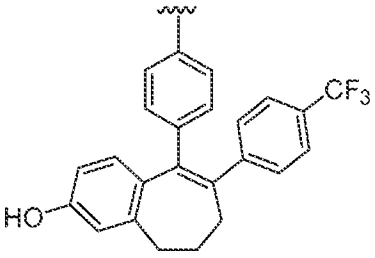
In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some

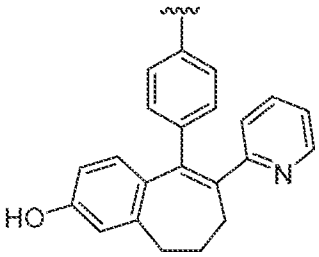
embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In

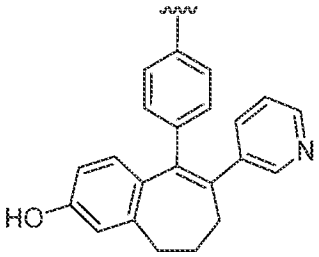
some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is

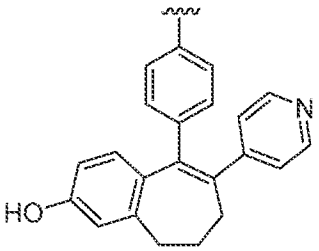


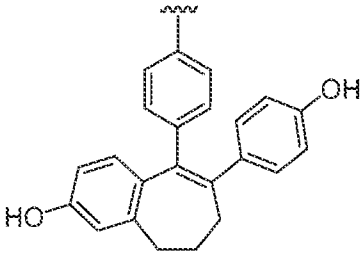
. In some embodiments, ERBM is 

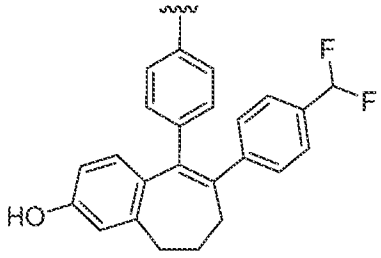
. In some embodiments, ERBM is 

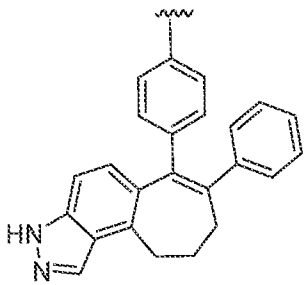
. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

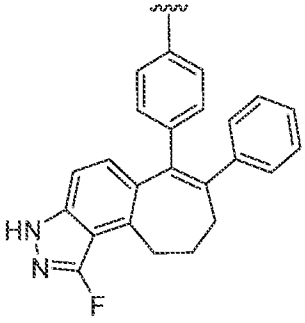
. In some embodiments, ERBM is 

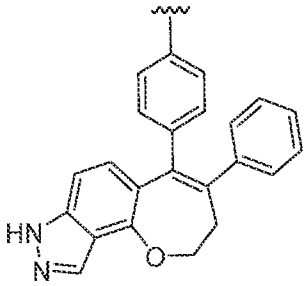
. In some embodiments, ERBM is 

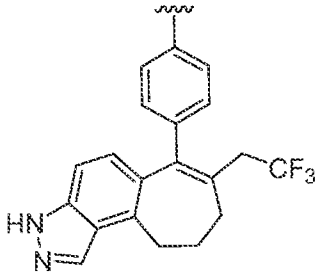
. In some embodiments, ERBM is 

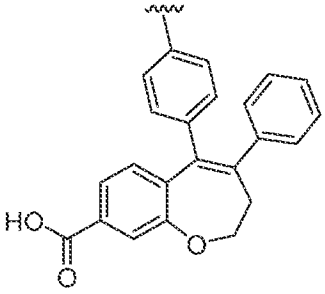
. In some embodiments, ERBM is 

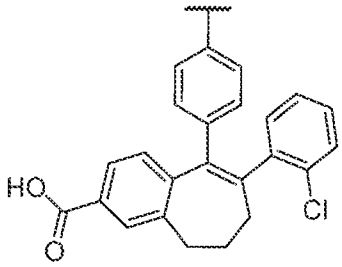
. In some embodiments, ERBM is

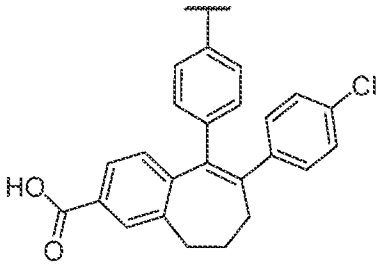


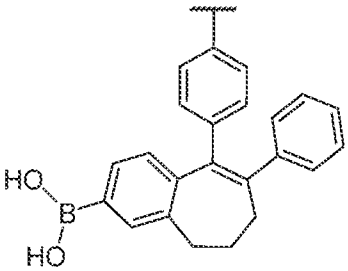
. In some embodiments, ERBM is 

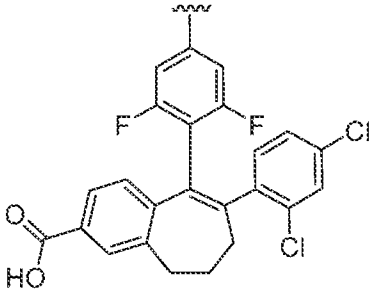
. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

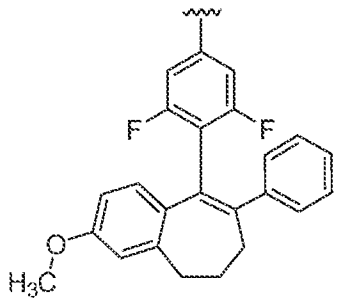
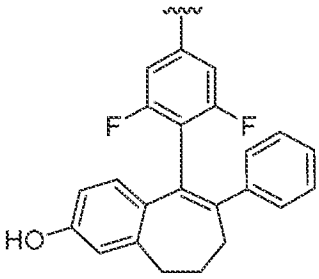
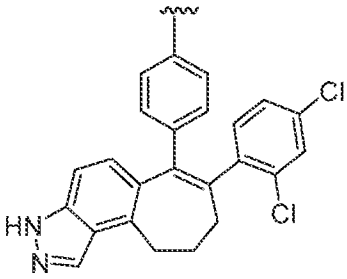
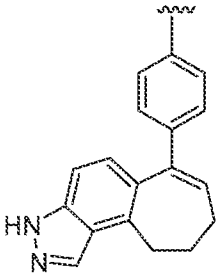
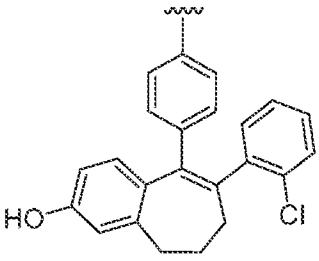
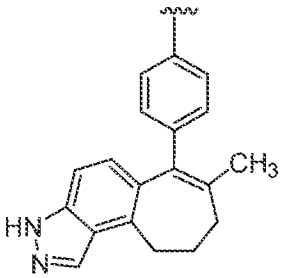
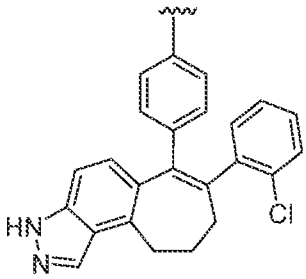
. In some embodiments, ERBM is 

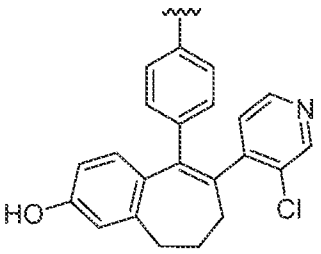
. In some embodiments, ERBM is 

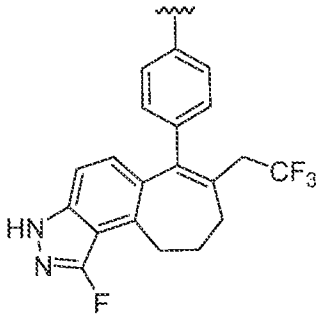
. In some embodiments, ERBM is 

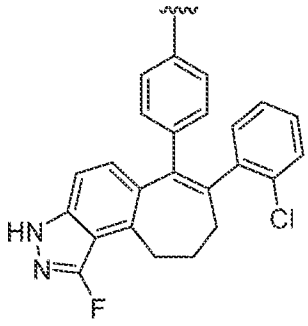
. In some embodiments, ERBM is 

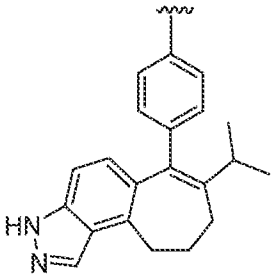
. In

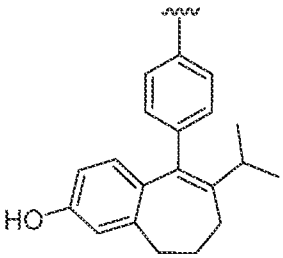
some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is

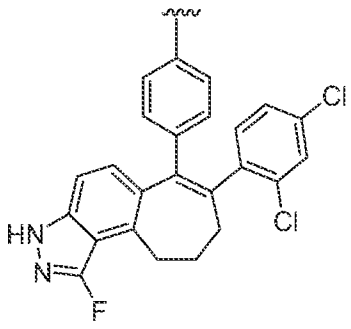


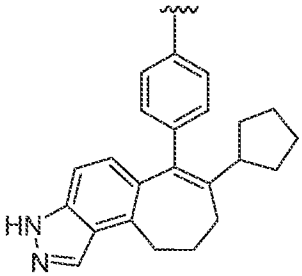
. In some embodiments, ERBM is 

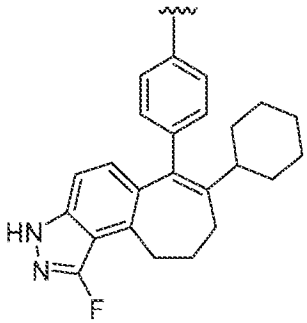
. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

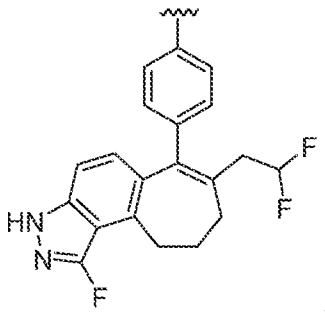
. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

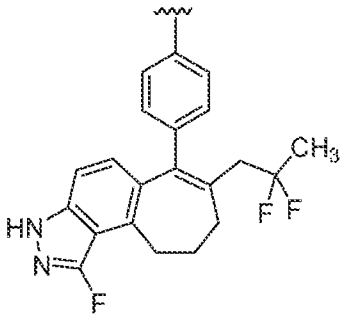
. In some embodiments, ERBM is 

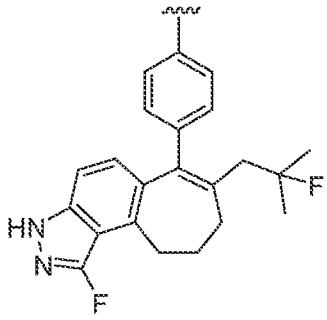
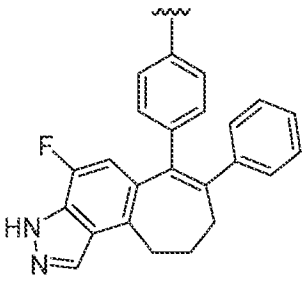
. In some embodiments, ERBM is 

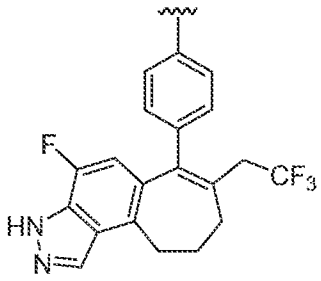
. In some

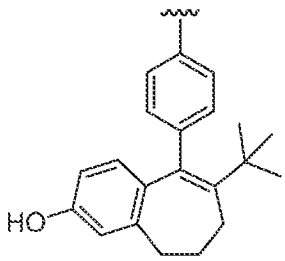
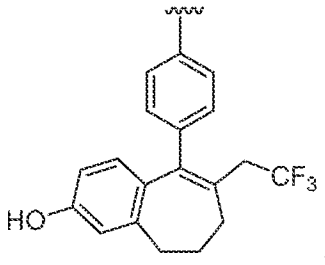


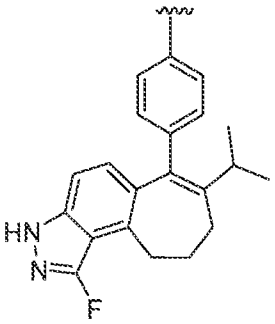
embodiments, ERBM is . In some embodiments, ERBM is

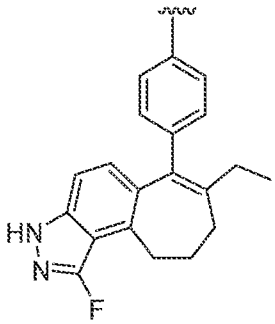


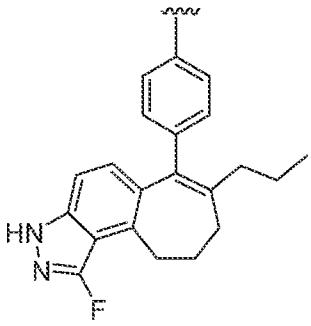
. In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is

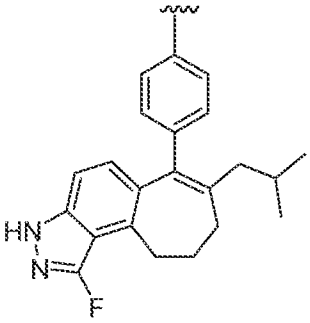


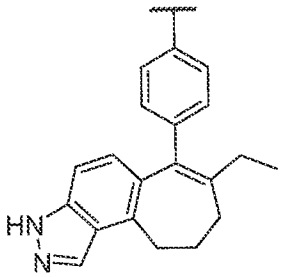
. In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is

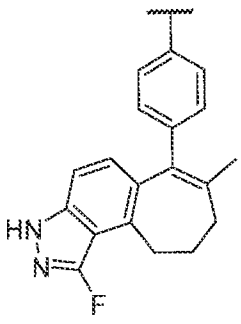


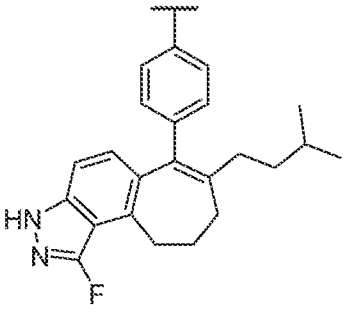
. In some embodiments, ERBM is 

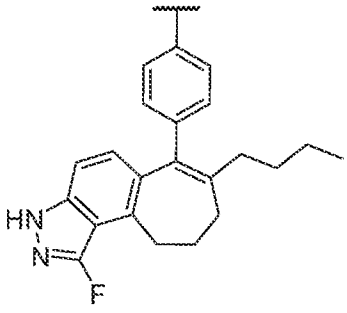
. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

. In some embodiments, ERBM is 

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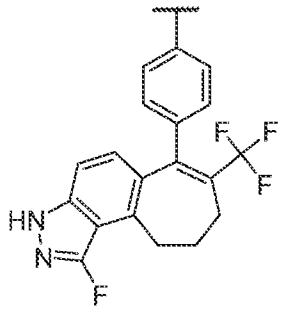
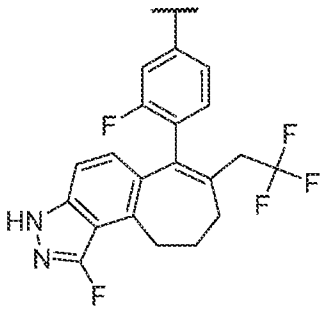
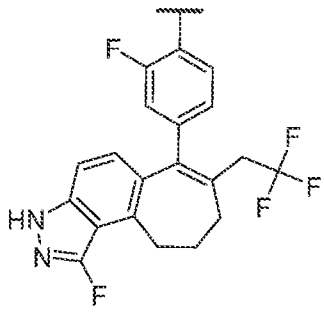
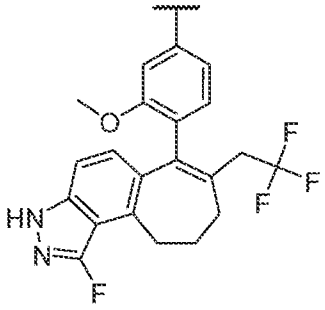


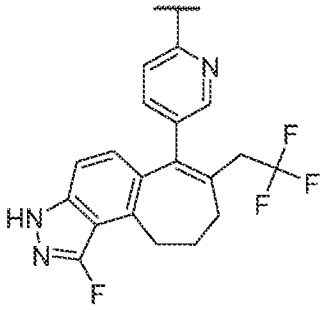
some embodiments, ERBM is . In some embodiments, ERBM is

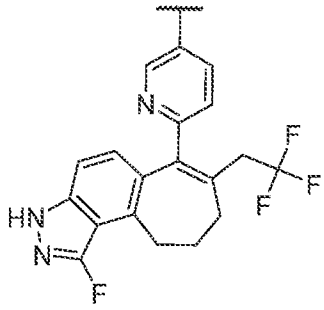


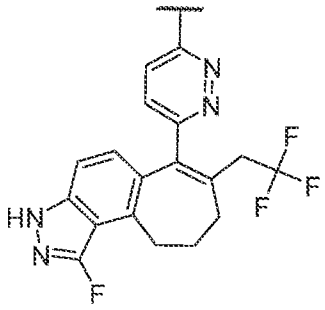
. In some embodiments, ERBM is  . In some



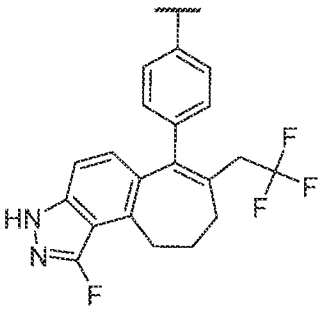
embodiments, ERBM is . In some embodiments, ERBM is

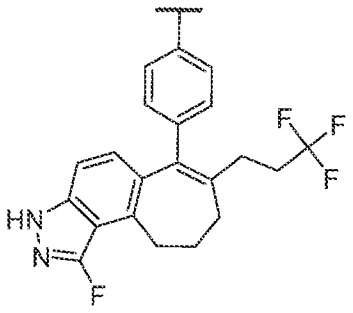
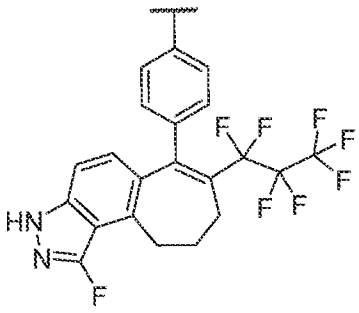
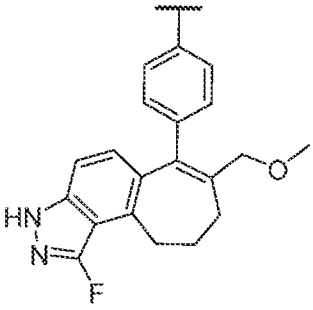
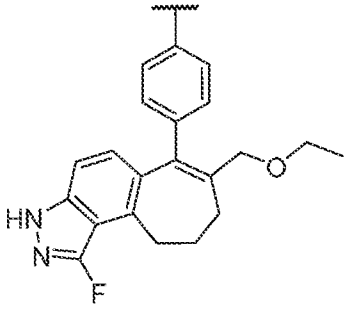
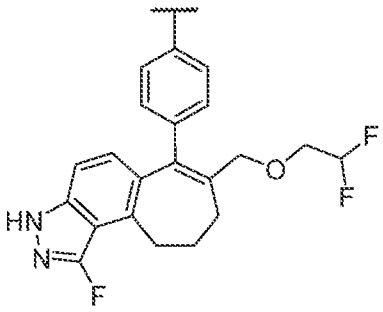
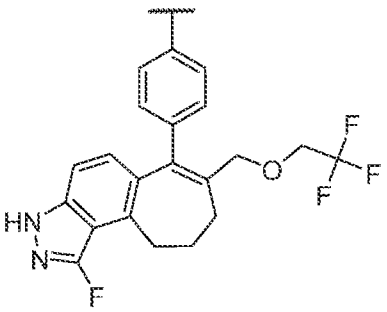
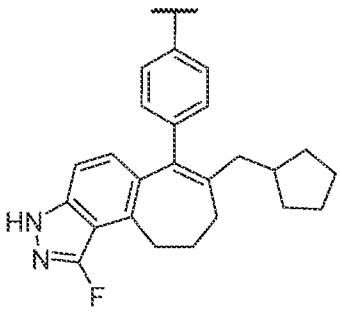


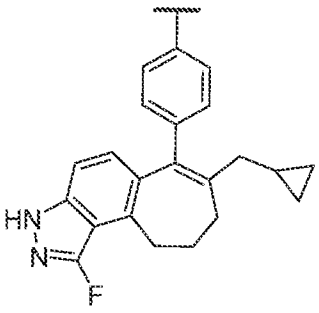
. In some embodiments, ERBM is  . In some



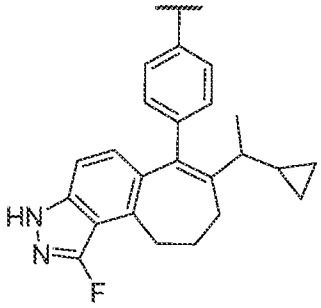
embodiments, ERBM is . In some embodiments, ERBM is



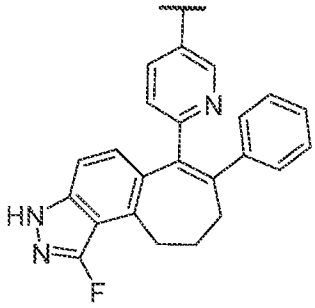
. In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In



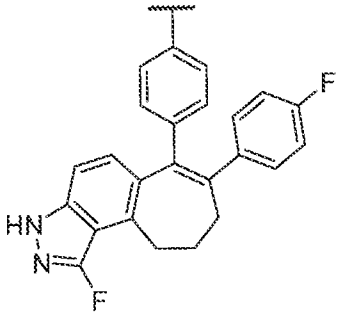
some embodiments, ERBM is . In some embodiments, ERBM is



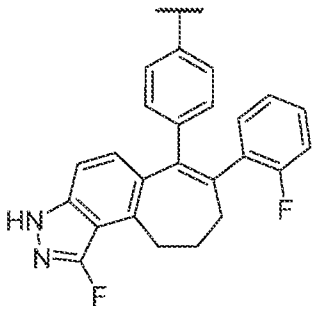
. In some embodiments, ERBM is



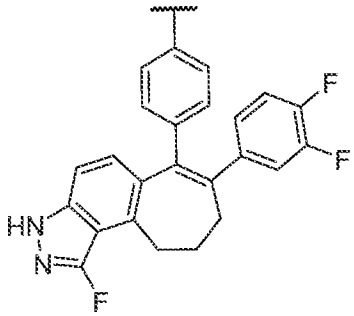
. In some embodiments, ERBM is



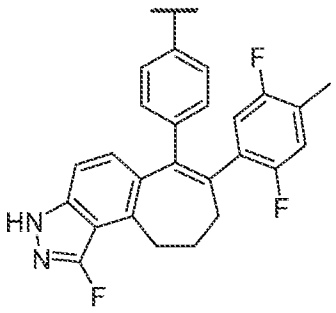
. In some embodiments, ERBM is



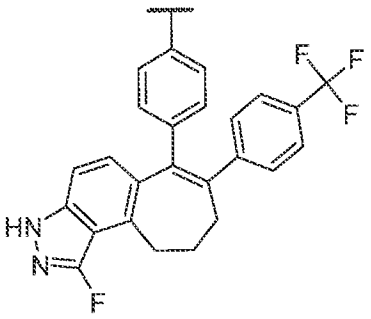
. In some embodiments, ERBM is

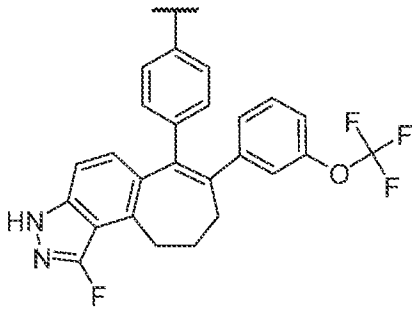


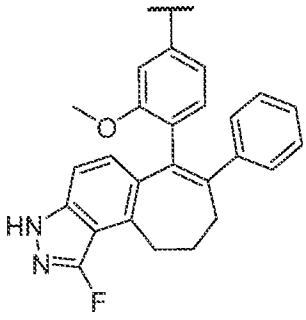
. In some embodiments, ERBM is



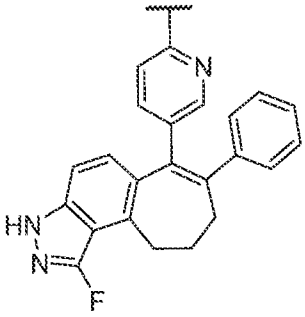
. In some embodiments, ERBM is

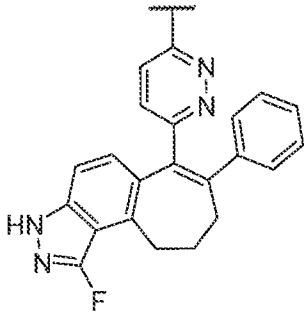


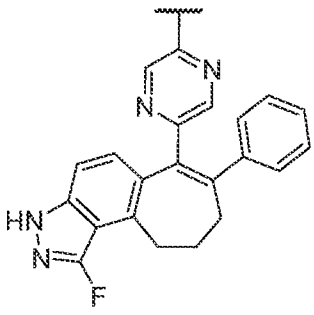
. In some embodiments, ERBM is  .



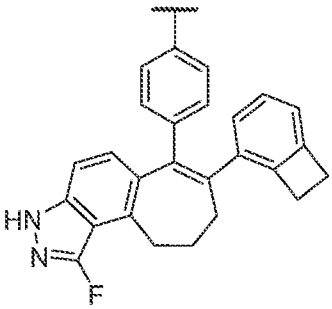
In some embodiments, ERBM is . In some embodiments, ERBM is

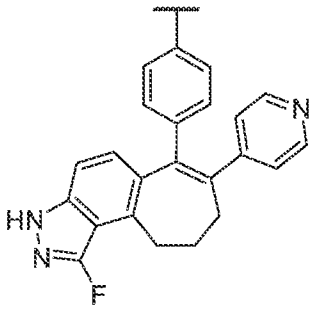


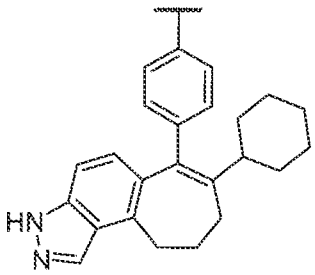
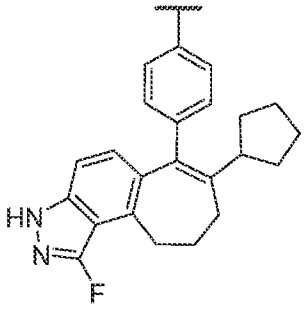
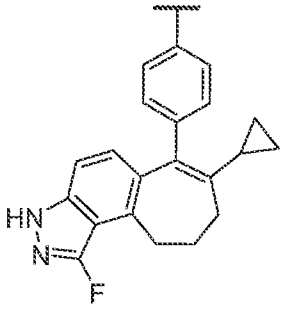
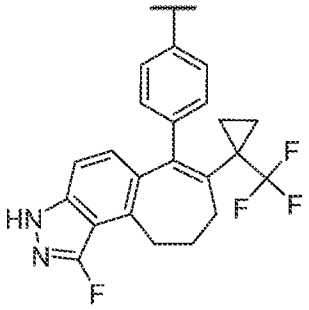
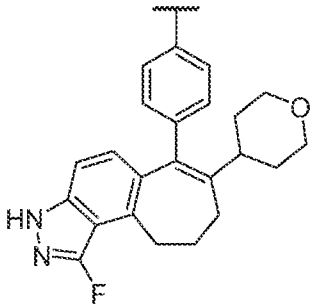
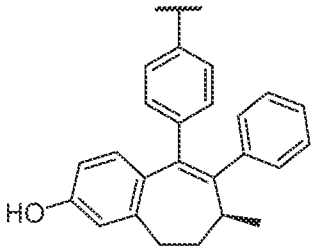
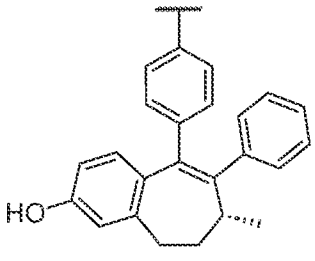
. In some embodiments, ERBM is  . In some



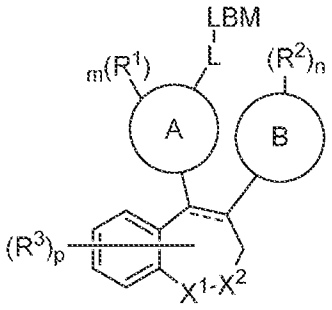
embodiments, ERBM is . In some embodiments, ERBM is



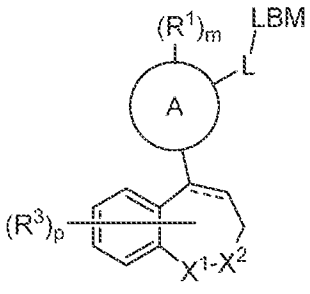
. In some embodiments, ERBM is  . In some

embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  . In some embodiments, ERBM is  .

[0070] In some embodiments, provided are compounds of formula **I-d** or **I-e**



I-d



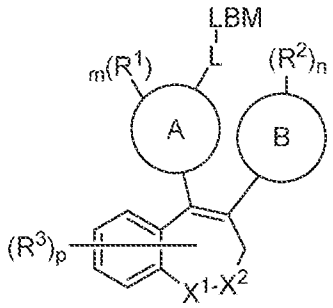
I-e

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^1, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

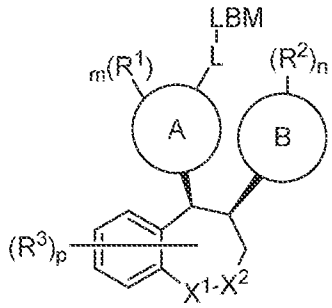
[0071] In some embodiments, the compound is a compound of formula **I-d** or a pharmaceutically acceptable salt thereof.

[0072] In some embodiments, the compound is a compound of formula **I-e** or a pharmaceutically acceptable salt thereof.

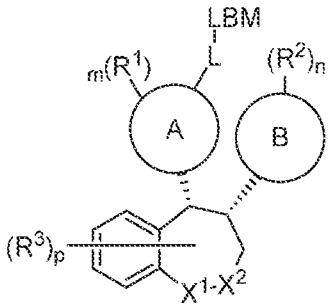
[0073] In some embodiments, the compound is a compound of formula **I-f**, **I-g**, **I-h**, **I-i**, **I-j** or **I-k**:



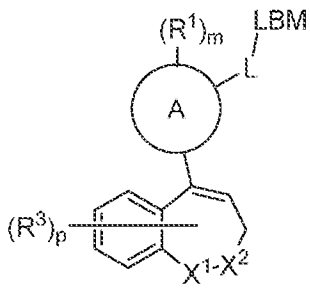
I-f



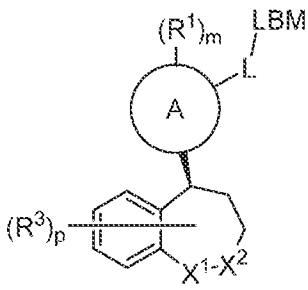
I-g



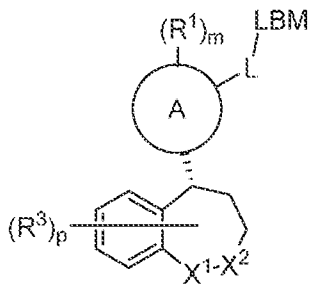
I-h



I-i



I-j



I-k

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^1, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0074] In some embodiments, the compound is a compound of formula **I-f**, **I-g**, **I-i** or **I-j**, or a pharmaceutically acceptable salt thereof.

[0075] In some embodiments, the compound is a compound of formula **I-f**, **I-g** or **I-i**, or a pharmaceutically acceptable salt thereof.

[0076] In some embodiments, the compound is a compound of formula **I-f**, or a pharmaceutically acceptable salt thereof.

[0077] In some embodiments, the compound is a compound of formula **I-g**, or a pharmaceutically acceptable salt thereof.

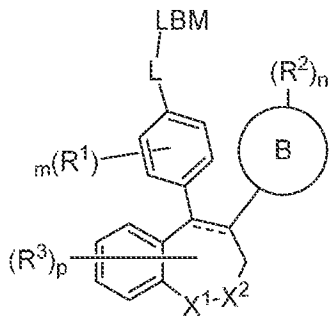
[0078] In some embodiments, the compound is a compound of formula **I-h**, or a pharmaceutically acceptable salt thereof.

[0079] In some embodiments, the compound is a compound of formula **I-i**, or a pharmaceutically acceptable salt thereof.

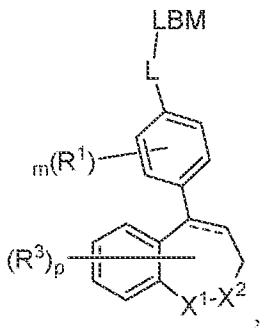
[0080] In some embodiments, the compound is a compound of formula **I-j**, or a pharmaceutically acceptable salt thereof.

[0081] In some embodiments, the compound is a compound of formula **I-k**, or a pharmaceutically acceptable salt thereof.

[0082] In some embodiments, provided are compounds of formula **I-l** or **I-m:**



I-l



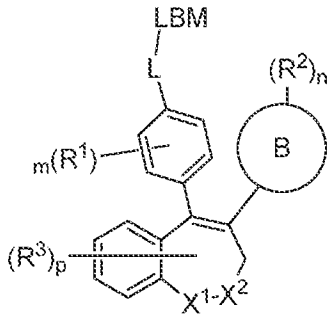
I-m

or a pharmaceutically acceptable salt thereof wherein each of Ring B, R^1, R^2, R^3, X^1, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

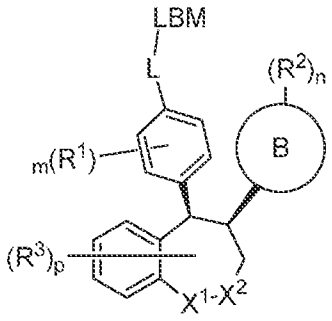
[0083] In some embodiments, the compound is a compound of formula **I-l**, or a pharmaceutically acceptable salt thereof.

[0084] In some embodiments, the compound is a compound of formula **I-m**, or a pharmaceutically acceptable salt thereof.

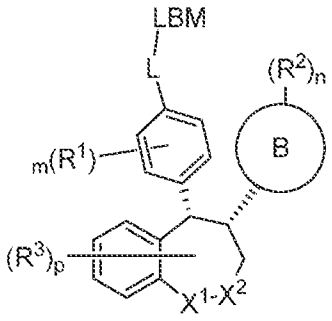
[0085] In some embodiments, provided are compounds of formula **I-n**, **I-o**, **I-p**, **I-q**, **I-r** or **I-s**:



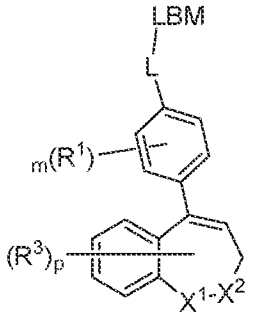
I-n



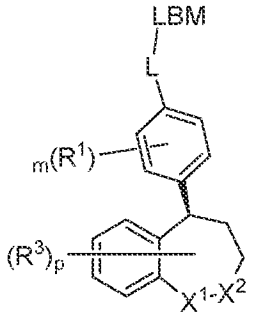
I-o



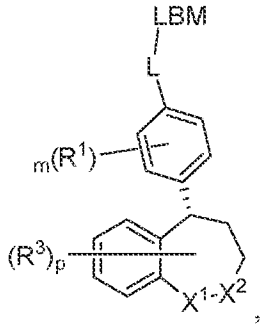
I-p



I-q



I-r



I-s

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, X^1, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0086] In some embodiments, the compound is a compound of formula **I-n**, **I-o**, **I-q** or **I-r**, or a pharmaceutically acceptable salt thereof.

[0087] In some embodiments, the compound is a compound of formula **I-n**, **I-o** or **I-q**, or a pharmaceutically acceptable salt thereof.

[0088] In some embodiments, the compound is a compound of formula **I-n**, or a pharmaceutically acceptable salt thereof.

[0089] In some embodiments, the compound is a compound of formula **I-o**, or a pharmaceutically acceptable salt thereof.

[0090] In some embodiments, the compound is a compound of formula **I-p**, or a pharmaceutically acceptable salt thereof.

[0091] In some embodiments, the compound is a compound of formula **I-q**, or a pharmaceutically acceptable salt thereof.

[0092] In some embodiments, the compound is a compound of formula **I-r**, or a pharmaceutically acceptable salt thereof.

[0093] In some embodiments, the compound is a compound of formula **I-s**, or a pharmaceutically acceptable salt thereof.

[0094] In some embodiments, ERBM is selected from the groups depicted in the compounds in **Table 1**.

[0095] As defined generally above, each of X^1 and X^2 is independently $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, –S(O)–, $–S(O)_2–$, or $–N(R^{A2})–$.

[0096] In some embodiments, X^1 is selected from $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, $–S(O)_2–$, and $–N(R^{A2})–$, provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

[0097] In some embodiments, X^1 is selected from $–CH_2–$ and –O– provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

[0098] In some embodiments, X^1 is $–CH_2–$. In some embodiments, X^1 is $–CH(R^{A1})–$. In some embodiments, X^1 is $–C(R^{A1})_2–$. In some embodiments, X^1 is –O– provided that X^2 is not a heteroatom. In some embodiments, X^1 is –S– provided that X^2 is not a heteroatom. In some embodiments, X^1 is –S(O)– provided that X^2 is not a heteroatom. In some embodiments, X^1 is $–S(O)_2–$ provided that X^2 is not a heteroatom. In some embodiments, X^1 is $–N(R^{A2})–$ provided that X^2 is not a heteroatom.

[0099] In some embodiments, X^1 is selected from the groups depicted in the compounds in **Table 1**.

[0100] In some embodiments, X^2 is selected from $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, $–S(O)_2–$, and $–N(R^{A2})–$.

[0101] In some embodiments, X^2 is selected from $–CH(R^{A1})–$, $–C(R^{A1})_2–$ and –O–.

[0102] In some embodiments, X^2 is $–CH(R^{A1})–$ or $–C(R^{A1})_2–$.

[0103] In some embodiments, X^2 is $–CH_2–$. In some embodiments, X^2 is $–CH(R^{A1})–$. In some embodiments, X^2 is $–C(R^{A1})_2–$. In some embodiments, X^2 is –O–. In some embodiments, X^2 is –S–. In some embodiments, X^2 is –S(O)–. In some embodiments, X^2 is $–S(O)_2–$. In some embodiments, X^2 is $–N(R^{A2})–$.

[0104] In some embodiments, X^2 is selected from the groups depicted in the compounds in **Table 1**.

[0105] As defined generally above, each instance of R^1, R^2, R^4, R^5, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C.

[0106] In some embodiments, R^1 is R^A substituted by 0-4 instances of R^C. In some embodiments, R^1 is R^B substituted by 0-4 instances of R^C.

[0107] In some embodiments, each R^1 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –SR, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$ and $–N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain substituted with 0-3 instances of halo.

[0108] In some embodiments, each R^1 is independently selected from –Me, –Et, –F, –Cl, $–SCF_3$, $–OCF_3$, $–CF_3$, –CN, –OH, –OMe, $–NH_2$, –NHMe and $–NMe_2$.

[0109] In some embodiments, R^1 is selected from fluoro and methyl. In some embodiments, R^1 is fluoro. In some embodiments, R^1 is methyl.

[0110] In some embodiments, R^1 is selected from the groups depicted in the compounds in **Table 1**.

[0111] In some embodiments, R^2 is R^A substituted by 0-4 instances of R^C. In some embodiments, R^2 is R^B substituted by 0-4 instances of R^C.

[0112] In some embodiments, each R^2 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$ and $–N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain, optionally substituted with 1-3 instances of halo.

[0113] In some embodiments, each R^2 is independently selected from –Me, –Et, –F, –Cl, $–CF_3$, $–CHF_2$, –CN, –OH, –OMe, $–OCF_3$, $–SCF_3$, $–NH_2$, –NHMe and $–NMe_2$.

[0114] In some embodiments, each R^2 is independently selected from –Me, –Et, –F, –Cl, $–CF_3$, –CN, –OH, –OMe, $–NH_2$, –NHMe and $–NMe_2$.

[0115] In some embodiments, each R^2 is independently selected from –F, –Cl, $–CF_3$, $–CHF_2$, –OH, $–OCF_3$, and $–SCF_3$.

[0116] In some embodiments, each R^2 is independently selected from –F, –Cl and $–SCF_3$.

[0117] In some embodiments, R^2 is methyl. In some embodiments, R^2 is trifluoromethyl.

[0118] In some embodiments, R^2 is fluoro. In some embodiments, R^2 is chloro. In some embodiments, R^2 is $-SCF_3$. In some embodiments, R^2 is $-OH$. In some embodiments, R^2 is $-OCF_3$. In some embodiments, R^2 is $-CHF_2$.

[0119] In some embodiments, R^2 is selected from the groups depicted in the compounds in **Table 1**.

[0120] In some embodiments, R^4 is R^A substituted by 0-4 instances of R^C. In some embodiments, R^4 is R^B substituted by 0-4 instances of R^C.

[0121] In some embodiments, each R^4 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, $-CN$, $-OR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2NR_2$ and $-N(R)S(O)_2R$, wherein R is $-H$ or a C_{1-6} aliphatic chain.

[0122] In some embodiments, each R^4 is independently selected from $-Me$, $-Et$, $-F$, $-Cl$, $-CF_3$, $-CN$, $-OH$, $-OMe$, $-NH_2$, $-NHMe$ and $-NMe_2$.

[0123] In some embodiments, R^4 is fluoro.

[0124] In some embodiments, R^4 is selected from the groups depicted in the compounds in **Table 1**.

[0125] In some embodiments, R^5 is R^A substituted by 0-4 instances of R^C. In some embodiments, R^5 is R^B substituted by 0-4 instances of R^C.

[0126] In some embodiments, each R^5 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, $-CN$, $-OR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)(NR)R$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2NR_2$ and $-N(R)S(O)_2R$, wherein R is $-H$ or a C_{1-6} aliphatic chain.

[0127] In some embodiments, each R^5 is independently selected from $-Me$, $-Et$, $-F$, $-Cl$, $-CF_3$, $-CN$, $-OH$, $-OMe$, $-NH_2$, $-NHMe$ and $-NMe_2$.

[0128] In some embodiments, each R^5 is independently selected from $-Me$ and $-F$.

[0129] In some embodiments, R^5 is selected from the groups depicted in the compounds in **Table 1**.

[0130] In some embodiments, R^{A1} is R^A substituted by 0-4 instances of R^C. In some embodiments, R^{A1} is R^B substituted by 0-4 instances of R^C.

[0131] In some embodiments, each R^{A1} is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –$C(O)NR_2$, –C(O)N(R)OR, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)S(O)_2NR_2$ and –$N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

[0132] In some embodiments, each R^{A1} is independently selected from –Me, –Et, –F, –Cl, –CF_3, –CN, –OH, –OMe, –NH_2, –NHMe and –NMe_2.

[0133] In some embodiments, each R^{A1} is independently selected from –Me, –F, –OH and –OMe. In some embodiments, each R^{A1} is independently selected from –Me and –F. In some embodiments, each R^{A1} is independently –F. In some embodiments, each R^{A1} is independently –Me.

[0134] In some embodiments, R^{A1} is selected from the groups depicted in the compounds in **Table 1**.

[0135] In some embodiments, R^{A2} is R^A substituted by 0-4 instances of R^C. In some embodiments, R^{A2} is R^B substituted by 0-4 instances of R^C.

[0136] In some embodiments, each R^{A2} is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, –$S(O)_2R$, –$S(O)_2NR_2$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –$C(O)NR_2$, –C(O)OR, and –C(O)R, wherein R is –H or a C_{1-6} aliphatic chain.

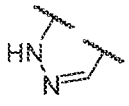
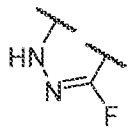
[0137] In some embodiments, each R^{A2} is independently selected from –Me, –Et, –CH_2CF_3, –$S(O)_2Me$, –$S(O)_2NMe_2$, –S(O)Me, –$S(O)NMe_2$, –$C(O)NMe_2$, –$C(O)NR_2$, –C(O)OMe, and –C(O)Me.

[0138] In some embodiments, each R^{A2} is independently selected from –Me, –CH_2CF_3, and –C(O)Me. In some embodiments, each R^{A2} is independently selected from –Me and –C(O)Me. In some embodiments, each R^{A1} is independently –C(O)Me. In some embodiments, each R^{A1} is independently –Me.

[0139] In some embodiments, R^{A2} is selected from the groups depicted in the compounds in **Table 1**.

[0140] As defined generally above, R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur which is is substituted by 0-4 instances of R^C.

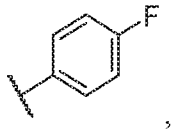
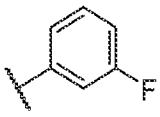
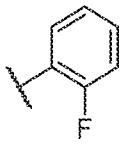
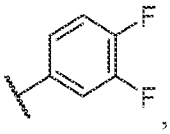
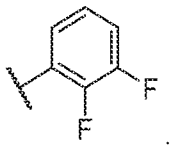
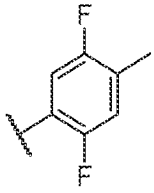
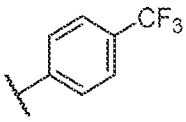
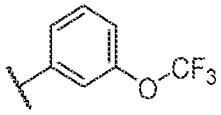
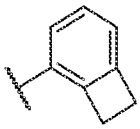
[0141] In some embodiments, R^3 is R^A substituted by 0-4 instances of R^C. In some embodiments, R^3 is R^B substituted by 0-4 instances of R^C. In some embodiments, two R^3 groups are taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur which is is substituted by 0-4 instances of R^C.

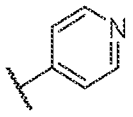
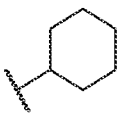
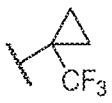
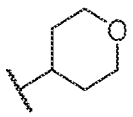
[0142] In some embodiments, two R^3 groups are taken together to form  . In some embodiments, two R^3 groups are taken together to form  .

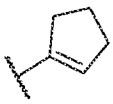
[0143] In some embodiments, each R^3 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$ and $–B(OR)_2$, wherein R is –H or a C_{1-6} aliphatic chain.

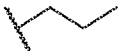
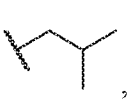
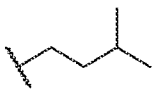
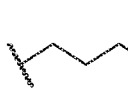
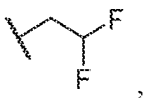
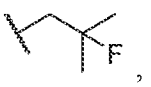
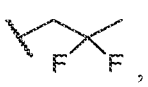
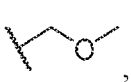
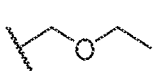
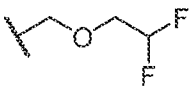
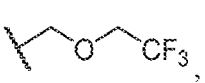
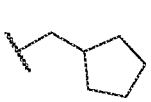
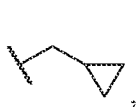
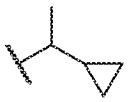
[0144] In some embodiments, each R^3 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$ and $–N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

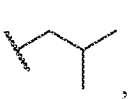
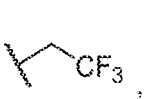
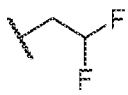
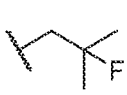
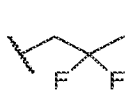
[0145] In some embodiments, each R^3 is phenyl. In some embodiments, each R^3 is substituted or unsubstituted phenyl. . In some embodiments, each R^3 is substituted with 1-4 substituents each independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}haloalkoxy. In some embodiments, each R^3 is phenyl substituted with 1-3 halogen (e.g.,

fluoro). In some embodiments, R^3 is fluorophenyl. In some embodiments, R^3 is  ,  , or  . In some embodiments, R^3 is di-fluorophenyl. In some embodiments, R^3 is  , or  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, each R^3 is 5-8 membered aryl fused ring. In some embodiments, each R^3 is  .

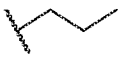
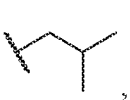
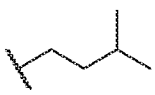
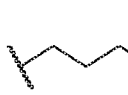
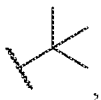
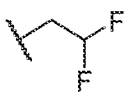
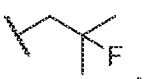
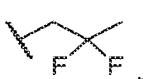
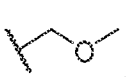
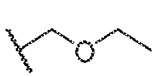
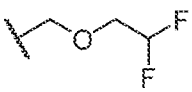
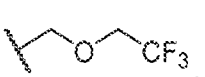
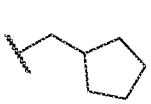
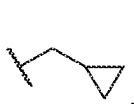
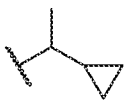
[0146] In some embodiments, each R^3 is a 5-6 membered monocyclic heteroaryl ring. In some embodiments, each R^3 is  . In some embodiments, each R^3 is a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, each R^3 is , , or  . In some embodiments, each R^3 is a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring optionally substituted with 1-4 substituents each independently selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}haloalkoxy. In some embodiments, each R^3 is  . In some embodiments, each R^3 is a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring. In some embodiments, each R^3 is  . In some embodiments, each R^3 is a 5-12 membered

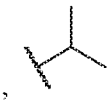
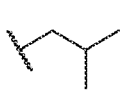
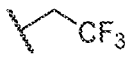
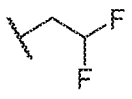
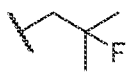
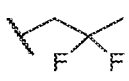
saturated or partially unsaturated bicyclic carbocyclic ring. In some embodiments, each R^3 is  .

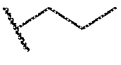
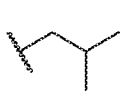
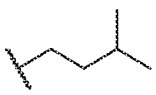
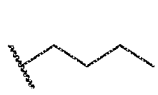
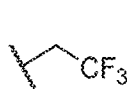
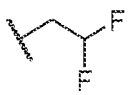
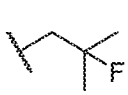
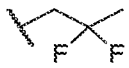
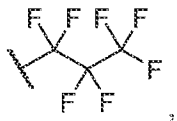
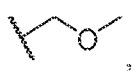
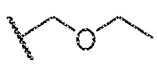
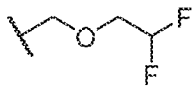
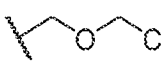
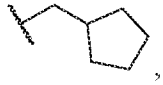
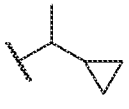
[0147] In some embodiments, each R^3 is independently selected from –Me, –Et,  , ,  ,  ,  , , –F, –Cl, –CF_3, ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  , –CO_2H, –CN, –OH, –OMe, –NH_2, –NHMe, –NMe_2 and –$B(OH)_2$.

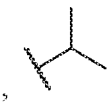
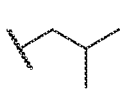
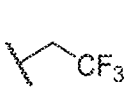
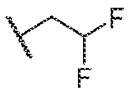
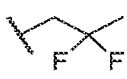
[0148] In some embodiments, each R^3 is independently selected from –Me, –Et, , ,  , , –F, –Cl, –CF_3,  ,  ,  ,  , –CO_2H, –CN, –OH, –OMe, –NH_2, –NHMe, –NMe_2 and –$B(OH)_2$.

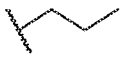
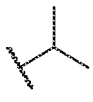
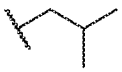
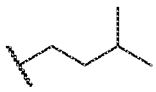
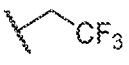
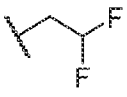
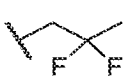
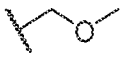
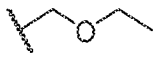
[0149] In some embodiments, each R^3 is independently selected from –Me, –Et, –F, –Cl, –CF_3, –CO_2H, –CN, –OH, –OMe, –NH_2, –NHMe and, –NMe_2 .

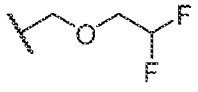
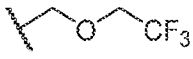
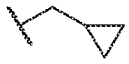
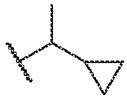
[0150] In some embodiments, each R^3 is independently selected from –Me, –Et,  , ,  ,  ,  ,  , –F, –CF_3, ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  , –CO_2H, –OH, –OMe, and –$B(OH)_2$.

[0151] In some embodiments, R^3 is independently selected from –Me, –Et, ,  ,  , , –F, –CF_3,  ,  ,  ,  , –CO_2H, –OH, –OMe, and –$B(OH)_2$.

[0152] In some embodiments, each R^3 is independently selected from –Me, –Et,  , ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  , and .

[0153] In some embodiments, R^3 is independently selected from –Me, –Et, ,  ,  , ,  ,  , , and  .

[0154] In some embodiments, R^3 is independently selected from –Me. In some embodiments, R^3 is –Et. In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is . In some embodiments, R^3 is . In some embodiments, R^3 is –CF_3. In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is . In some embodiments, R^3 is  . In some embodiments, R^3 is . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some

embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is . In some embodiments, R^3 is  . In some embodiments, R^3 is  .

[0155] In some embodiments, R^3 is $-CF_3$.

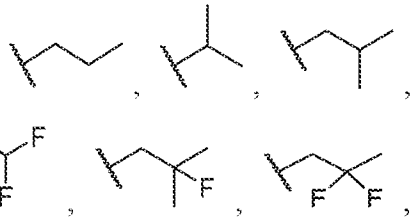
[0156] In some embodiments, R^3 is selected from –F, –OH, –OMe, $-B(OH)_2$ and $-CO_2H$.

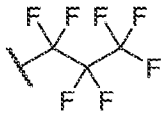
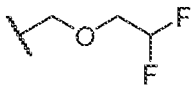
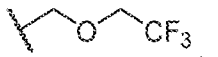
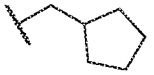
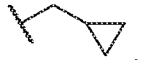
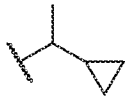
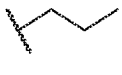
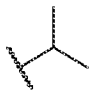
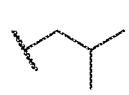
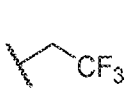
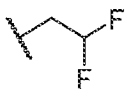
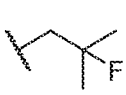
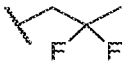
[0157] In some embodiments, R^3 is selected from –F, –OH, and $-CO_2H$.

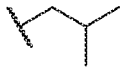
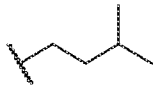
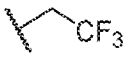
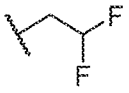
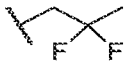
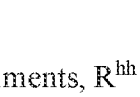
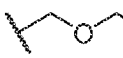
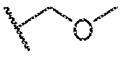
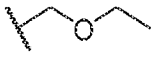
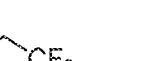
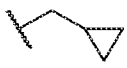
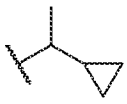
[0158] In some embodiments, R^3 is selected from –OH and $-CO_2H$.

[0159] In some embodiments, R^3 is –OH. In some embodiments, R^3 is $-CO_2H$. In some embodiments, R^3 is fluoro. In some embodiments, R^3 is –OMe. In some embodiments, R^3 is $-B(OH)_2$. In some embodiments, R^3 is $-CO_2H$.

[0160] In some embodiments, R^3 is selected from the groups depicted in the compounds in **Table 1**.

[0161] As generally defined herein, R^{hh} is C_1–C_6 alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, R^{hh} is C_1–C_6 alkyl substituted with 0, 1, 2, 3, or 4 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, R^{hh} is C_1–C_6 alkyl substituted with 0, 1, 2, 3, or 4 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, or cyclopentyl. In some embodiments, R^{hh} is C_1–C_6 alkyl substituted with 0, 1, 2, 3, or 4 instances of –F, –OMe, $-OCH_2CHF_2$, or $-OCH_2CF_3$. In some embodiments, R^{hh} is C_1–C_6 alkyl substituted with 0, 1, 2, 3, or 4 instances of cyclopropyl or cyclopentyl. In some embodiments, R^{hh} is C_1–C_6 alkyl substituted with 0, 1, 2, 3, or 4 instances of –F. In some embodiments, R^{hh} is C_1–C_6 alkyl. In some embodiments, R^{hh} is independently selected from –Me, –Et,  .

 , , ,  ,  ,  ,  ,  . In some embodiments, R^{hh} is independently selected from –Me, –Et,  ,  ,  , ,  ,  ,  and  .

[0162] In some embodiments, R^{hh} is –Me. In some embodiments, R^{hh} is –Et. In some embodiments, R^{hh} is . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is $-CF_3$. In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is . In some embodiments, R^{hh} is  . In some embodiments, R^{hh} is  .

[0163] As defined generally above, each instance of R^A is independently oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –S(O)(NCN)R, –S(NCN)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)C(NR)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$, –$P(O)R_2$, –P(O)(R)OR, or –$B(OR)_2$.

[0164] In some embodiments, R^A is oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –S(O)(NCN)R, –S(NCN)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR,

–OC(O)R, –OC(O)NR_2, –N(R)C(O)OR, –N(R)C(O)R, –N(R)C(O)NR_2, –N(R)C(NR)NR_2, –N(R)$S(O)_2NR_2$, –N(R)$S(O)_2$R, –P(O)R_2, –P(O)(R)OR, or –$B(OR)_2$.

[0165] In some embodiments, R^A is independently selected from deuterium, halogen, –CN, –OR, –NR_2, –$S(O)_2$R, –$S(O)_2NR_2$, –S(O)R, –S(O)NR_2, –S(O)(NR)R, –C(O)OR, –C(O)NR_2, –C(O)N(R)OR, –OC(O)NR_2, –N(R)C(O)OR, –N(R)C(O)R, –N(R)C(O)NR_2, –N(R)$S(O)_2NR_2$ and –N(R)$S(O)_2$R, wherein R is –H or a C_{1-6} aliphatic chain.

[0166] In some embodiments, R^A is fluoro. In some embodiments, R^A is –OH. In some embodiments, R^A is –CO_2H.

[0167] In some embodiments, R^A is selected from the groups depicted in the compounds in **Table 1**.

[0168] As defined generally above, each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0169] In some embodiments, R^B is a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0170] In some embodiments, each R^B is C_{1-6} aliphatic chain substituted with 0-3 instances of halo.

[0171] In some embodiments, R^B is methyl. In some embodiments, R^B together with its R^C sunstituents is trifluoromethyl.

[0172] In some embodiments, R^B is selected from the groups depicted in the compounds in **Table 1**.

[0173] As defined generally above, each instance of R^C is independently oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)C(NR)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$, –$P(O)R_2$, –P(O)(R)OR, –$B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0174] In some embodiments, R^C is oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)C(NR)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$, –$P(O)R_2$, –P(O)(R)OR, –$B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0175] In some embodiments, R^C is halo. In some embodiments R^C is fluoro.

[0176] In some embodiments, R^C is selected from the groups depicted in the compounds in **Table 1**.

[0177] As defined generally above, each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally

substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0178] In some embodiments, R is hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0179] In some embodiments, R is selected from H or a C_{1-6} aliphatic chain. In some embodiments R is a C_{1-6} aliphatic chain. In some embodiments R is a C_{1-6} aliphatic chain substituted with 0-3 instances of halo. In some embodiments R is a C_{1-6} aliphatic chain substituted with 0-3 instances of fluoro.

[0180] In some embodiments, R is selected from –H, –Me, –Et, –Pr, –^{i}Pr and –^{t}Bu. In some embodiments, R is selected from –H and –Me. In some embodiments, R is –Me. In some embodiments, R is hydrogen.

[0181] In some embodiments, R is selected from the groups depicted in the compounds in **Table 1**.

[0182] As defined generally above, Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0183] In some embodiments, Ring A and Ring B are each independently phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0184] In some embodiments, Ring A is phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0185] In some embodiments, Ring A is phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0186] In some embodiments, Ring A is phenyl; a 5 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0187] In some embodiments, Ring A is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, oxadiazolyl, oxathiazolyl).

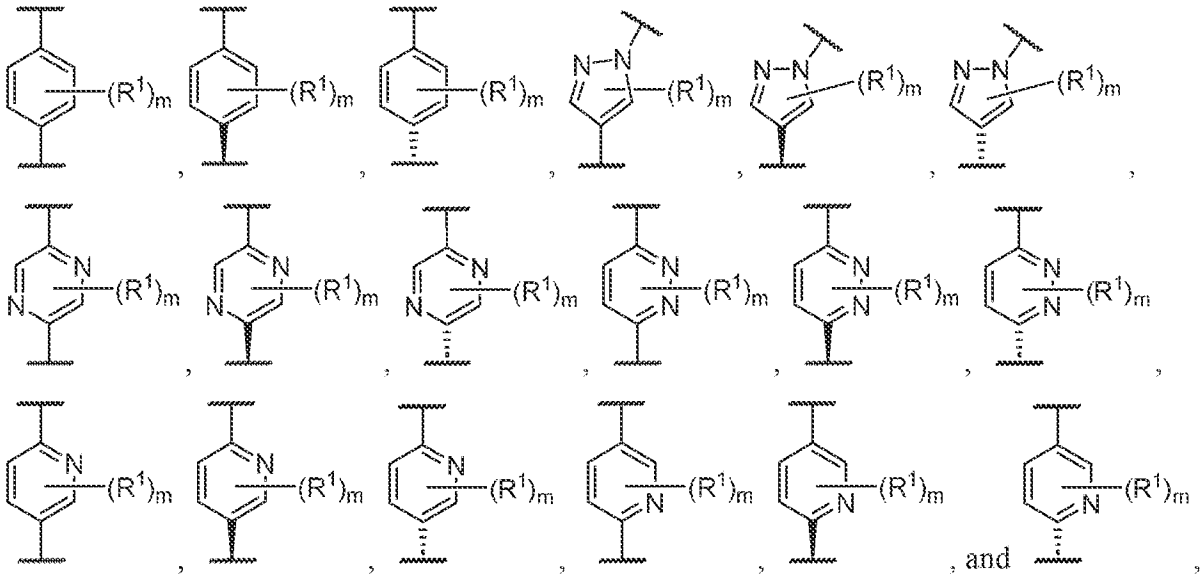
[0188] In some embodiments, Ring A is a 5-membered membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, oxadiazolyl, oxathiazolyl).

[0189] In some embodiments, Ring A is selected from phenyl, furanyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, oxadiazolyl and oxathiazolyl.

[0190] In some embodiments, Ring A is selected from phenyl and pyrazolyl.

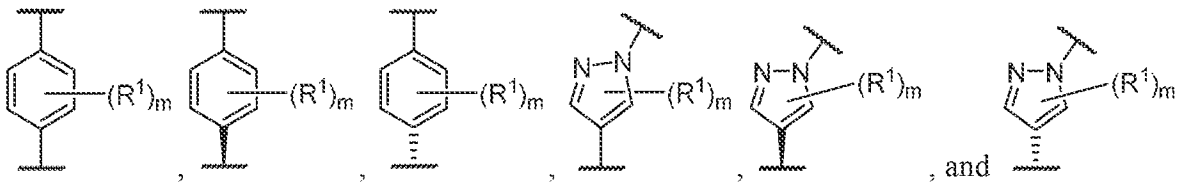
[0191] In some embodiments, Ring A is phenyl. In some embodiments, Ring A is pyrazolyl.

[0192] In some embodiments, Ring A together with its R^1 substituents is selected from



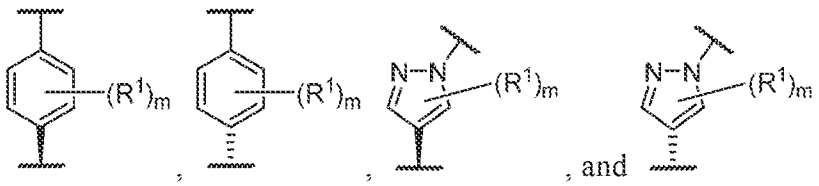
wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

[0193] In some embodiments, Ring A together with its R^1 substituents is selected from

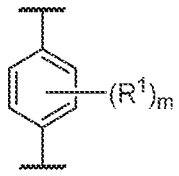


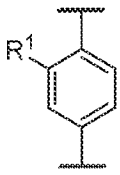
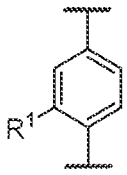
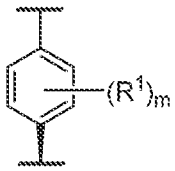
wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

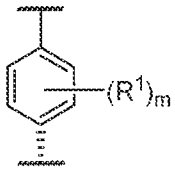
[0194] In some embodiments, Ring A together with its R^1 substituents is selected from



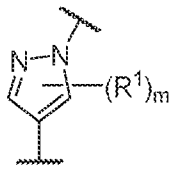
, wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the

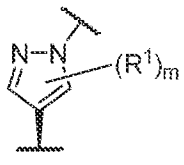


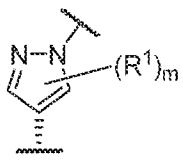
ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  or  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is



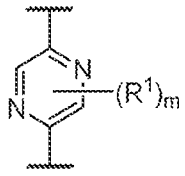
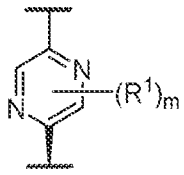
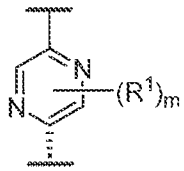
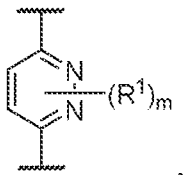
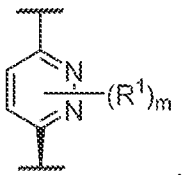
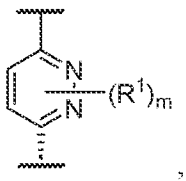
, wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A

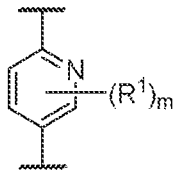
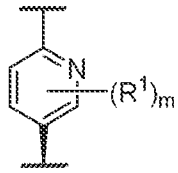
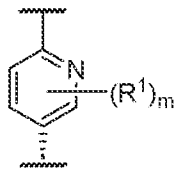
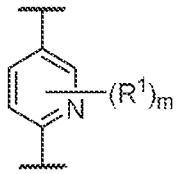
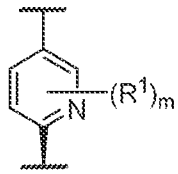
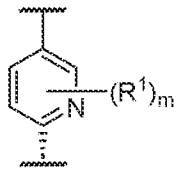


together with its R^1 substituents is , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is



, wherein the top attachment point connects to L and the bottom attachment point

connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together

with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety. In some embodiments, Ring A together with its R^1 substituents is  ,

[0195] In some embodiments, Ring A is selected from the groups depicted in the compounds in **Table 1**.

[0196] In some embodiments, Ring B is phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently

selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0197] In some embodiments, Ring B is phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0198] In some embodiments, Ring B is phenyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0199] In some embodiments, Ring B is phenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered

saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0200] In some embodiments, Ring B is phenyl; benzocyclobutenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0201] In some embodiments, Ring B is phenyl or benzocyclobutenyl.

[0202] In some embodiments, Ring B is phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0203] In some embodiments, Ring B is phenyl; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; or a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring.

[0204] In some embodiments, Ring B is phenyl; a 5 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0205] In some embodiments, Ring B is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, oxadiazolyl, oxathiazolyl).

[0206] In some embodiments, Ring B is a an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, quinolinyl,

isoquinolinyl, benzofuranyl, indolyl, benzimidazolyl, benzothiazolyl, benzothiophenyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl).

[0207] In some embodiments, Ring B is a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl).

[0208] In some embodiments, Ring B is 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring (*e.g.*, spiro [3.3] heptanyl, spiro [3,4] octanyl, adamantyl, dihydroindenyl (*e.g.*, 2,3-dihydro-1*H*-indenyl), tetrahydronaphthalenyl).

[0209] In some embodiments, Ring B is a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl).

[0210] In some embodiments, Ring B is selected from phenyl, benzocyclobutenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, spiro [3.3] heptanyl, spiro [3,4] octanyl, adamantyl, dihydroindenyl (*e.g.*, 2,3-dihydro-1*H*-indenyl), tetrahydronaphthalenyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, quinolinyl, isoquinolinyl, benzofuranyl, indolyl, benzimidazolyl, benzothiazolyl, benzothiophenyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, furanyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, oxadiazolyl and oxathiazolyl.

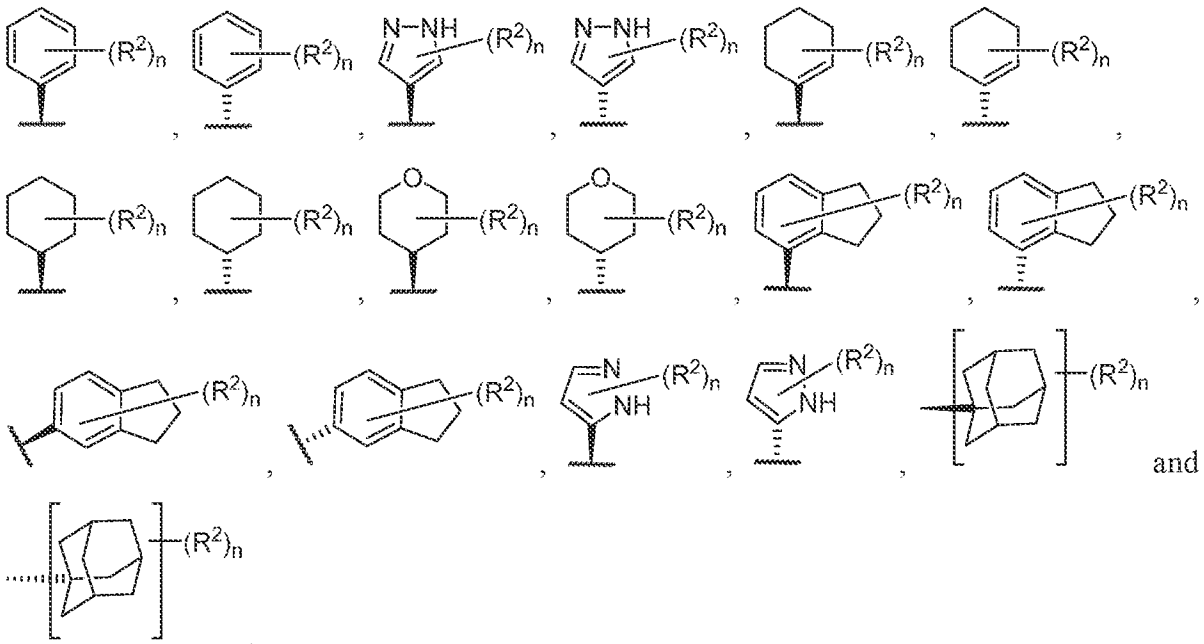
[0211] In some embodiments, Ring B is selected from phenyl, benzocyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, adamantyl, tetrahydropyranyl, dihydroindenyl (*e.g.*, 2,3-dihydro-1*H*-indenyl), dihydrobenzofuranyl, dihydroisobenzofuranyl, indolinyl, isoindolinyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and pyrazolyl.

[0212] In some embodiments, Ring B is selected from phenyl, benzocyclobutenyl, cyclohexyl, cyclohexenyl, adamantyl, tetrahydropyranyl, 2,3-dihydro-1*H*-indenyl, and pyrazolyl.

[0213] In some embodiments, Ring B is phenyl. In some embodiments, Ring B is pyrazolyl. In some embodiments, Ring B is adamantyl. In some embodiments, Ring B is 2,3-dihydro-1*H*-

indenyl. In some embodiments, Ring B is tetrahydrofuranyl. In some embodiments, Ring B is benzocyclobutenyl.

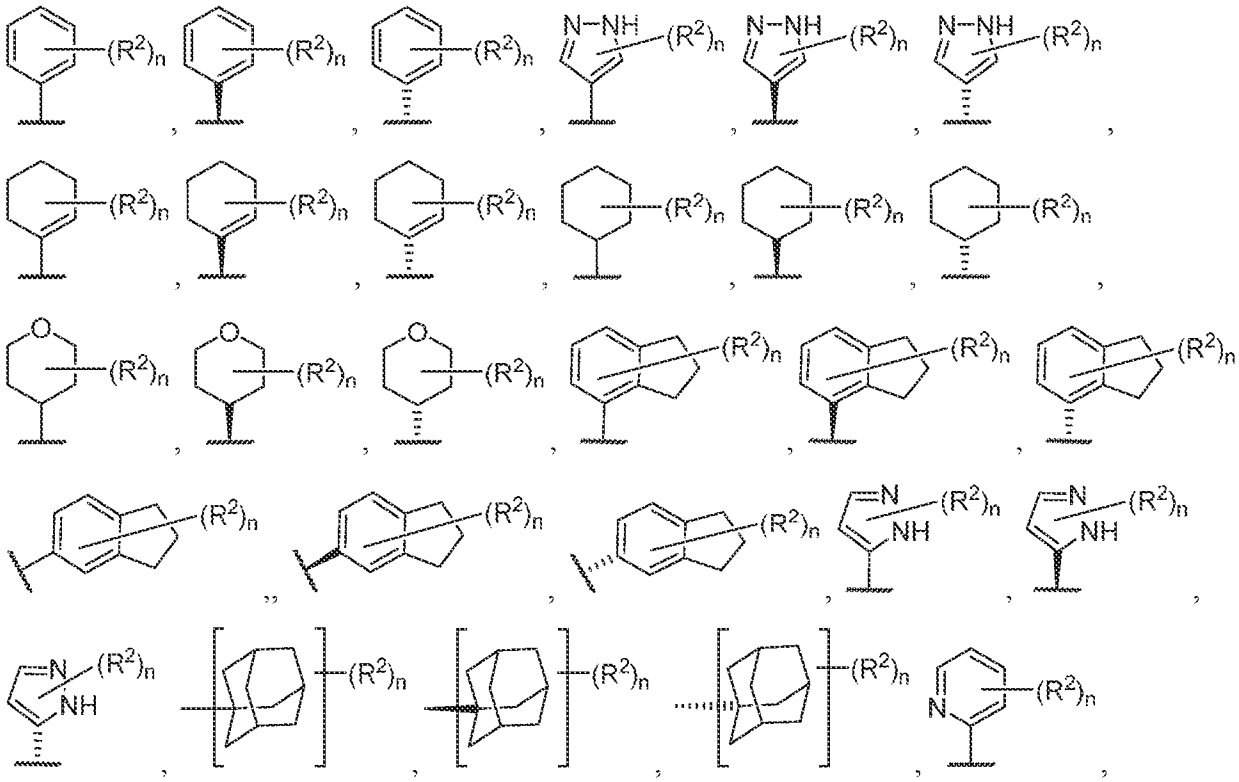
[0214] In some embodiments, Ring B together with its R^2 substituents is selected from

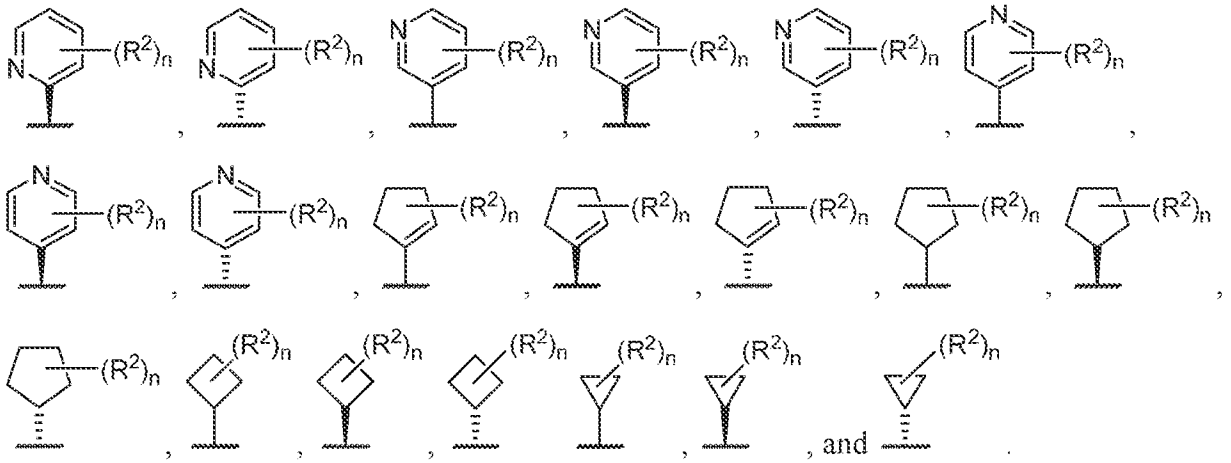


and

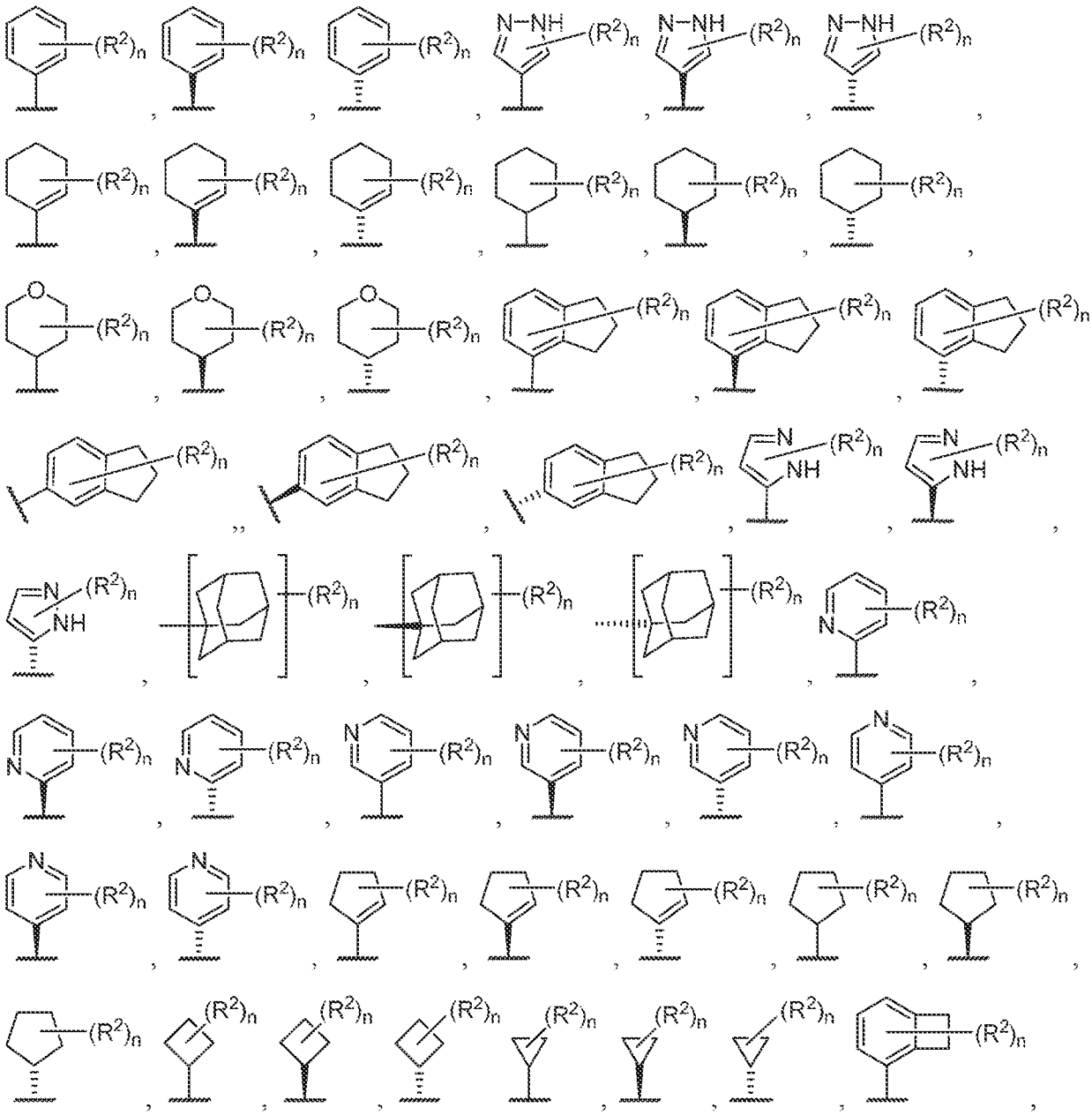
.

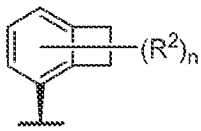
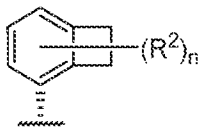
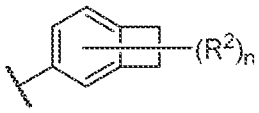
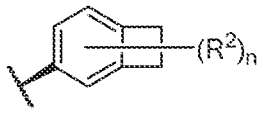
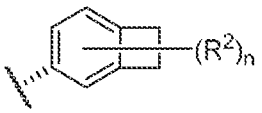
[0215] In some embodiments, Ring B together with its R^2 substituents is selected from

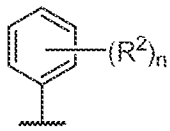
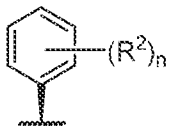
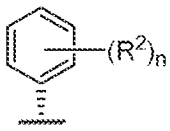
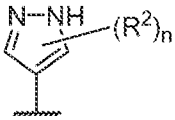
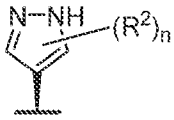
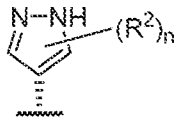
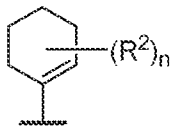


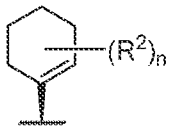
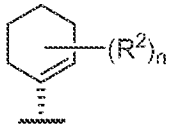
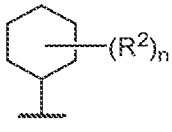
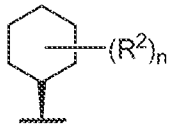


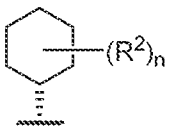
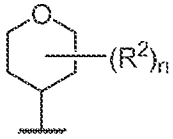
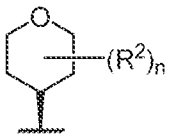
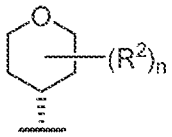
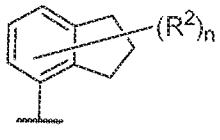
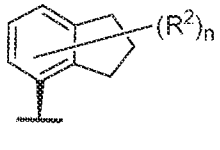
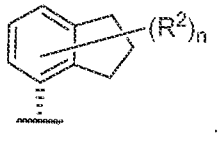
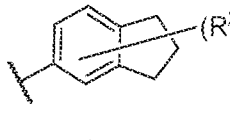
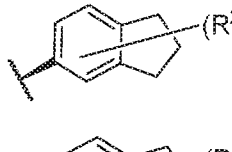
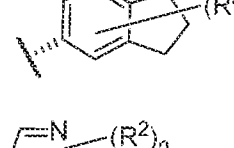
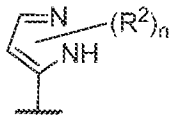
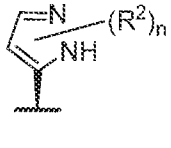
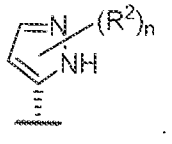
[0216] In some embodiments, Ring B together with its R^2 substituents is selected from

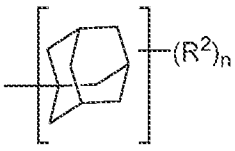
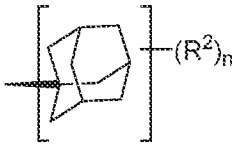
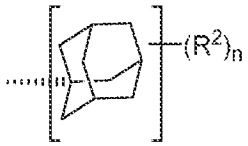
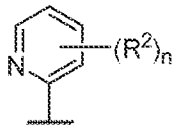
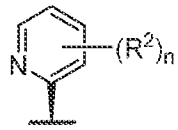
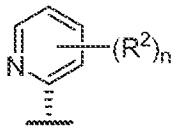
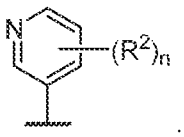
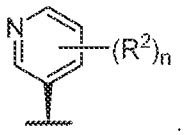
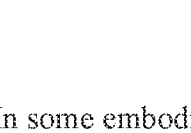
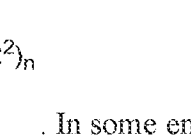
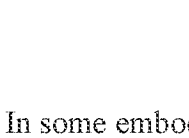
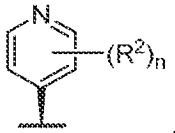
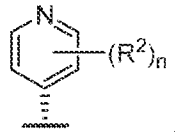
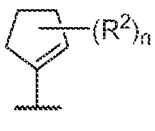


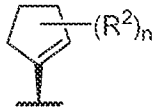
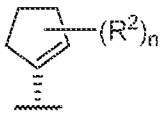
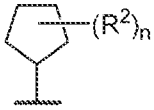
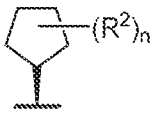
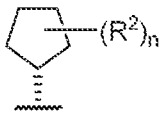
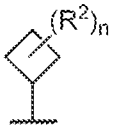
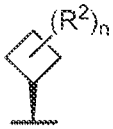
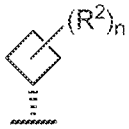
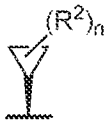
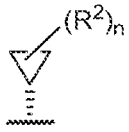
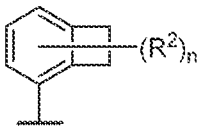
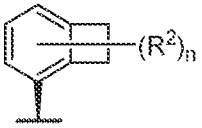
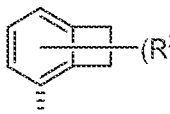




, and


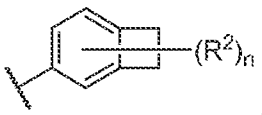
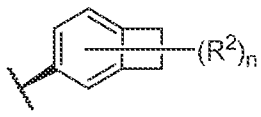
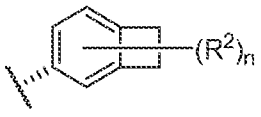
[0217] In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  .

In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  .

substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2

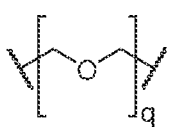
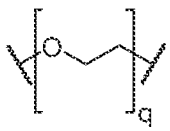
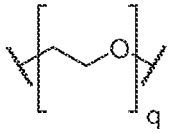
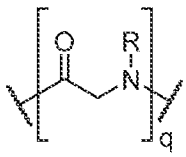
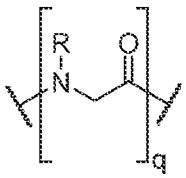
substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is . In some

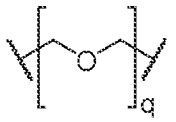
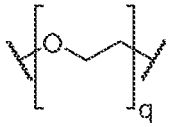
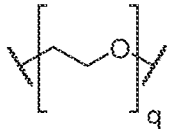
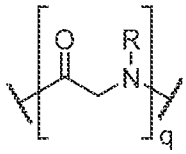
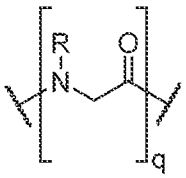
embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is . In some embodiments,

Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  . In some embodiments, Ring B together with its R^2 substituents is  .

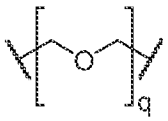
[0218] In some embodiments, Ring B is selected from the groups depicted in the compounds in **Table 1**.

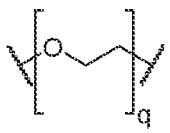
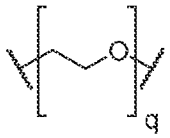
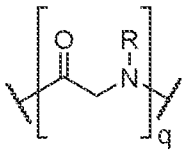
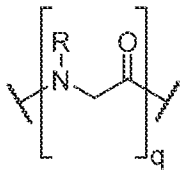
[0219] As defined generally above, L is a bivalent moiety that connects ERBM to LBM.

[0220] As defined generally above, L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, –$C(R)_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –$S(O)_2$–, –$NRS(O)_2$–, –$S(O)_2NR$–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,  ,  ,  , or  , wherein each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0221] In some embodiments, L is a covalent bond. In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, –$C(R)_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –$S(O)_2$–, –$NRS(O)_2$–, –$S(O)_2NR$–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,  ,  ,  , or  , wherein each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0222] In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 0, 1, 2 or 3 methylene units of L are independently replaced by –Cy–, –CH(R)–, –$C(R)_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –$S(O)_2$–, –

NRS(O)$_2$–, –S(O)$_2$NR–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,

 ,  ,  , or  .

[0223] In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 1, 2 or 3 methylene units of L are independently replaced by –Cy–, –CH(R)–, –C(R)$_2$–, –O– or–NR– .

[0224] In some embodiments, L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 1, 2 or 3 methylene units of L are independently replaced by –Cy– or–NR– .

[0225] In some embodiments, each –Cy– is independently an optionally substituted bivalent ring selected from a 4-7 membered saturated or partially unsaturated monocyclic carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated monocyclic heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered monocyclic saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1185-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0226] In some embodiments, each –Cy– is independently an optionally substituted bivalent ring selected from a 4-7 membered saturated or partially unsaturated monocyclic carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated monocyclic heterocyclylenyl containing 1-2 nitrogen atoms, a 5-11 membered monocyclic saturated or partially unsaturated spiro heterocyclylenyl containing 1-2 nitrogen atoms, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl containing

1-2 nitrogen atoms, and a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl containing 1-2 nitrogen atoms.

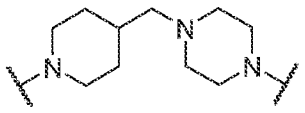
[0227] In some embodiments, the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from $–C_1–C_4$ alkyl, $–C_1–C_4$ haloalkyl, $–C_3–C_7$ cycloalkyl, $–O–C_1–C_4$ alkyl, halo, cyano, –OH, $–NH_2$, $–N(H)(C_1–C_4$ alkyl) and $–N(C_1–C_4$ alkyl$)_2$.

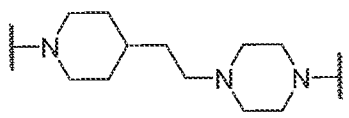
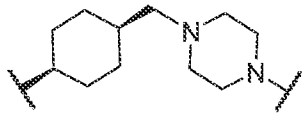
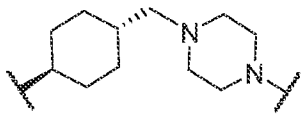
[0228] In some embodiments, the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from –Me, –Et, –Pr, –^{i}Pr, cyclopropyl, $–CF_3$, –OMe, –F, –Cl, –CN, $–NH_2$, –NHMe and $–NMe_2$.

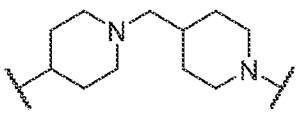
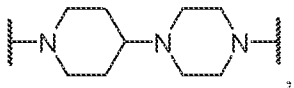
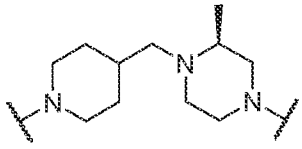
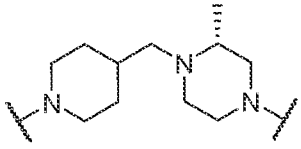
[0229] In some embodiments, the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from –Me, –OMe and –F.

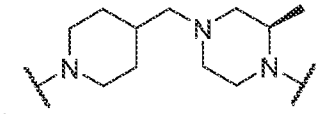
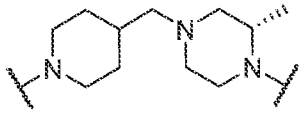
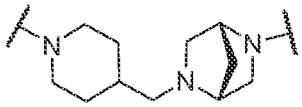
[0230] In some embodiments, the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 instances of –Me.

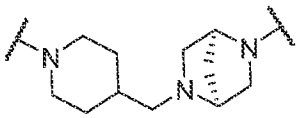
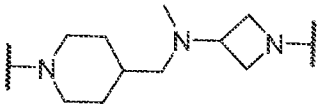
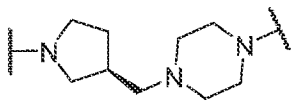
[0231] In some embodiments, the bivalent ring of each –Cy– is unsubstituted.

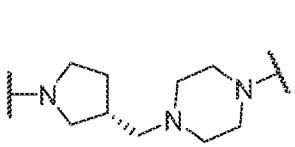
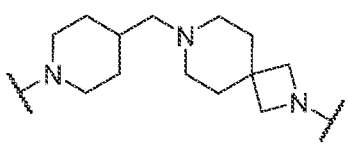
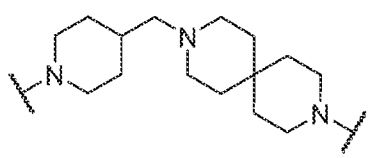
[0232] In some embodiments, L is selected from  ,

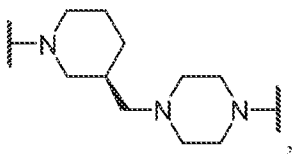
 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,
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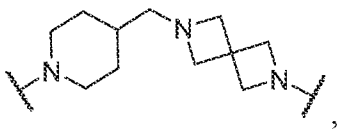
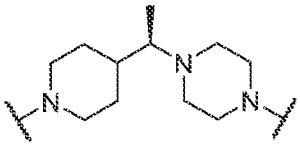
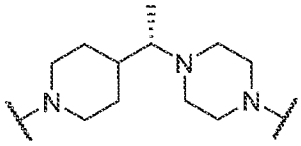
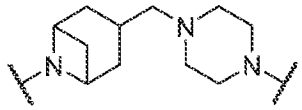
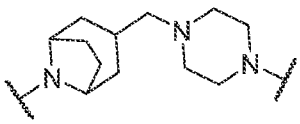
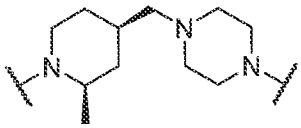
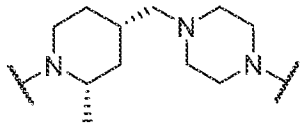
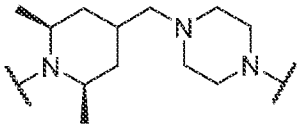
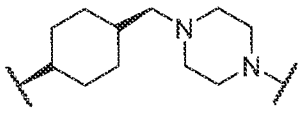
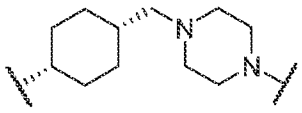
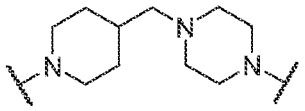
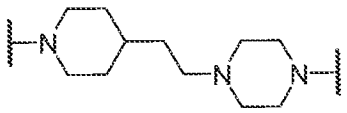
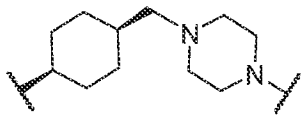
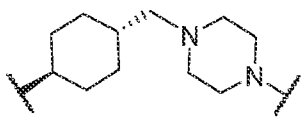
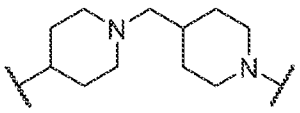
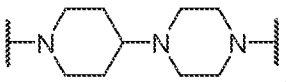
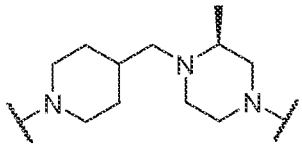
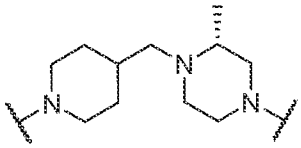
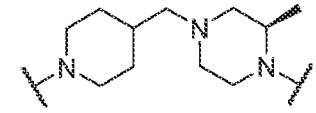
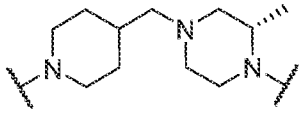
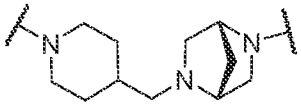
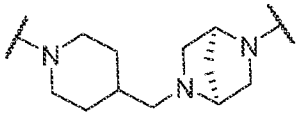
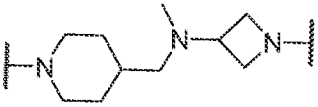
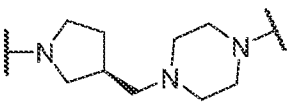
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 , and
 .

[0233] In some embodiments, L is selected from
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
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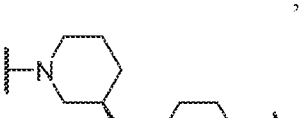
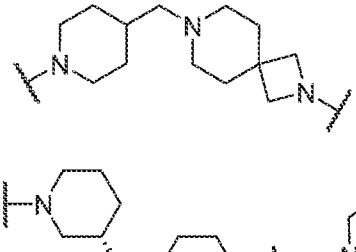
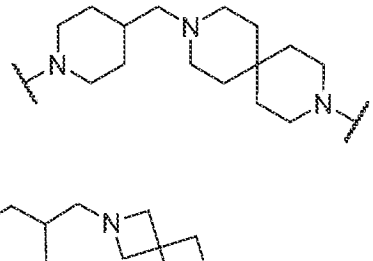
 ,
 ,
 ,
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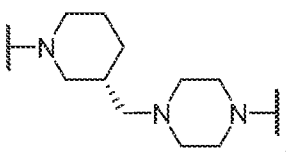
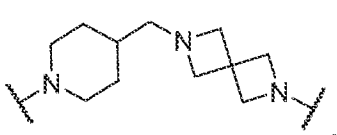
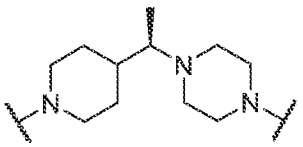
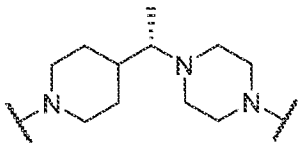
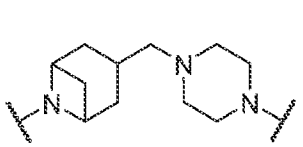
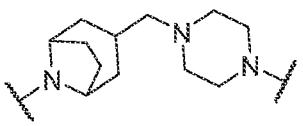
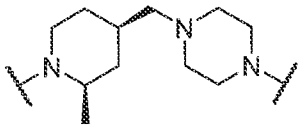
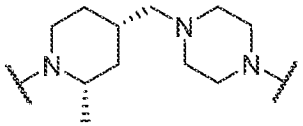
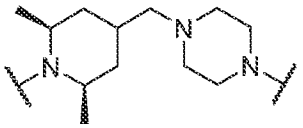
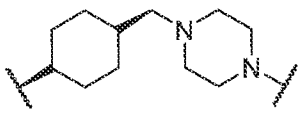
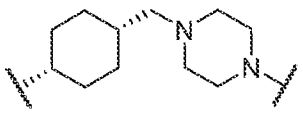
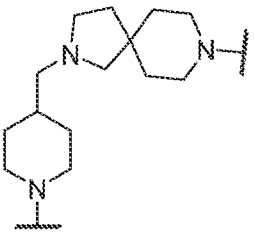
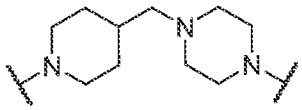
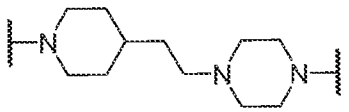
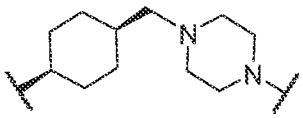
 ,
 .

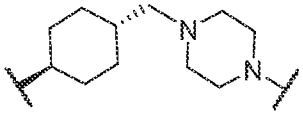
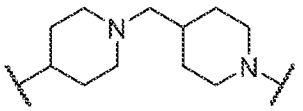
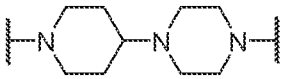
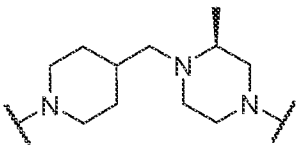
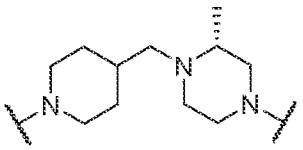
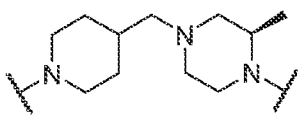
 ,  ,  ,

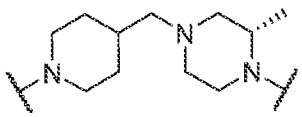
 ,  ,  ,

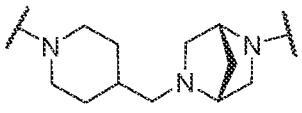
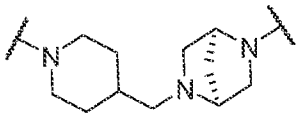
 ,  ,  , and

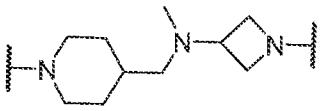
 .

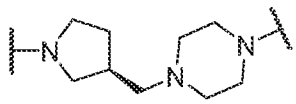
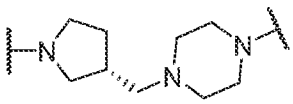
[0234] In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

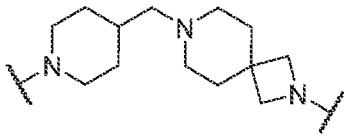
[0235] In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some

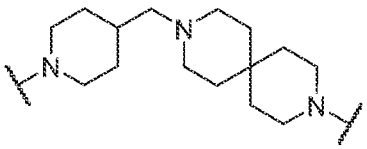
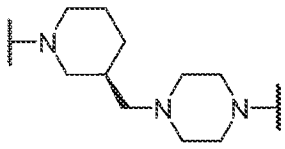
embodiments, L is  . In some embodiments, L is

 . In some embodiments, L is  . In some

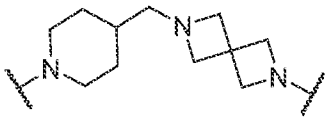
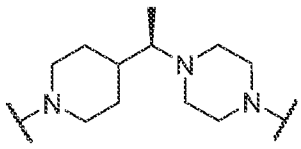
embodiments, L is  . In some embodiments, L is

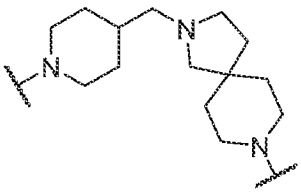
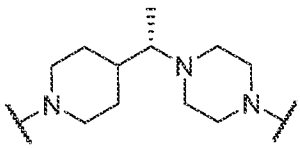
 . In some embodiments, L is  . In some

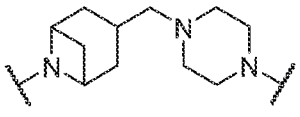
embodiments, L is  . In some embodiments, L is

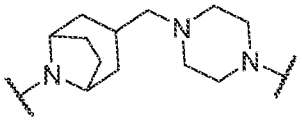
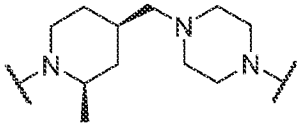
 . In some embodiments, L is  . In some

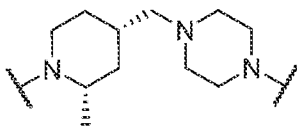
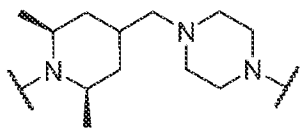
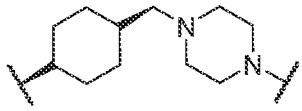
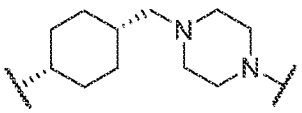
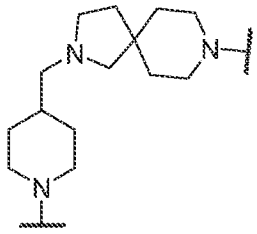
embodiments, L is . In some embodiments, L is

 . In some embodiments, L is  . In some

embodiments, L is  . In some embodiments, L is 

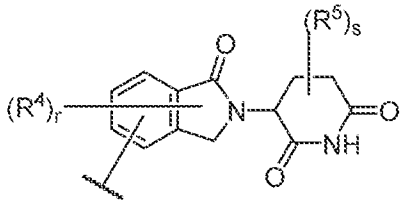
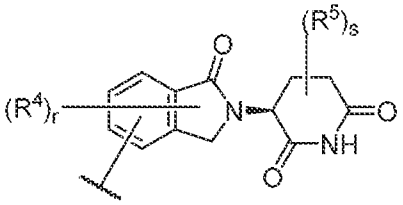
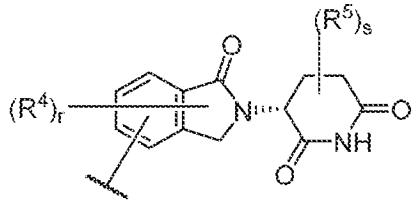
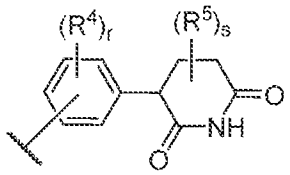
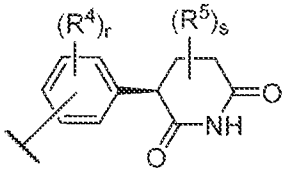
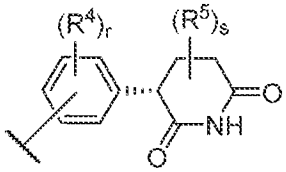
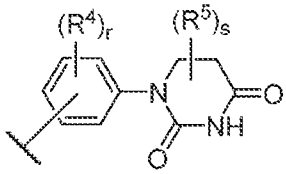
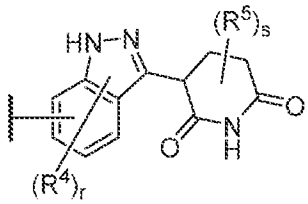
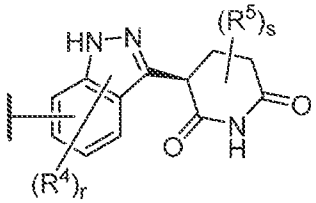
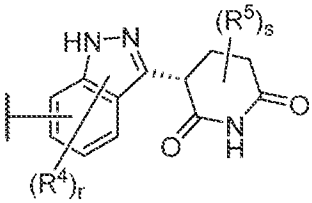
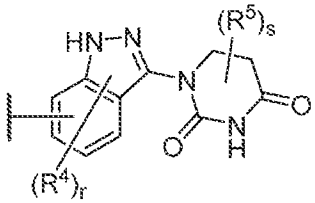
. In some embodiments, L is  . In some embodiments, L is

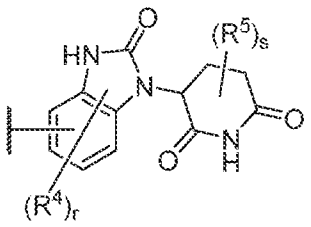
 . In some embodiments, L is  . In some

embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

[0236] In some embodiments, L is selected from the groups depicted in the compounds in **Table 1**.

[0237] As defined generally above, LBM is a ligase binding moiety.

[0238] As defined generally above, LBM is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,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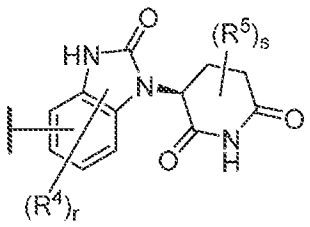
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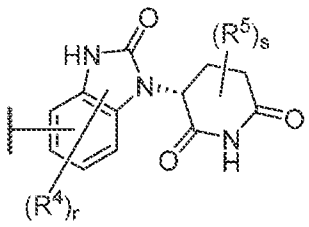
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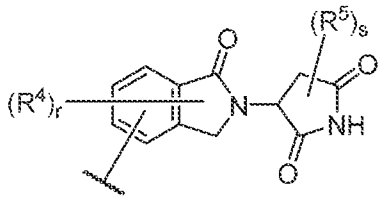
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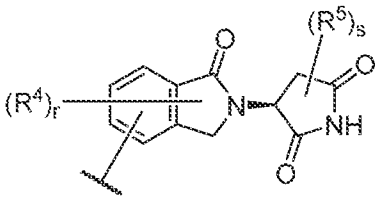
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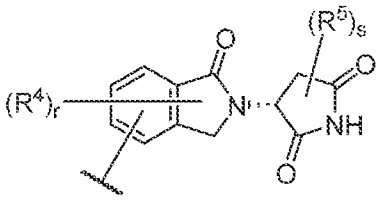
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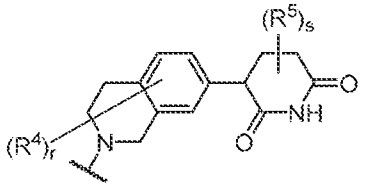
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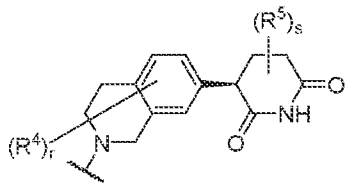
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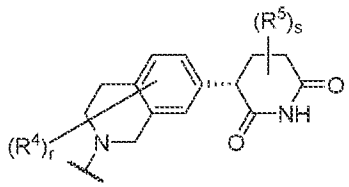
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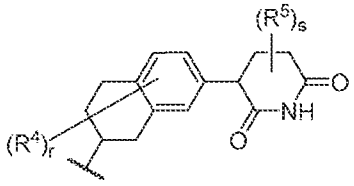
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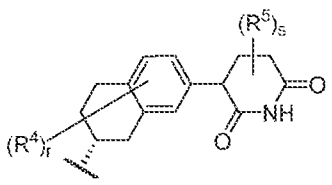
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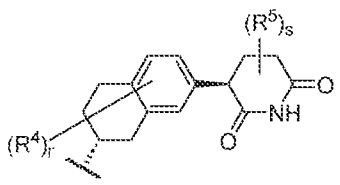
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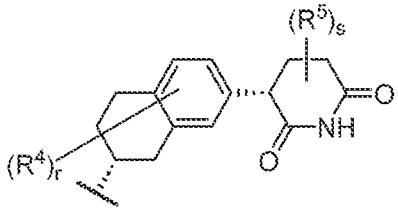
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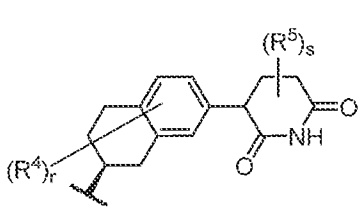
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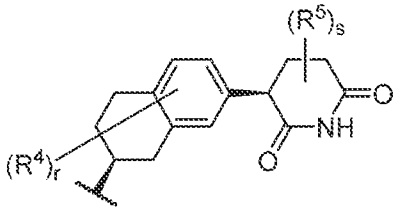
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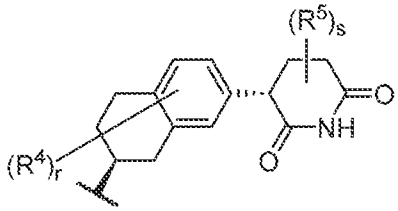
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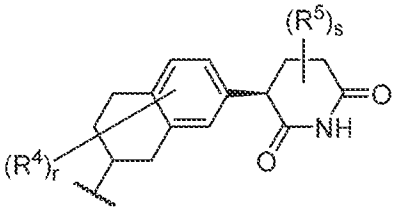
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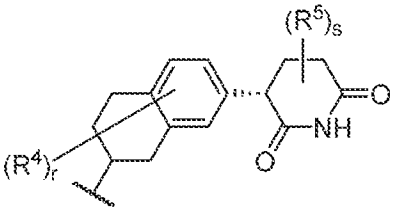
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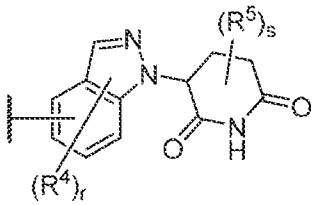
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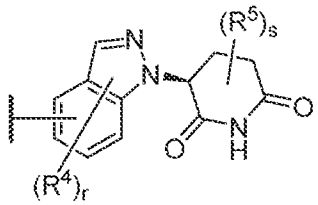
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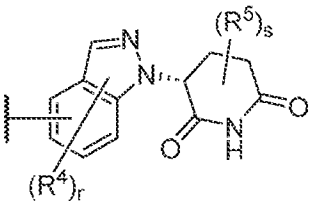
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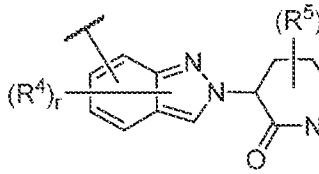
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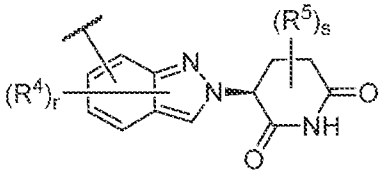
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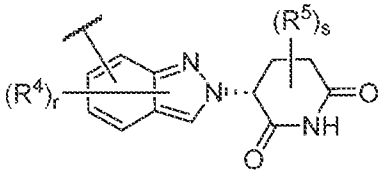
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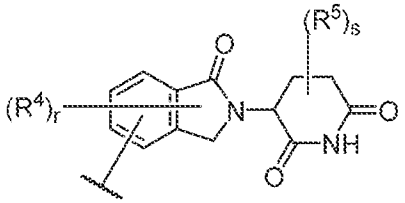
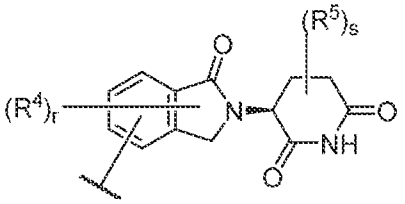
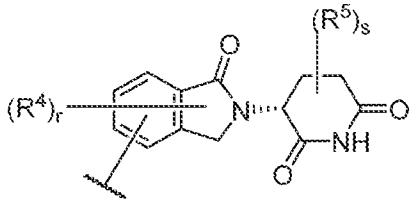
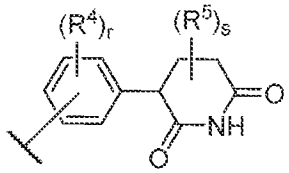
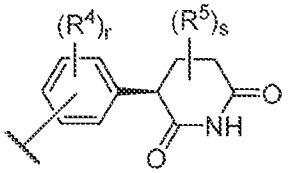
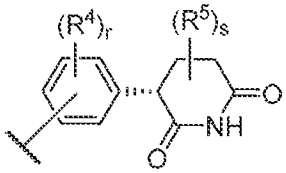
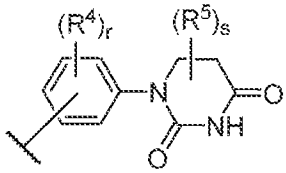
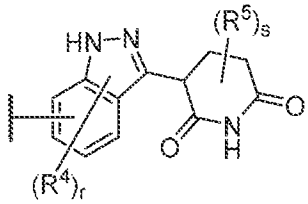
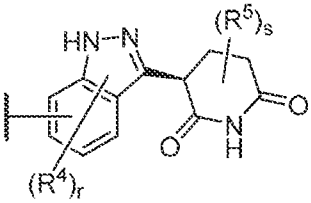
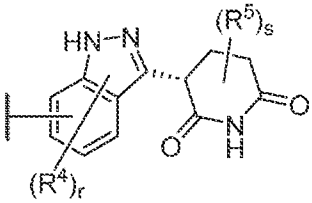
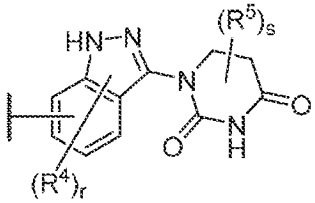
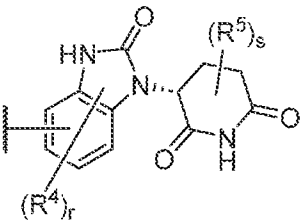
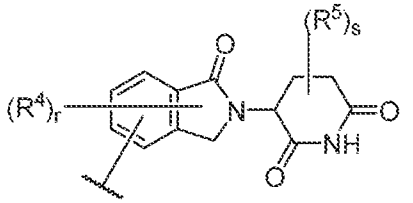
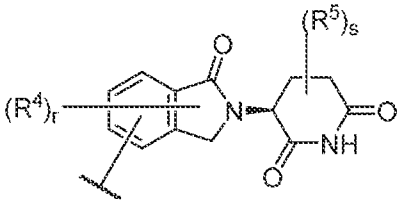


[0239] In some embodiments, LBM is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , and  .



[0240] In some embodiments, LBM is selected from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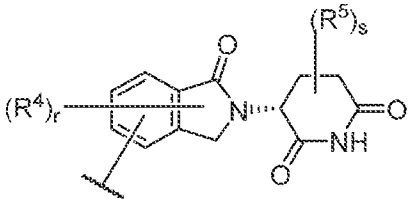
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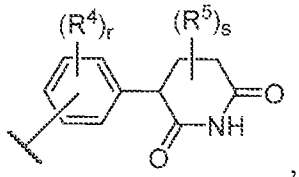
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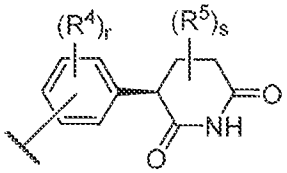
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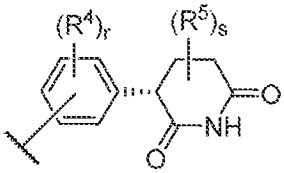
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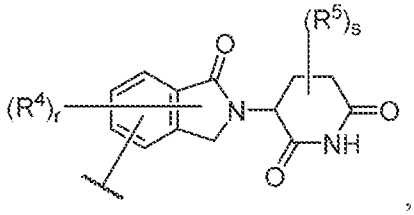
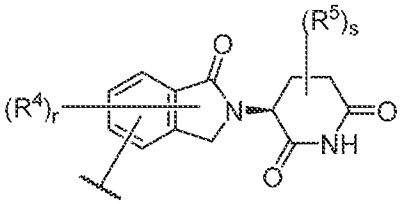


[0241] In some embodiments, LBM is selected from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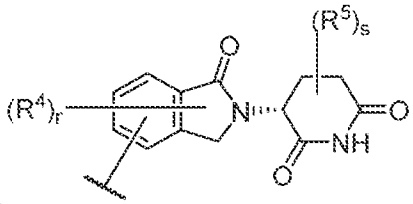
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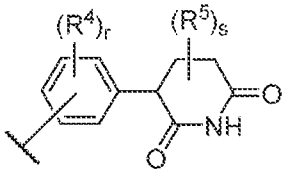
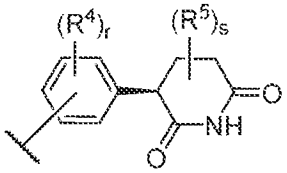


[0242] In some embodiments, LBM is selected from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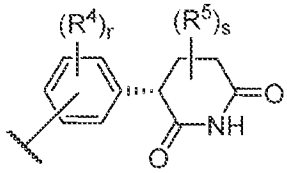
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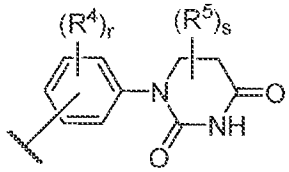
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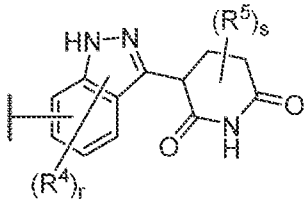
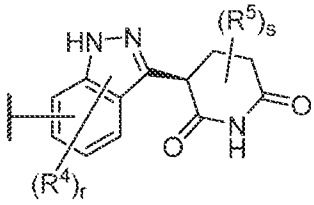


[0243] In some embodiments, LBM is selected from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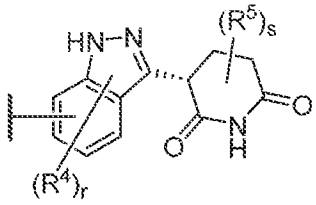
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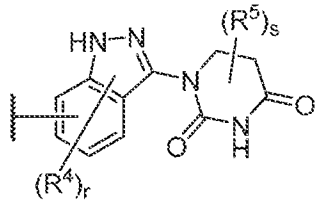
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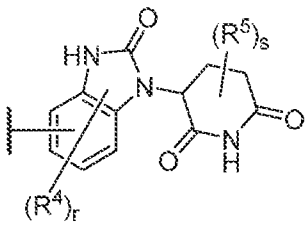
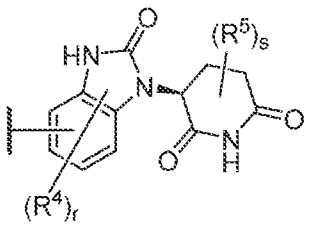


[0244] In some embodiments, LBM is selected from,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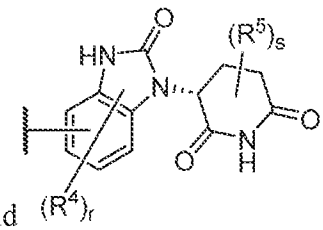
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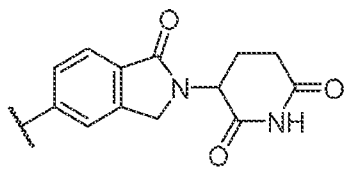
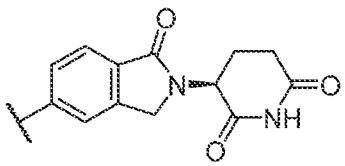


[0245] In some embodiments, LBM is selected from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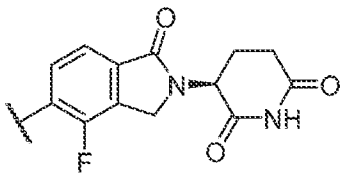
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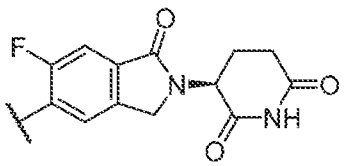
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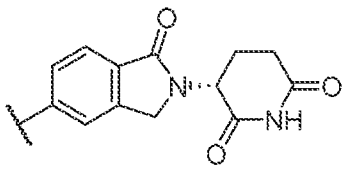
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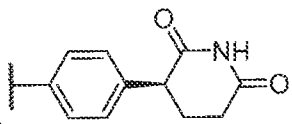
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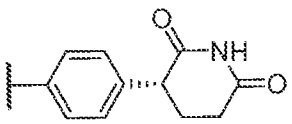
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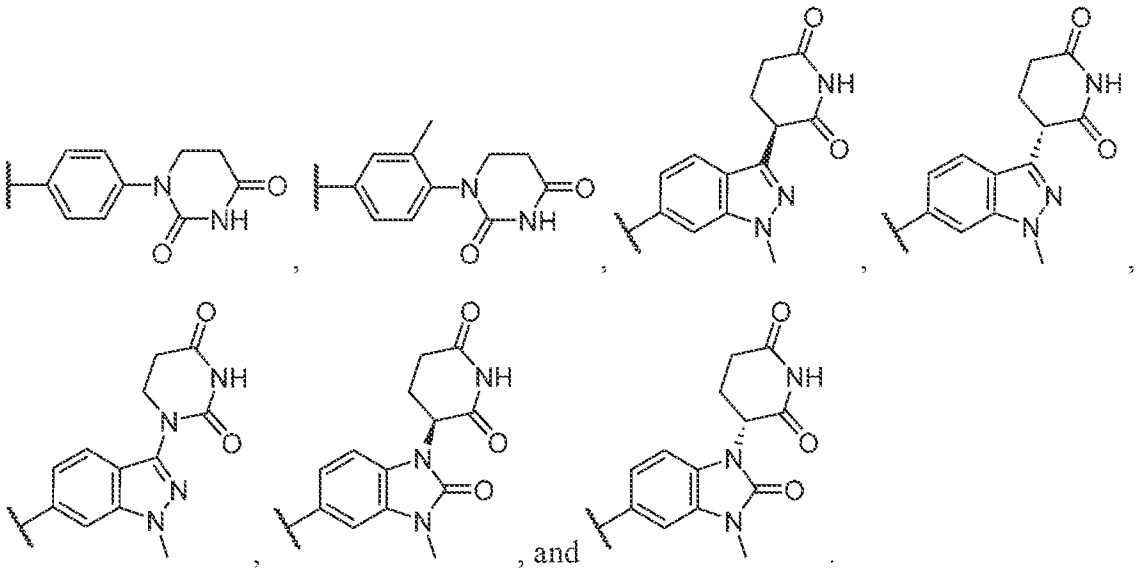
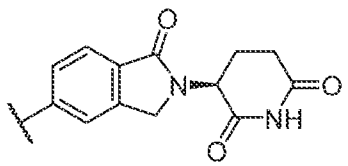
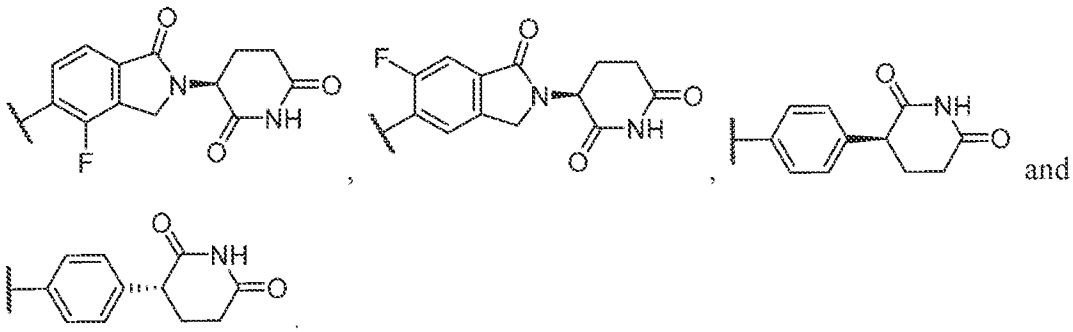
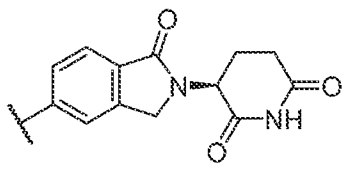
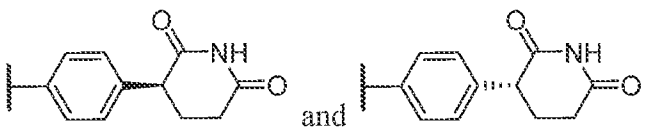
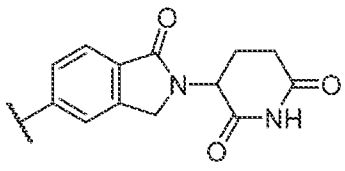
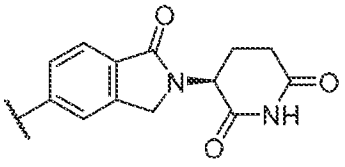
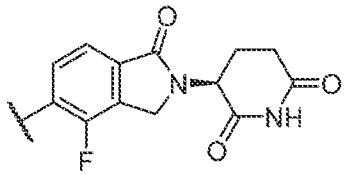
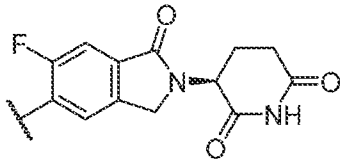
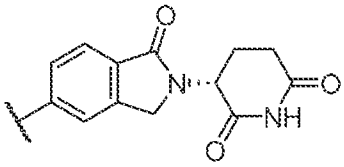
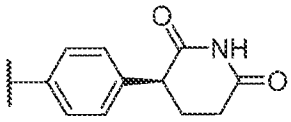
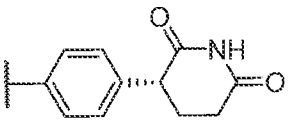
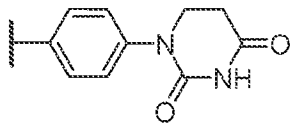
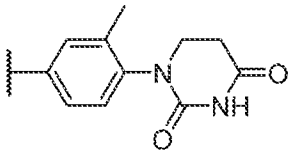
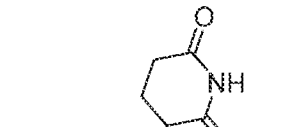


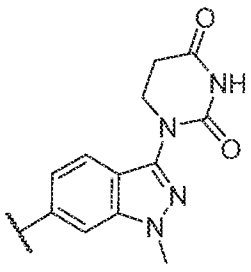
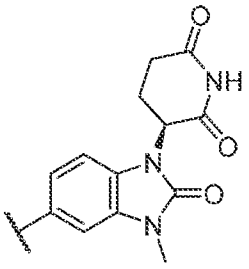
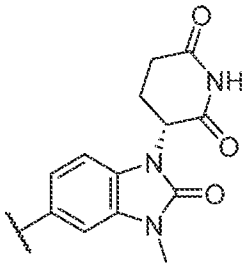
[0246] In some embodiments, LBM is selected from  ,



[0247] In some embodiments, LBM is selected from  ,



[0248] In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  .

In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  .

[0249] In some embodiments, LBM is selected from the groups depicted in the compounds in **Table 1**.

[0250] As defined generally above, m is 0, 1, 2, 3, or 4. In some embodiments, m is 0, 1, 2 or 3. In some embodiments, m is 0, 1 or 2. In some embodiments, m is 0 or 1. In some embodiments m is 0. In some embodiments m is 1. In some embodiments m is 2. In some embodiments m is 3. In some embodiments m is 4.

[0251] In some embodiments, m is selected from the groups depicted in the compounds in **Table 1**.

[0252] As defined generally above, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0, 1, 2 or 3. In some embodiments, n is 0, 1 or 2. In some embodiments, n is 0 or 1.

[0253] In some embodiments n is 0. In some embodiments n is 1. In some embodiments n is 2. In some embodiments n is 3. In some embodiments n is 4.

[0254] In some embodiments, n is selected from the groups depicted in the compounds in **Table 1**.

[0255] As defined generally above, p is 0, 1, 2, 3, or 4. In some embodiments, p is 0, 1, 2 or 3. In some embodiments, p is 0, 1 or 2. In some embodiments, p is 0 or 1.

[0256] In some embodiments p is 0. In some embodiments p is 1. In some embodiments p is 2. In some embodiments p is 3. In some embodiments p is 4.

[0257] Of note, when the number of R3 groups is designated as "p-1" or "p-2", solely positive integers are contemplated (i.e., "p-1" can be 0, 1, 2 or 3 and "p-2" can be 0, 1 or 2).

[0258] In some embodiments, p is selected from the groups depicted in the compounds in **Table 1**.

[0259] As defined generally above, each of q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[0260] In some embodiments q is 1. In some embodiments q is 2. In some embodiments q is 3. In some embodiments q is 4. In some embodiments q is 5. In some embodiments q is 6. In some embodiments q is 7. In some embodiments q is 8. In some embodiments q is 9. In some embodiments q is 10.

[0261] In some embodiments, q is selected from the groups depicted in the compounds in **Table 1**.

[0262] As defined generally above, r is 0, 1, 2, 3, or 4. In some embodiments, r is 0, 1, 2 or 3. In some embodiments, r is 0, 1 or 2. In some embodiments, r is 0 or 1.

[0263] In some embodiments r is 0. In some embodiments r is 1. In some embodiments r is 2. In some embodiments r is 3. In some embodiments r is 4.

[0264] In some embodiments, r is selected from the groups depicted in the compounds in **Table 1**.

[0265] As defined generally above, s is 0, 1, 2, 3, or 4. In some embodiments, s is 0, 1, 2 or 3. In some embodiments, s is 0, 1 or 2. In some embodiments, s is 0 or 1.

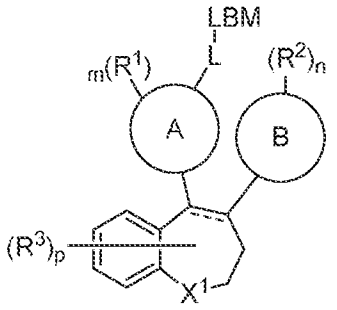
[0266] In some embodiments s is 0. In some embodiments s is 1. In some embodiments s is 2. In some embodiments s is 3. In some embodiments s is 4.

[0267] In some embodiments, s is selected from the groups depicted in the compounds in **Table 1**.

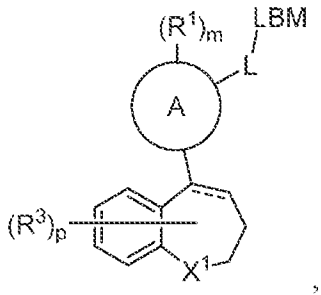
[0268] As defined generally above, X^1 and X^2 cannot both be heteroatoms simultaneously.

[0269] In some embodiments, X^1 and X^2 are selected from the group combinations depicted in the compounds in **Table 1**.

[0270] In certain embodiments, the present invention provides a compound of formula **II-1** or **II-2**



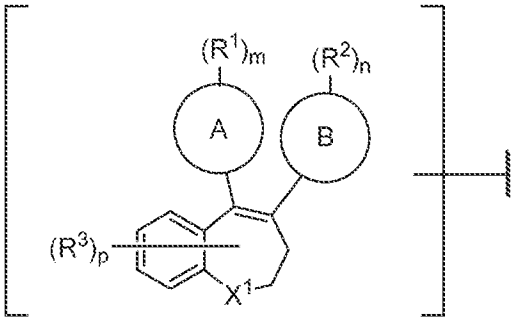
II-1

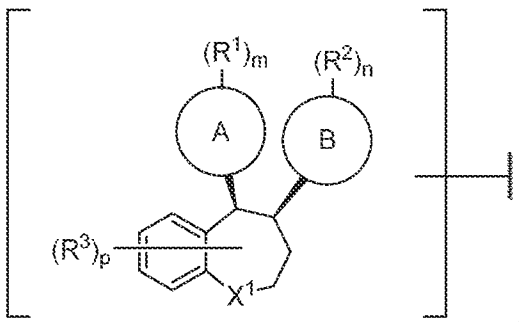


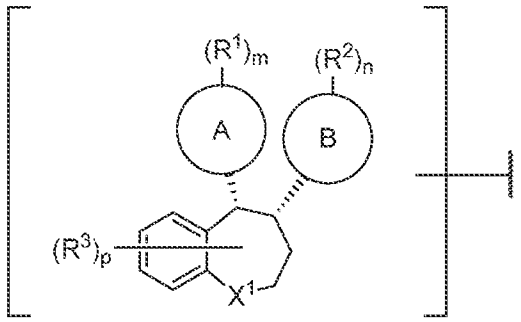
II-2

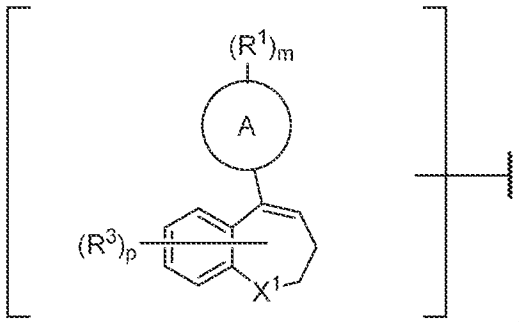
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

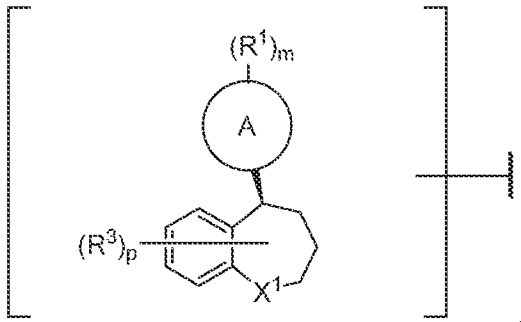
[0271] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is 

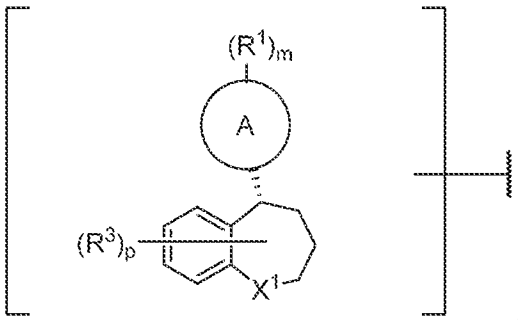




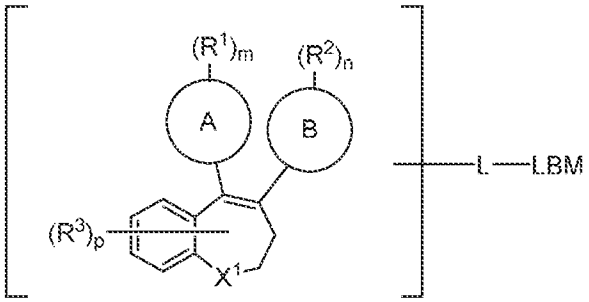




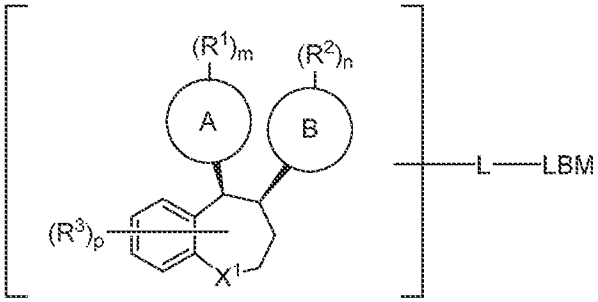
, or



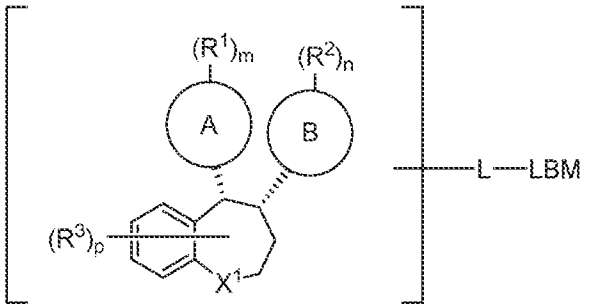
, thereby forming a compound of one of formulas **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, or **II-f**, respectively:



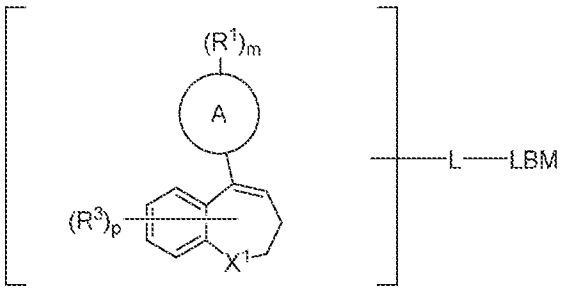
II-a



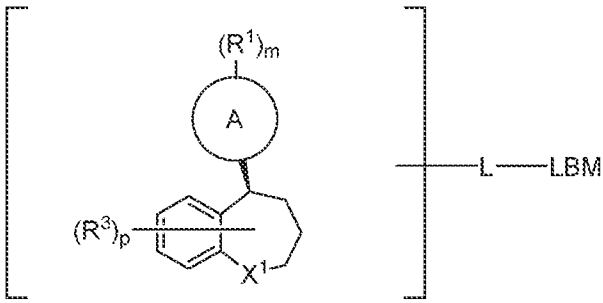
II-b



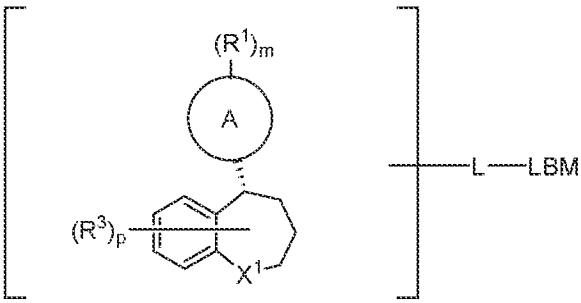
II-c



II-d



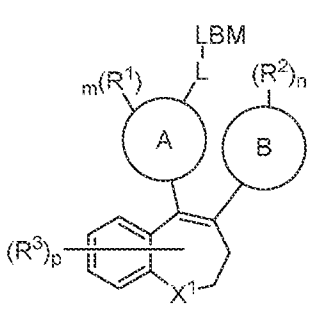
II-e



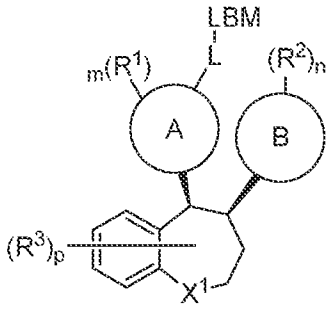
II-f

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

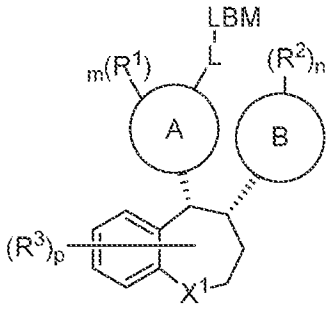
[0272] In some embodiments, the invention provides a compound of one of formulas **II-a-1**, **II-b-1**, **II-c-1**, **II-d-1**, **II-e-1**, or **II-f-1**:



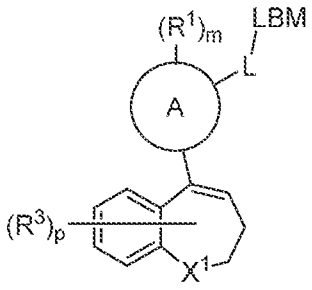
I-a-1



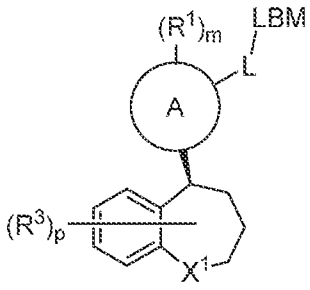
I-b-1



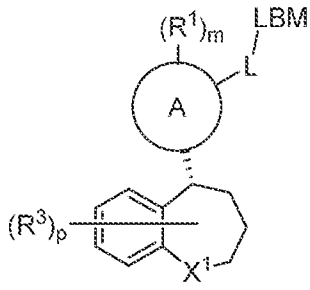
I-c-1



I-d-1



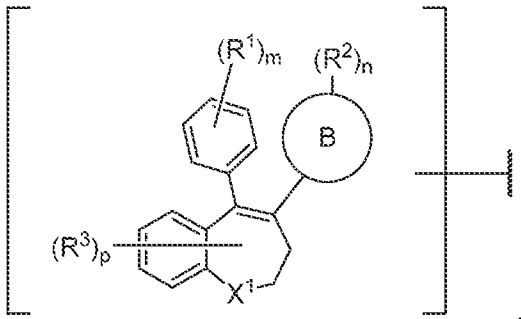
I-e-1

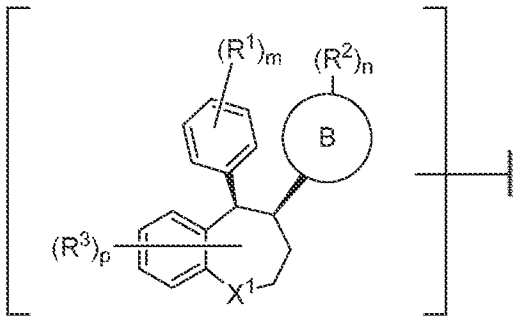
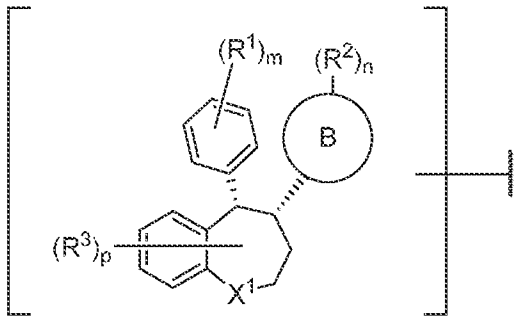


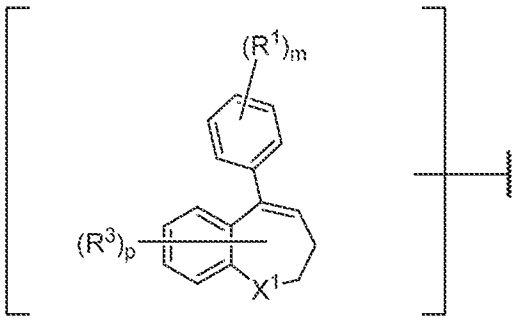
I-f-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0273] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

 ,  ,



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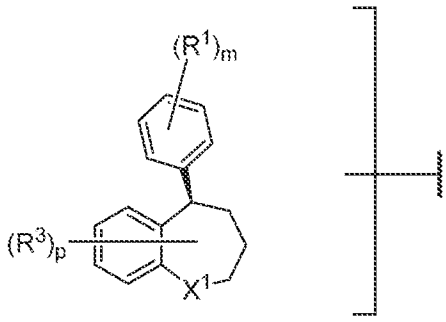
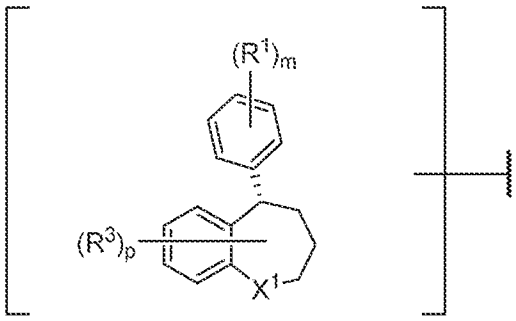
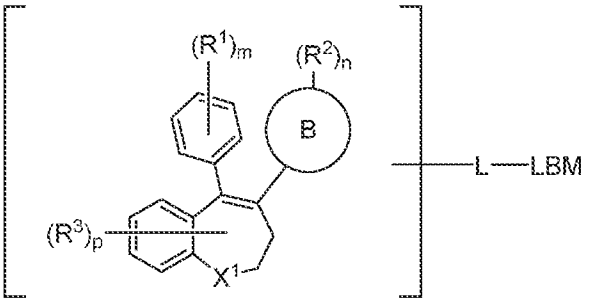


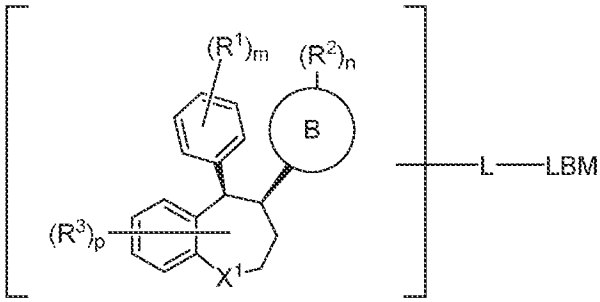
, or



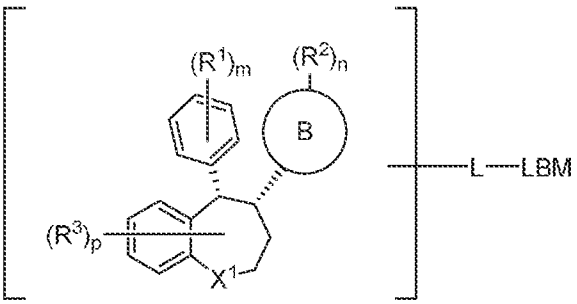
, thereby forming a compound of one of formulas **II-g**, **II-h**, **II-i**, **II-j**, **II-k**, or **II-l**, respectively:



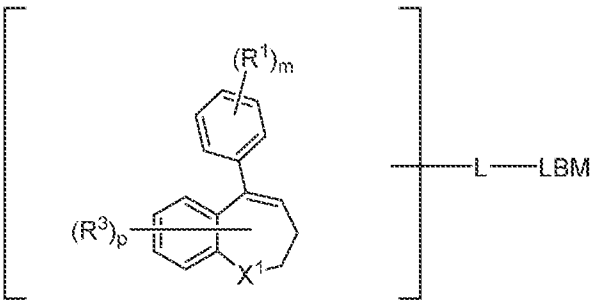
II-g



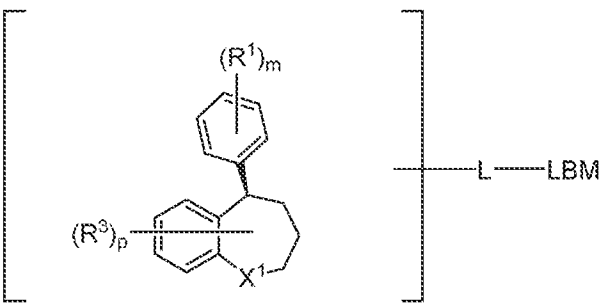
II-h

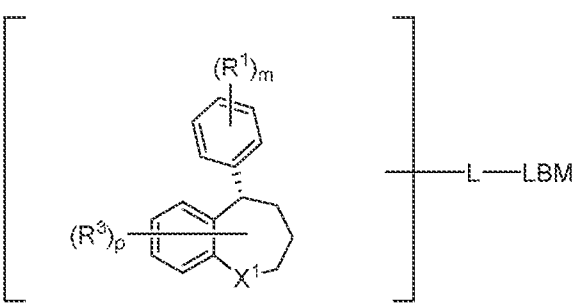


II-i



II-j

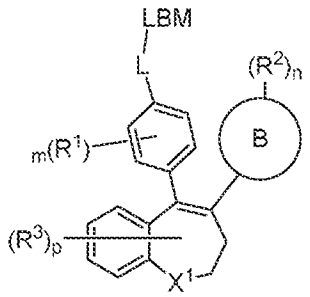




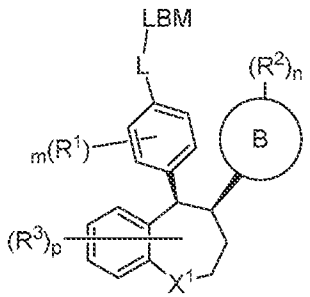
II-k **II-l**

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

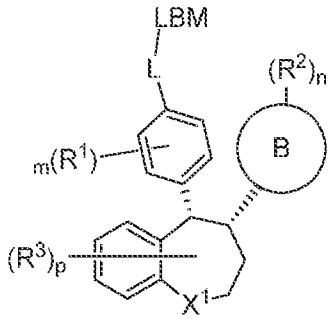
[0274] In some embodiments, the invention provides a compound of one of formulas **II-g-1**, **II-h-1**, **II-i-1**, **II-j-1**, **II-k-1**, or **II-l-1**:



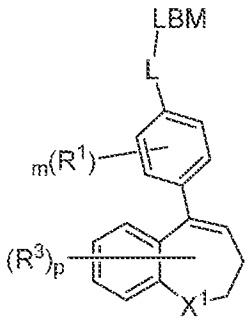
II-g-1



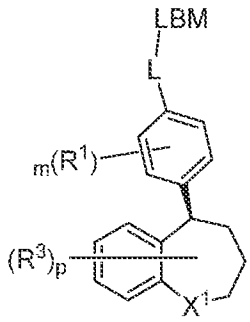
II-h-1



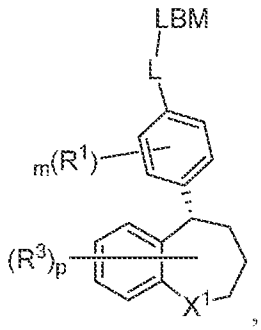
II-i-1



II-j-1



II-k-1



II-l-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0275] In some embodiments, the compound is a compound of formula **II-g-1**, or a pharmaceutically acceptable salt thereof.

[0276] In some embodiments, the compound is a compound of formula **II-h-1**, or a pharmaceutically acceptable salt thereof.

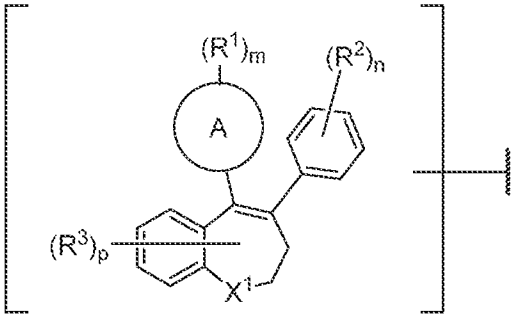
[0277] In some embodiments, the compound is a compound of formula **II-i-1**, or a pharmaceutically acceptable salt thereof.

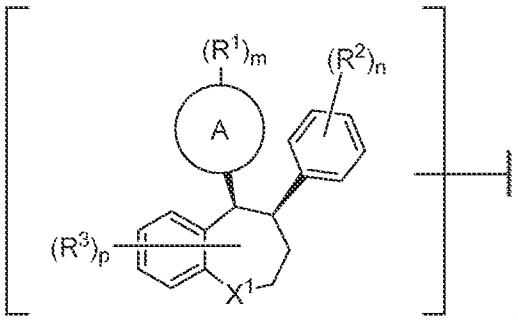
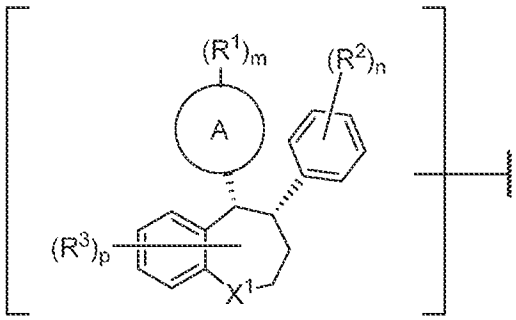
[0278] In some embodiments, the compound is a compound of formula **II-j-1**, or a pharmaceutically acceptable salt thereof.

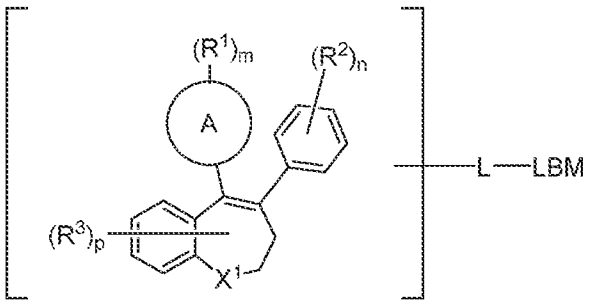
[0279] In some embodiments, the compound is a compound of formula **II-k-1**, or a pharmaceutically acceptable salt thereof.

[0280] In some embodiments, the compound is a compound of formula **II-l-1**, or a pharmaceutically acceptable salt thereof.

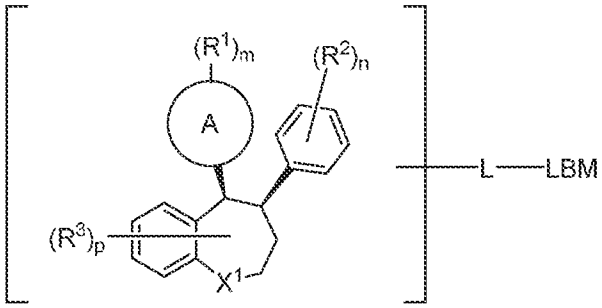
[0281] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

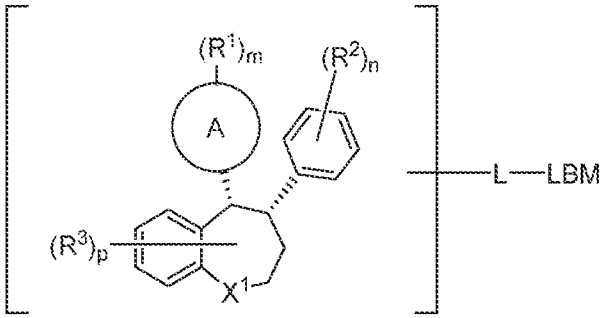
 , or  , thereby forming a compound of one of formulas **II-m**, **II-n**, or **II-o**, respectively:



II-m



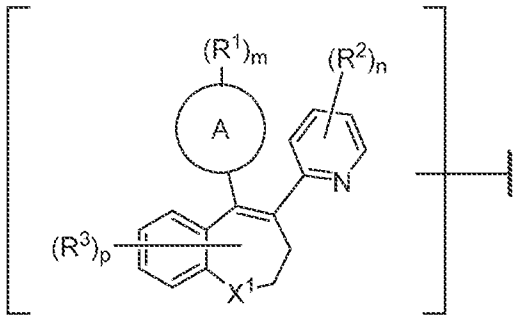
II-n

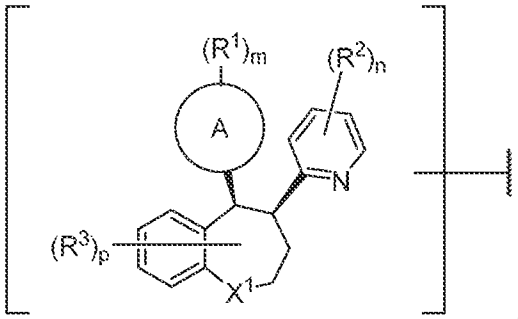
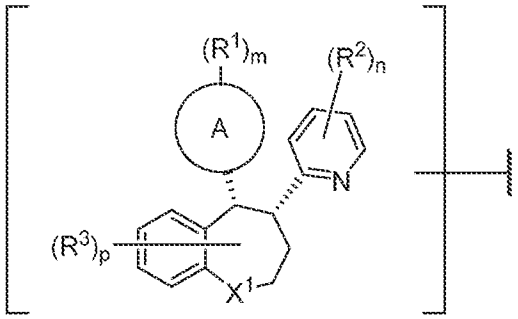


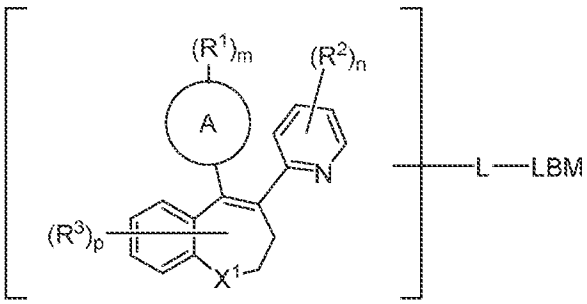
II-o

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

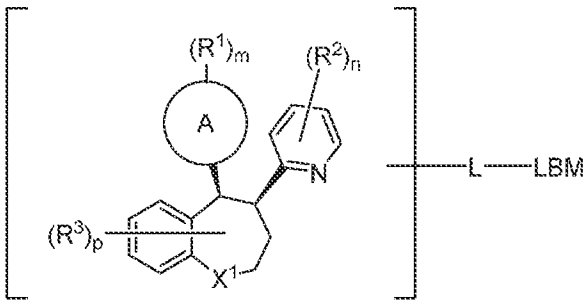
[0282] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

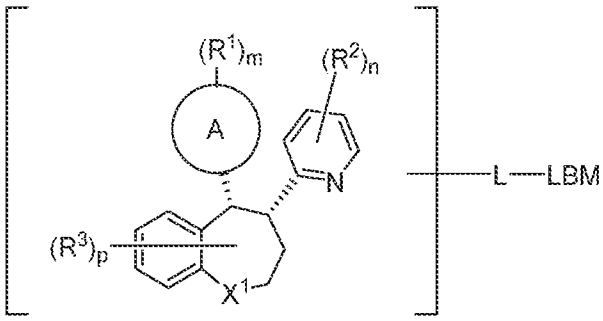
 , or  , thereby forming a compound of one of formulas **II-p**, **II-q**, or **II-r**, respectively:



II-p



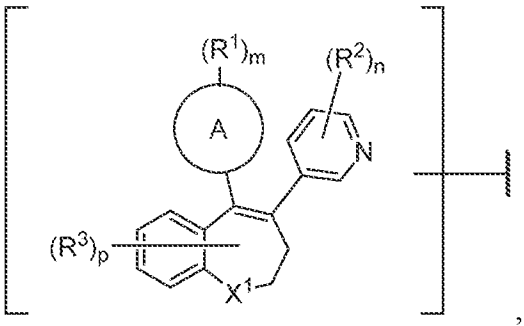
II-q

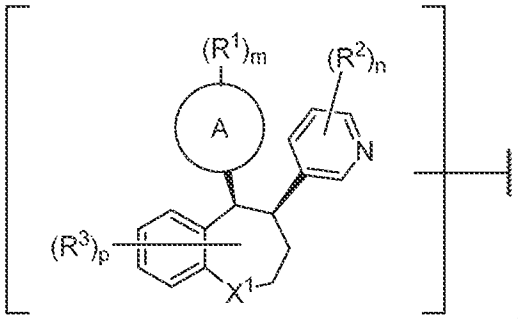
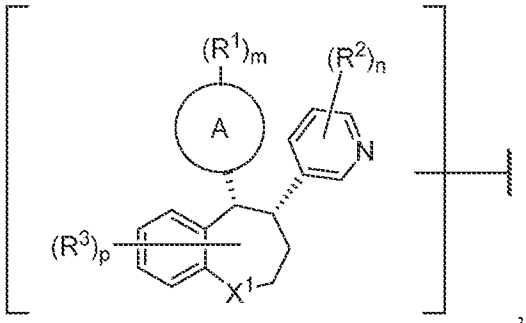


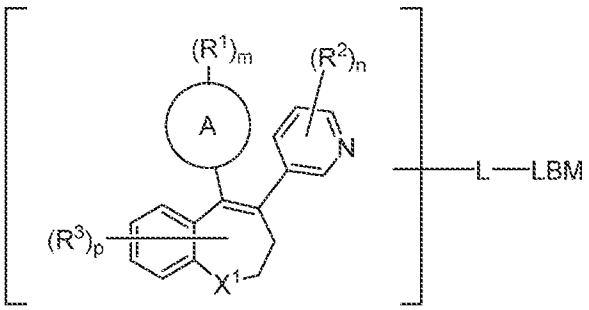
II-r

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

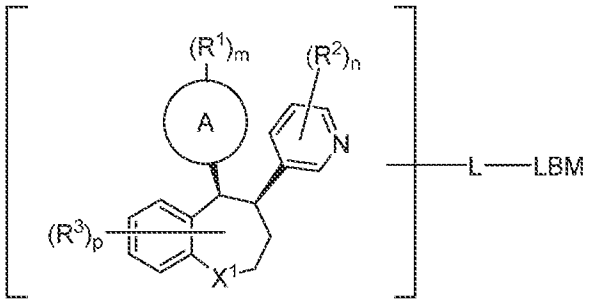
[0283] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

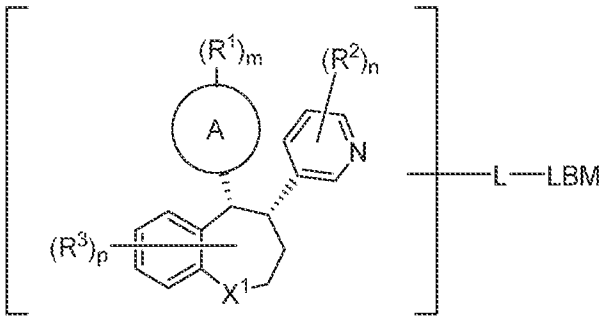
 , or  , thereby forming a compound of one of formulas **II-s**, **II-t**, or **II-u**, respectively:



II-s



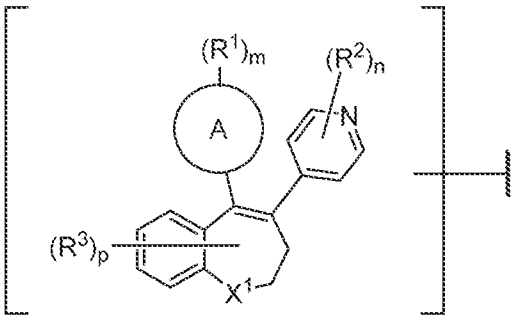
II-t

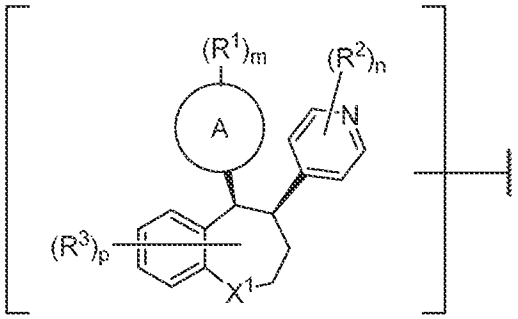
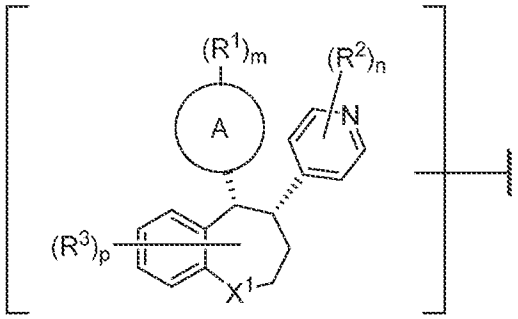


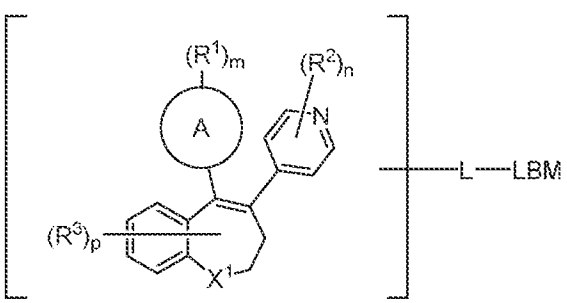
II-u

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

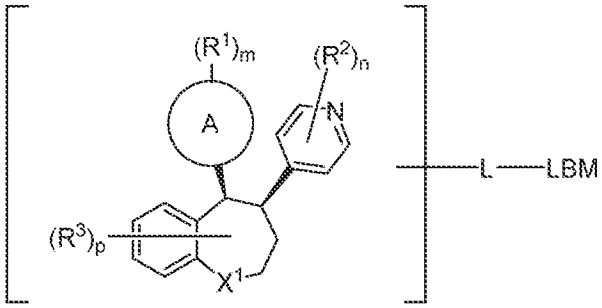
[0284] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

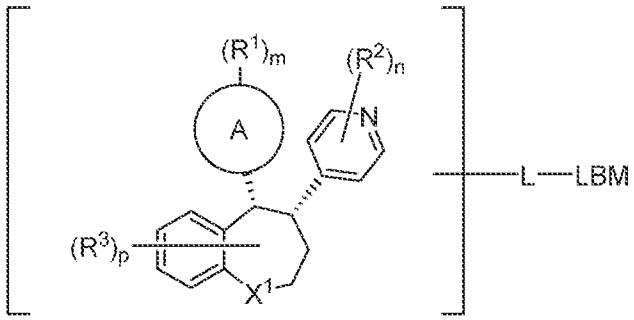
 , or  , thereby forming a compound of one of formulas **II-v**, **II-w**, or **II-x**, respectively:



II-v



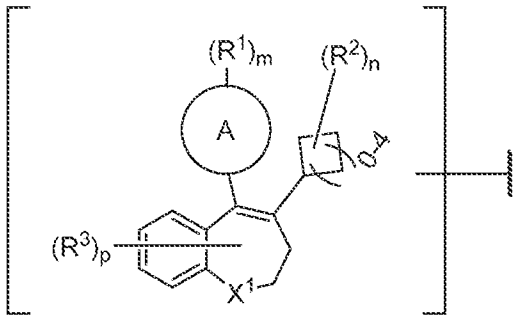
II-w

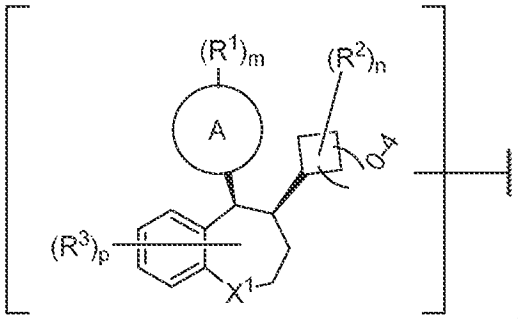
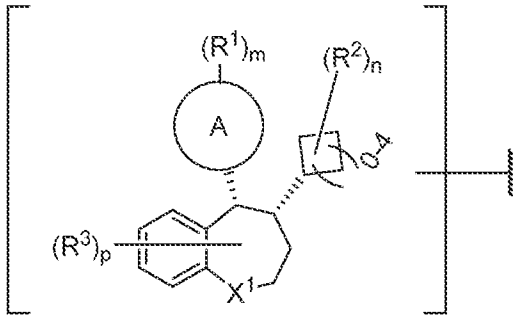


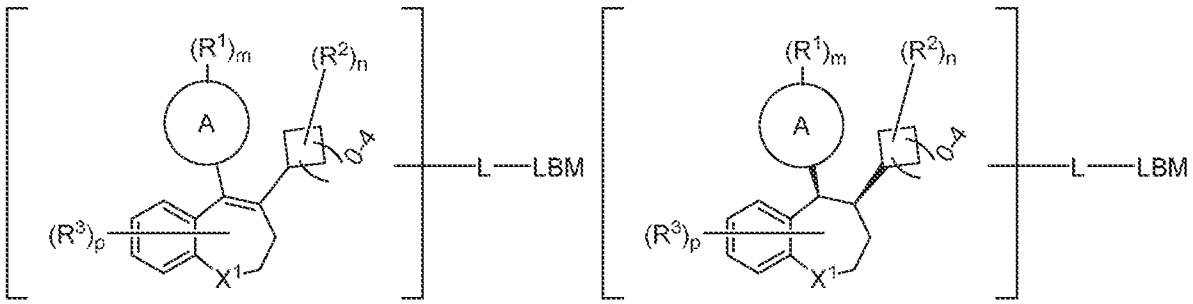
II-x

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

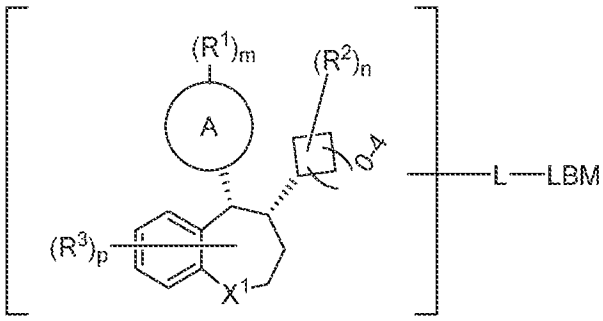
[0285] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

 , or  , thereby forming a compound of one of formulas **II-y**, **II-z**, or **II-aa**, respectively:



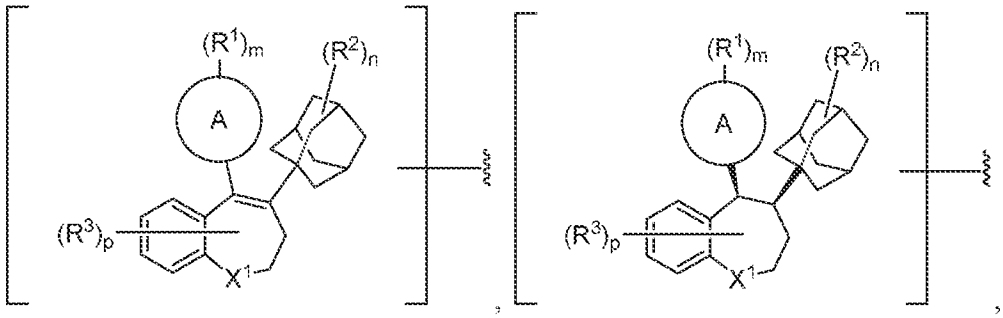
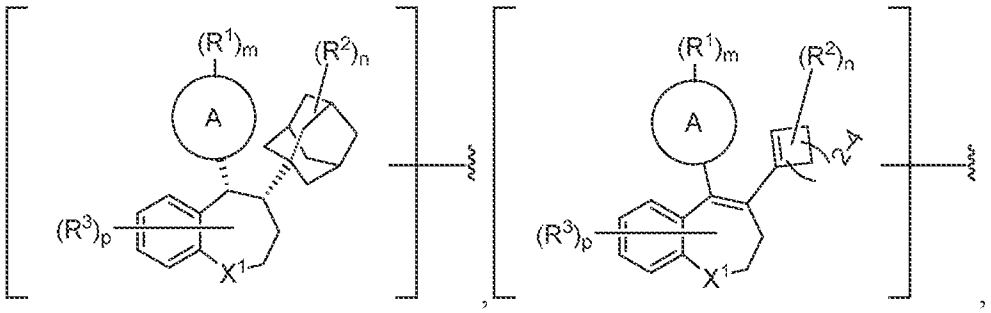
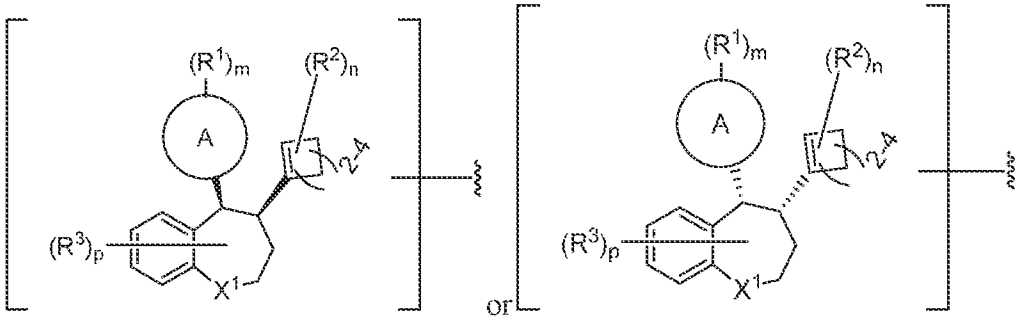
II-y **II-z**

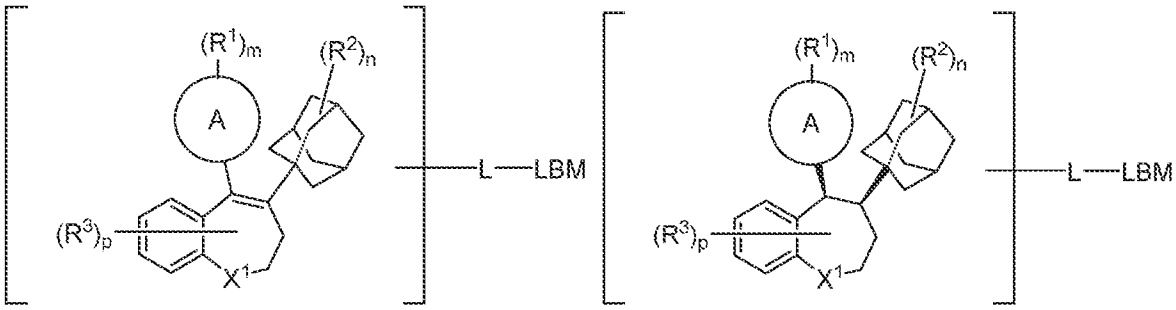


II-aa

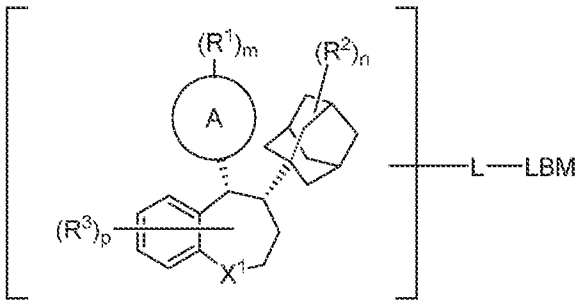
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0286] In certain embodiments, the present invention provides a compound of formula **I-a**,

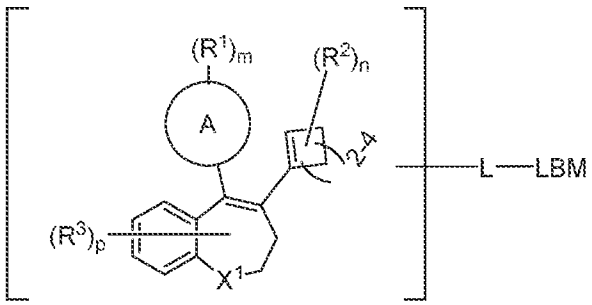
wherein ERBM is  ,  ,  , or , thereby forming a compound of one of formulas **II-bb**, **II-cc**, **II-dd**, **II-ee**, **II-ff**, or **II-gg**, respectively:



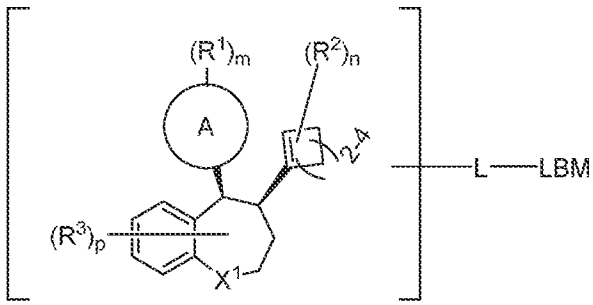
II-bb **II-cc**



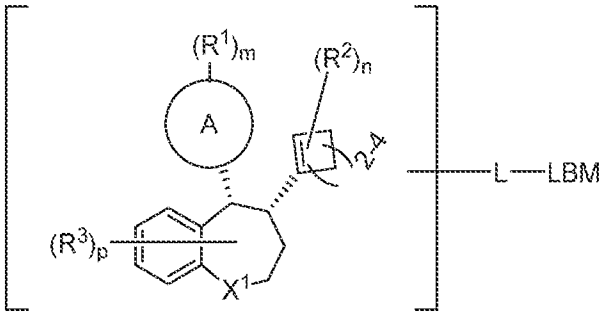
II-dd



II-ee



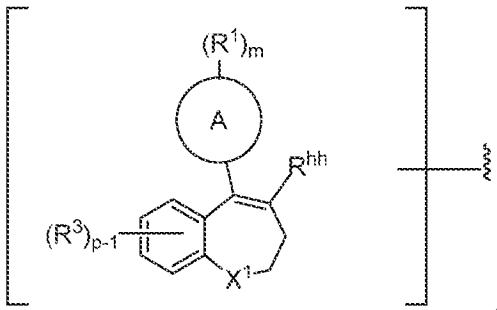
II-ff

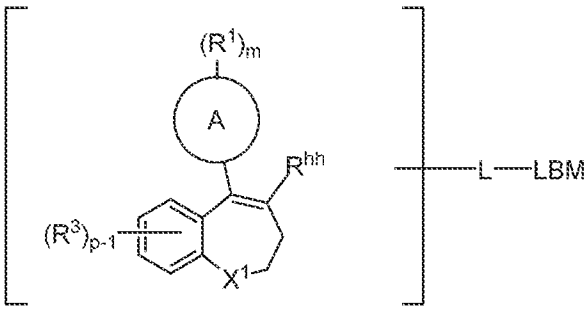


II-gg

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0287] In certain embodiments, the present invention provides a compound of formula **I-a**,

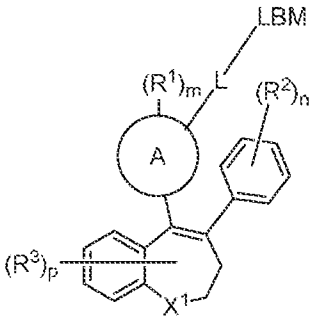
wherein ERBM is  , thereby forming a compound of formula **II-hh**:



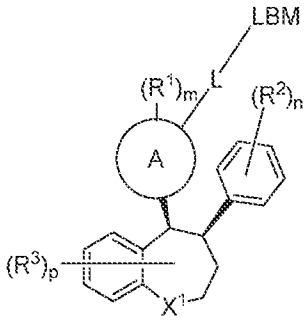
II-hh

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, R^{hh}, and LBM is as defined in embodiments and classes and subclasses herein.

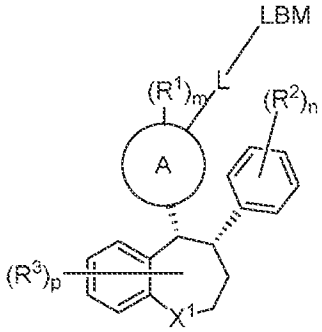
[0288] In some embodiments, the invention provides a compound of one of formulas **II-m-1**, **II-n-1**, **II-o-1**, **II-p-1**, **II-q-1**, **II-r-1**, **II-s-1**, **II-t-1**, **II-u-1**, **II-v-1**, **II-w-1**, **II-x-1**, **II-y-1**, **II-z-1**, or **II-aa-1**:



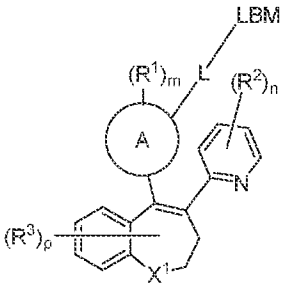
II-m-1



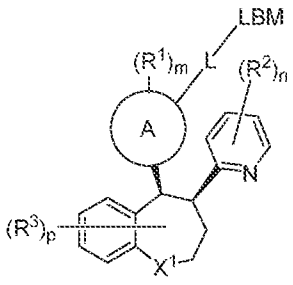
II-n-1



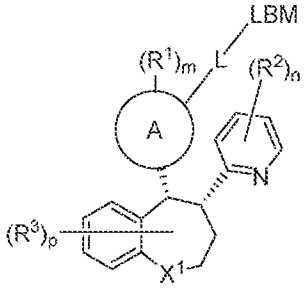
II-o-1



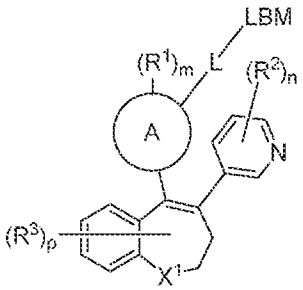
II-p-1



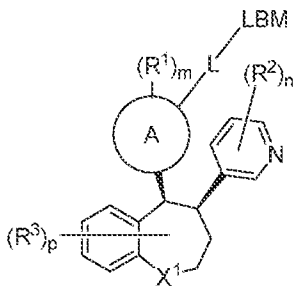
II-q-1



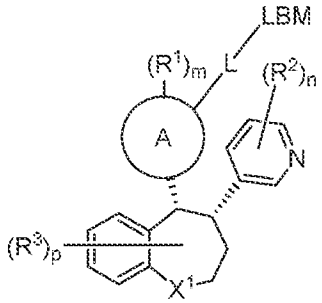
II-r-1



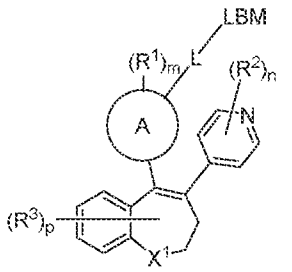
II-s-1



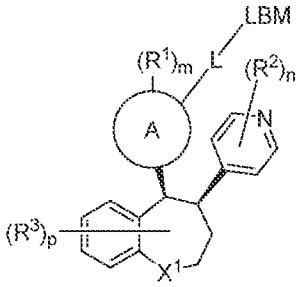
II-t-1



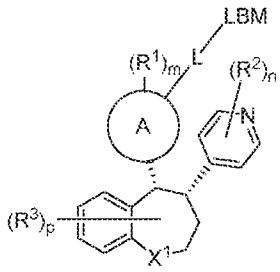
II-u-1



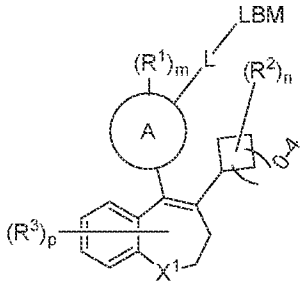
II-v-1



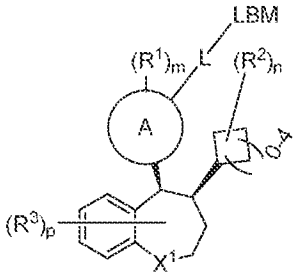
II-w-1



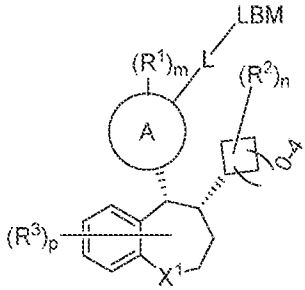
II-x-1



II-y-1



II-z-1



II-aa-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0289] In some embodiments, the compound is a compound of formula **II-m-1**, or a pharmaceutically acceptable salt thereof.

[0290] In some embodiments, the compound is a compound of formula **II-n-1**, or a pharmaceutically acceptable salt thereof.

[0291] In some embodiments, the compound is a compound of formula **II-o-1**, or a pharmaceutically acceptable salt thereof.

[0292] In some embodiments, the compound is a compound of formula **II-p-1**, or a pharmaceutically acceptable salt thereof.

[0293] In some embodiments, the compound is a compound of formula **II-q-1**, or a pharmaceutically acceptable salt thereof.

[0294] In some embodiments, the compound is a compound of formula **II-r-1**, or a pharmaceutically acceptable salt thereof.

[0295] In some embodiments, the compound is a compound of formula **II-s-1**, or a pharmaceutically acceptable salt thereof.

[0296] In some embodiments, the compound is a compound of formula **II-t-1**, or a pharmaceutically acceptable salt thereof.

[0297] In some embodiments, the compound is a compound of formula **II-u-1** or a pharmaceutically acceptable salt thereof.

[0298] In some embodiments, the compound is a compound of formula **II-v-1**, or a pharmaceutically acceptable salt thereof.

[0299] In some embodiments, the compound is a compound of formula **II-w-1**, or a pharmaceutically acceptable salt thereof.

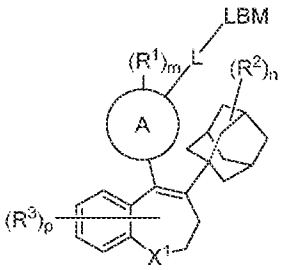
[0300] In some embodiments, the compound is a compound of formula **II-x-1**, or a pharmaceutically acceptable salt thereof.

[0301] In some embodiments, the compound is a compound of formula **II-y-1**, or a pharmaceutically acceptable salt thereof.

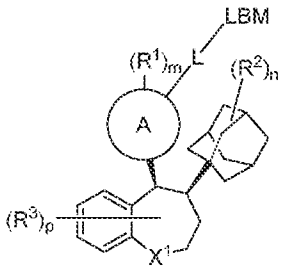
[0302] In some embodiments, the compound is a compound of formula **II-z-1**, or a pharmaceutically acceptable salt thereof.

[0303] In some embodiments, the compound is a compound of formula **II-aa-1**, or a pharmaceutically acceptable salt thereof.

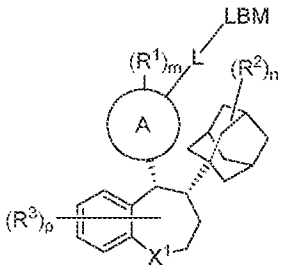
[0304] In some embodiments, invention provides a compound one of formulas **II-bb-1**, **II-cc-1**, **II-dd-1**, **II-ee-1**, **II-ff-1** or **II-gg-1**:



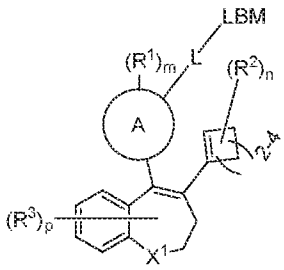
II-bb-1



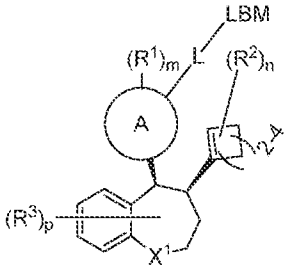
II-cc-1



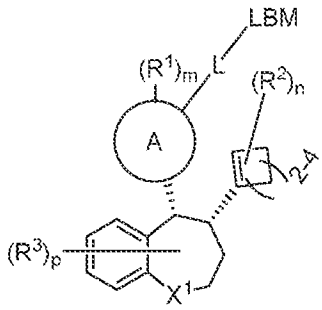
II-dd-1



II-ee-1



II-ff-1



II-gg-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0305] In some embodiments, the compound is a compound of formula **II-bb-1**, or a pharmaceutically acceptable salt thereof.

[0306] In some embodiments, the compound is a compound of formula **II-cc-1**, or a pharmaceutically acceptable salt thereof.

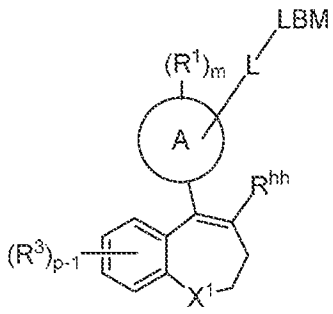
[0307] In some embodiments, the compound is a compound of formula **II-dd-1**, or a pharmaceutically acceptable salt thereof.

[0308] In some embodiments, the compound is a compound of formula **II-ee-1**, or a pharmaceutically acceptable salt thereof.

[0309] In some embodiments, the compound is a compound of formula **II-ff-1**, or a pharmaceutically acceptable salt thereof.

[0310] In some embodiments, the compound is a compound of formula **II-gg-1**, or a pharmaceutically acceptable salt thereof.

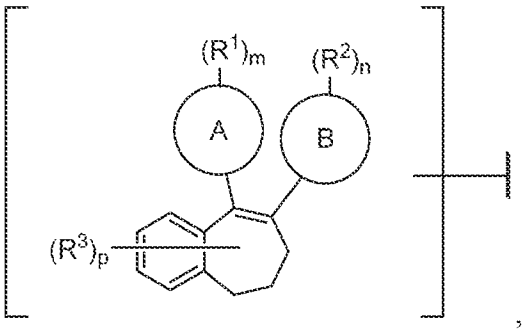
[0311] In some embodiments, the invention provides a of formula **II-hh-1**:

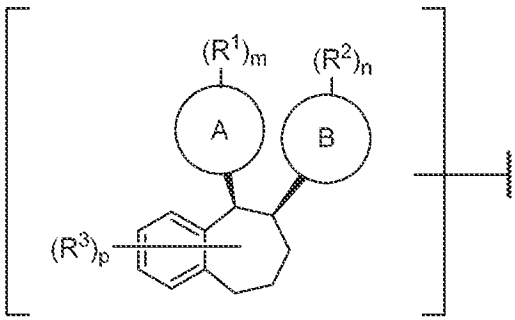
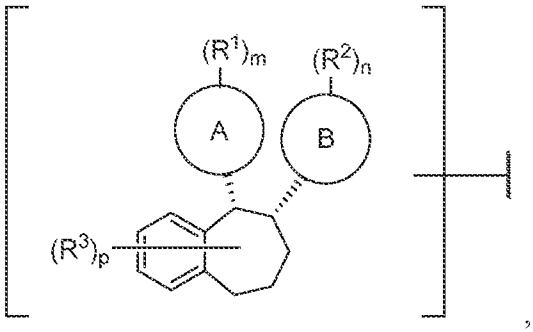


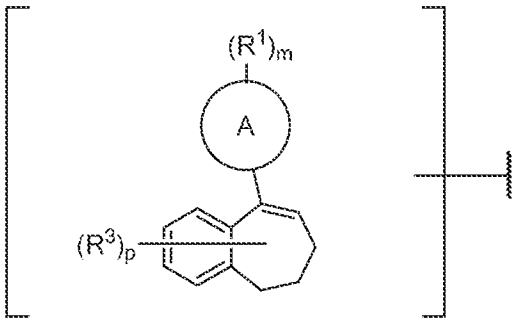
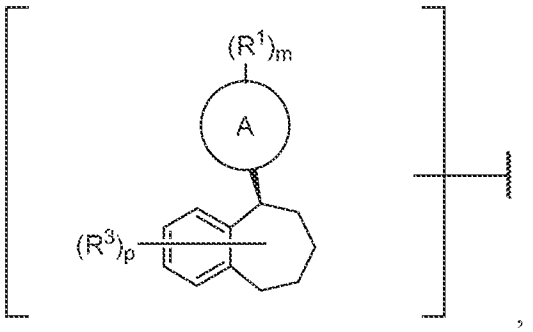
II-hh-1

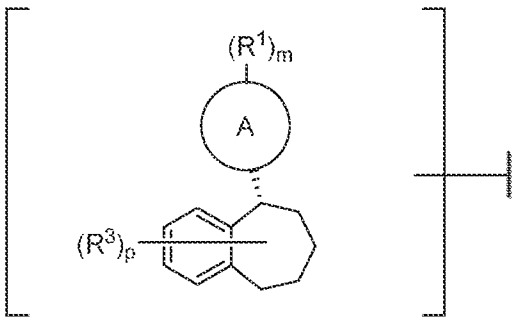
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^1, m, n, p, L, R^{hh} and LBM is as defined in embodiments and classes and subclasses herein.

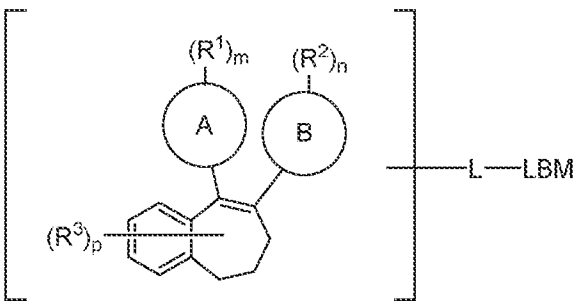
[0312] In certain embodiments, the present invention provides a compound of formula **I-a**,

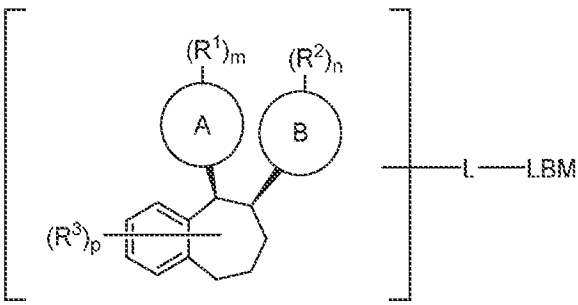
wherein ERBM is  ,

 ,  ,

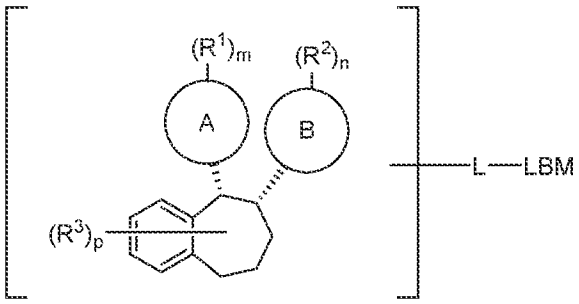
 ,  , or

 , thereby forming a compound of one of formulas **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, or **III-f**, respectively:

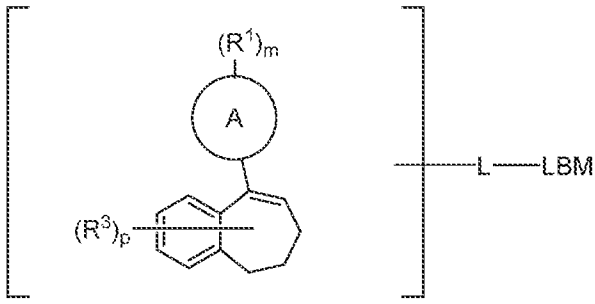




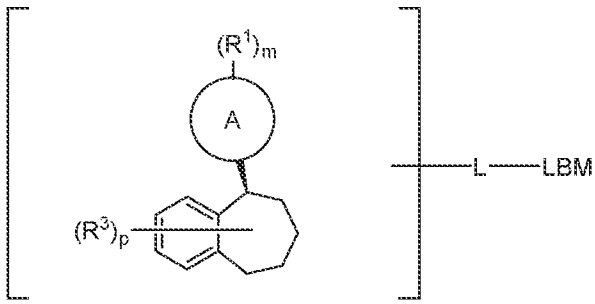
III-a



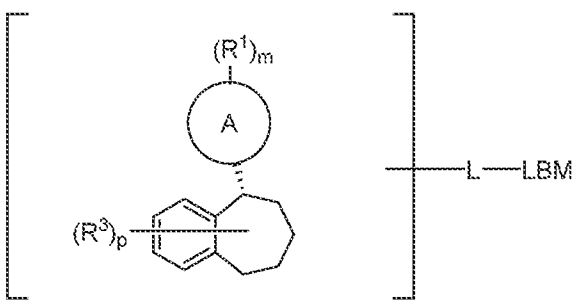
III-b



III-c



III-d

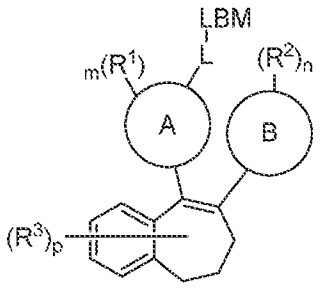


III-e

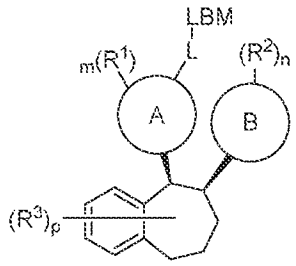
III-f

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

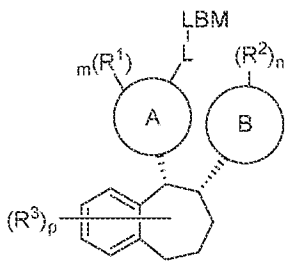
[0313] In some embodiments, the invention provides a compound of one of formulas **III-a-1**, **III-b-1**, **III-c-1**, **III-d-1**, **III-e-1**, or **III-f-1**:



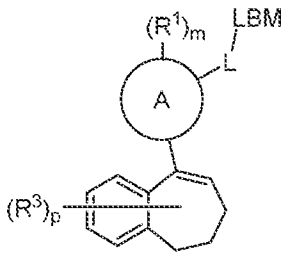
II-a-1



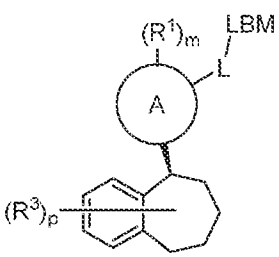
III-b-1



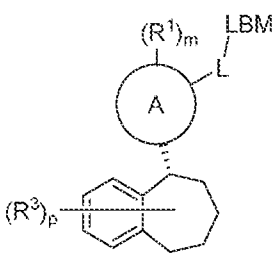
III-c-1



III-d-1



III-e-1



III-f-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0314] In some embodiments, the compound is a compound of formula **III-b-1**, or a pharmaceutically acceptable salt thereof.

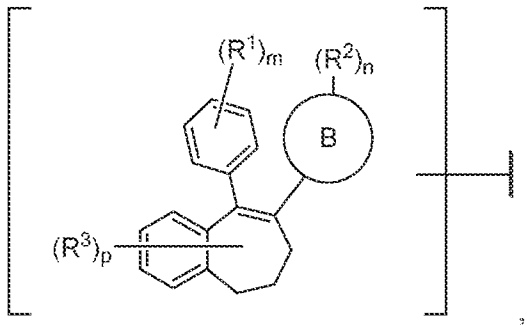
[0315] In some embodiments, the compound is a compound of formula **III-c-1**, or a pharmaceutically acceptable salt thereof.

[0316] In some embodiments, the compound is a compound of formula **III-d-1**, or a pharmaceutically acceptable salt thereof.

[0317] In some embodiments, the compound is a compound of formula **III-e-1**, or a pharmaceutically acceptable salt thereof.

[0318] In some embodiments, the compound is a compound of formula **III-f-1**, or a pharmaceutically acceptable salt thereof.

[0319] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is 

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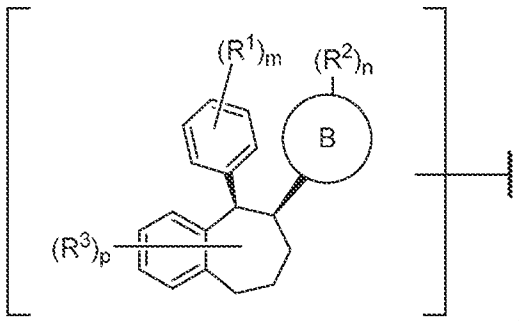
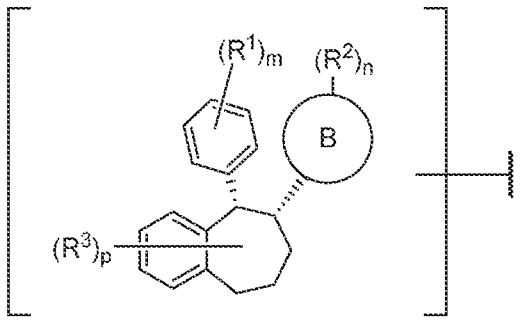


, 

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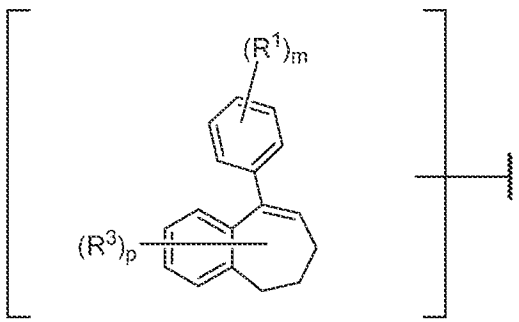
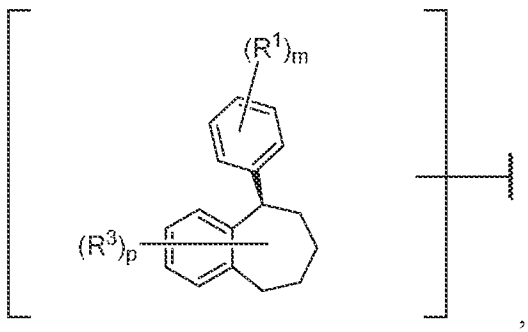


, 

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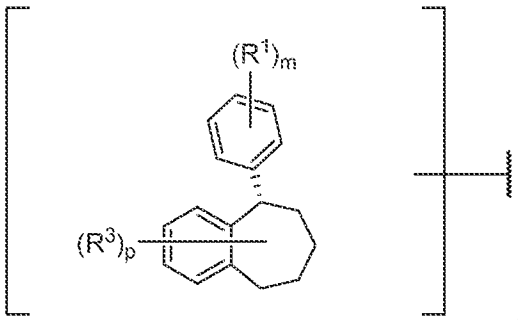
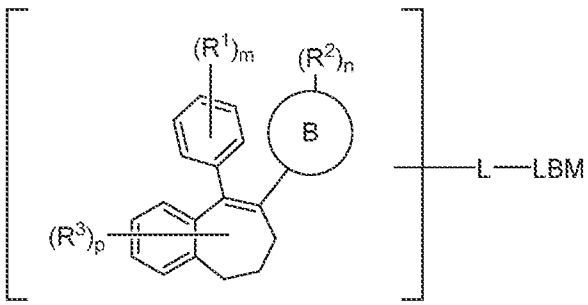
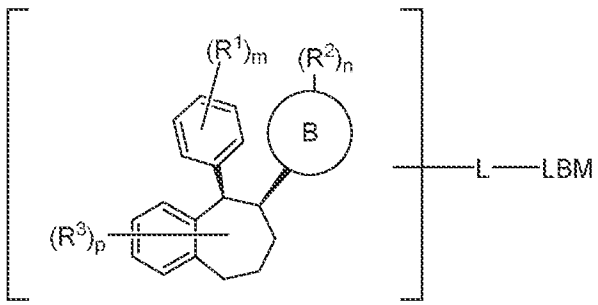


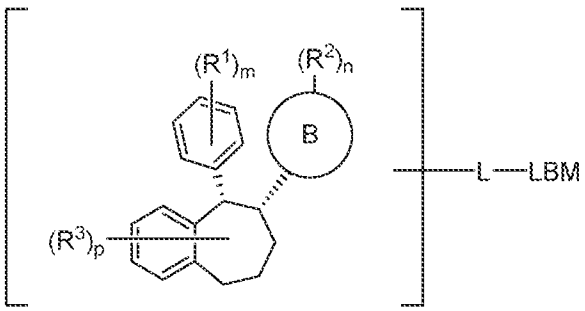
, thereby forming a compound of one of formulas **III-g**, **III-h**, **III-i**, **III-j**, **III-k**, or **III-l**, respectively:



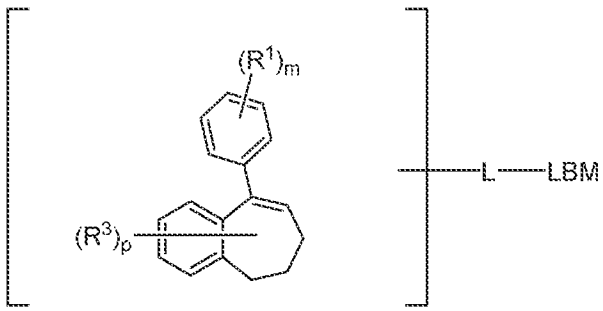
III-g



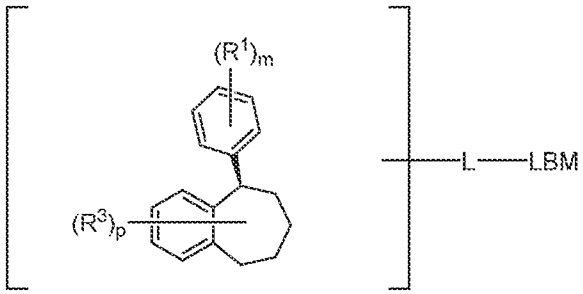
III-h



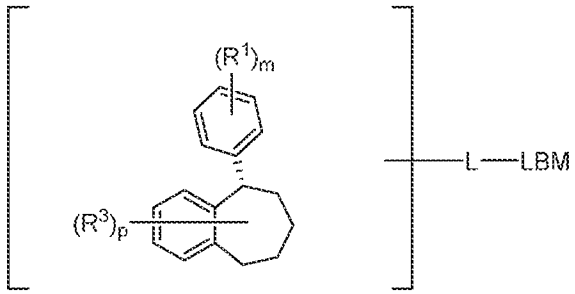
III-i



III-j



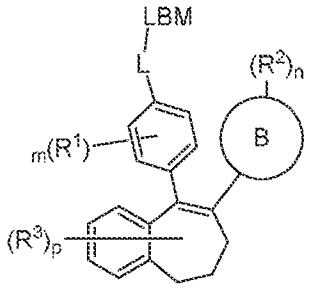
III-k



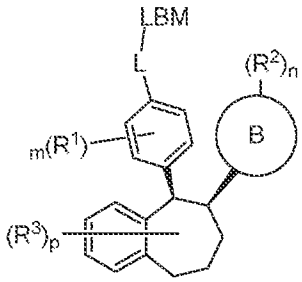
III-l

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

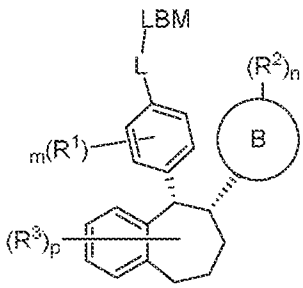
[0320] In some embodiments, the invention provides a compound of one of formulas **III-g-1**, **III-h-1**, **III-i-1**, **V-f**, **III-k-1**, or **III-l-1**:



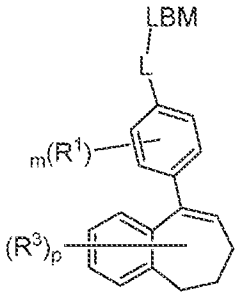
III-g-1



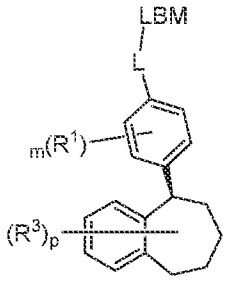
III-h-1



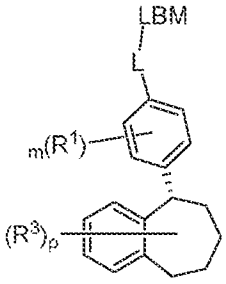
III-i-1



V-f



III-k-1



III-l-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0321] In some embodiments, the compound is a compound of formula **III-g-1**, or a pharmaceutically acceptable salt thereof.

[0322] In some embodiments, the compound is a compound of formula **III-h-1**, or a pharmaceutically acceptable salt thereof.

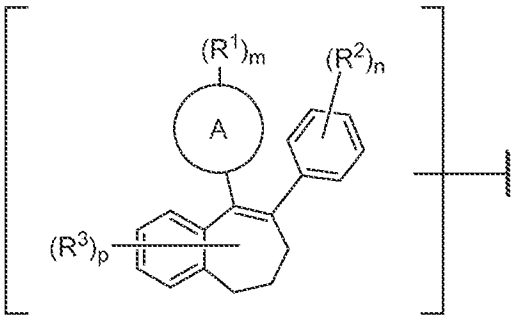
[0323] In some embodiments, the compound is a compound of formula **III-i-1**, or a pharmaceutically acceptable salt thereof.

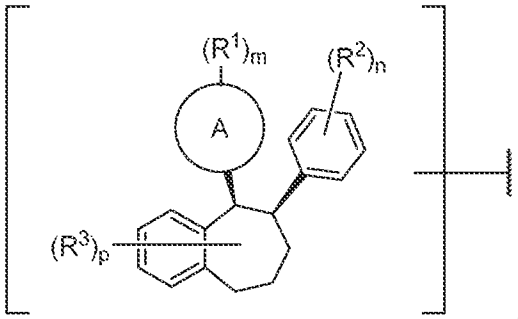
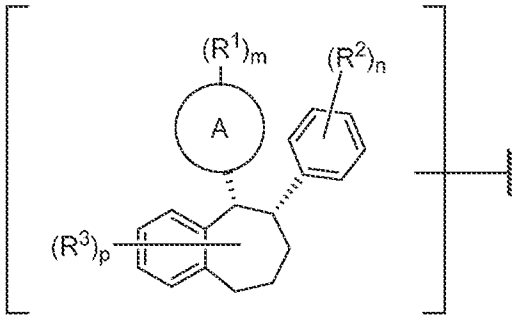
[0324] In some embodiments, the compound is a compound of formula **V-f**, or a pharmaceutically acceptable salt thereof.

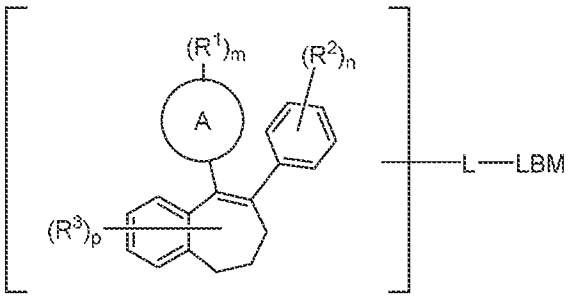
[0325] In some embodiments, the compound is a compound of formula **III-k-1**, or a pharmaceutically acceptable salt thereof.

[0326] In some embodiments, the compound is a compound of formula **III-l-1**, or a pharmaceutically acceptable salt thereof.

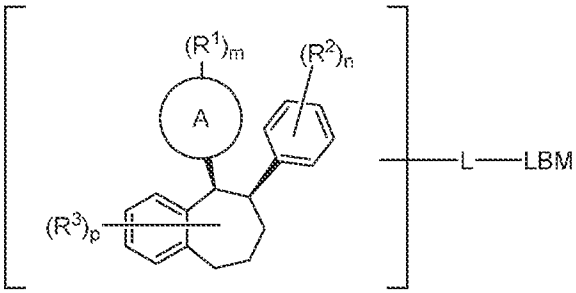
[0327] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

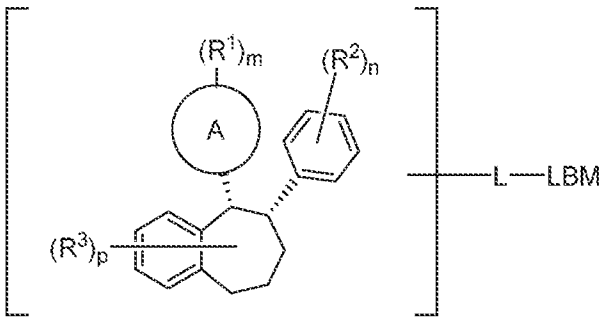
 , or  , thereby forming a compound of one of formulas **III-m**, **III-n**, or **III-o**, respectively:



III-m



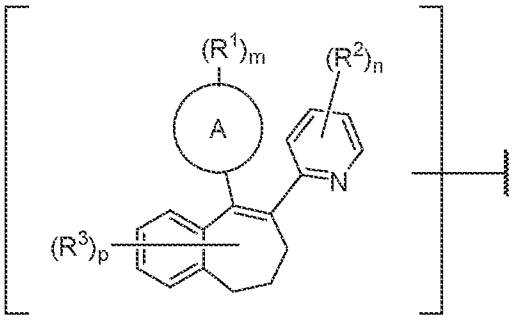
III-n

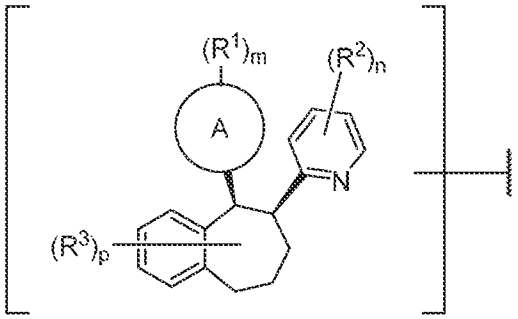
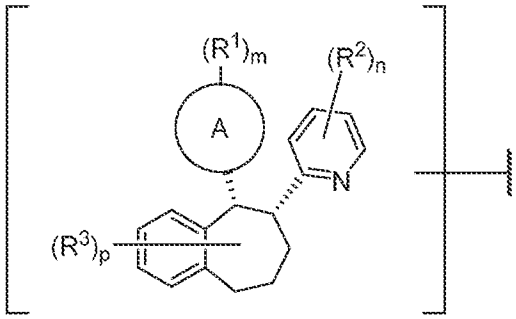


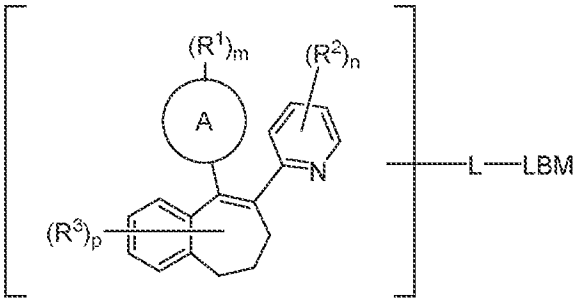
III-o

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

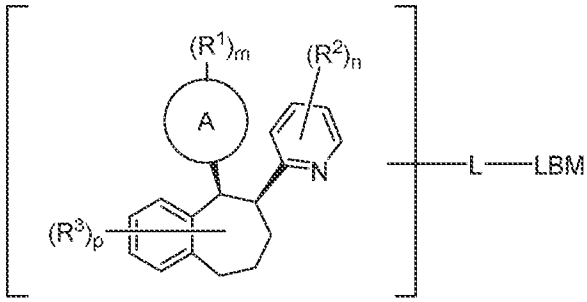
[0328] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

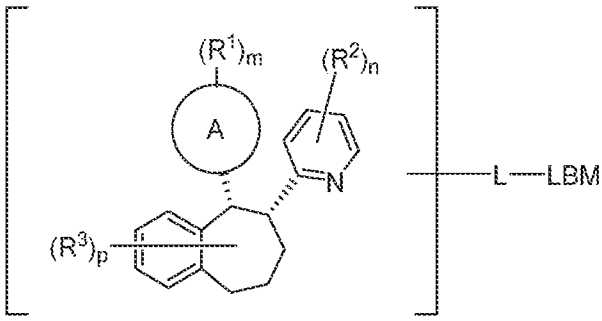
 , or  , thereby forming a compound of one of formulas **III-p**, **III-q**, or **III-r**, respectively:



III-p



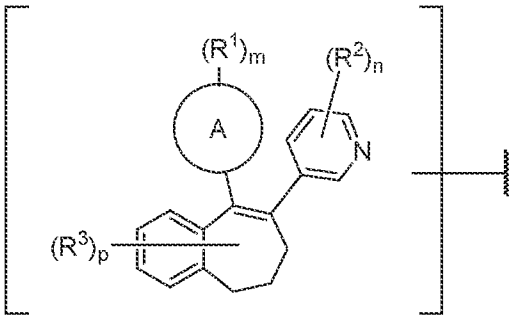
III-q

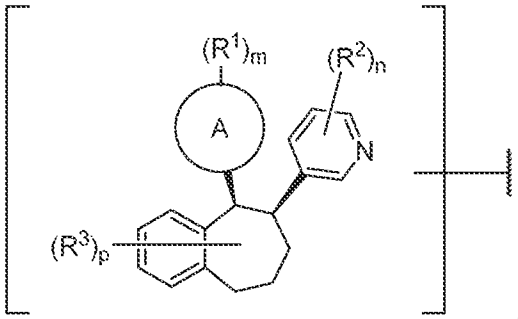
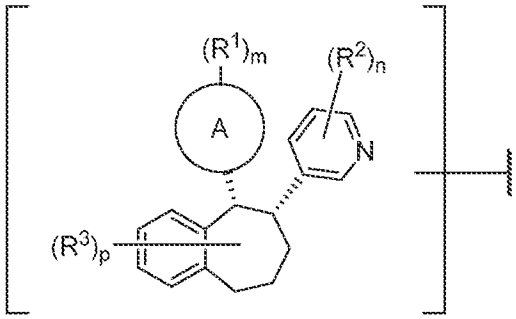


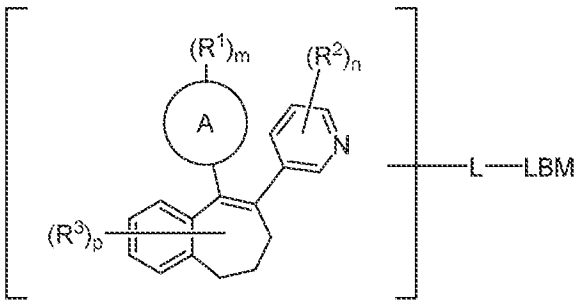
III-r

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

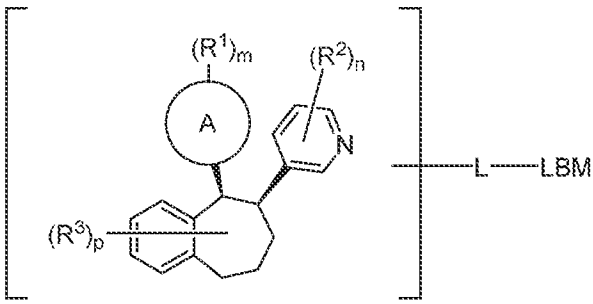
[0329] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

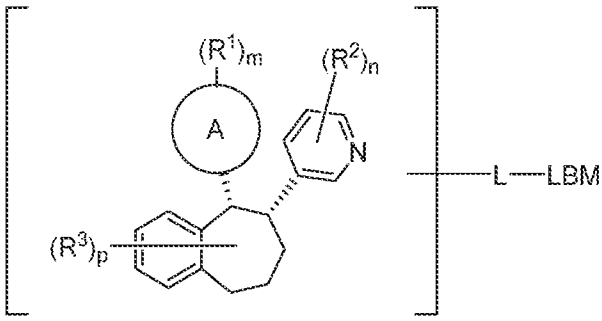
 , or  , thereby forming a compound of one of formulas **III-s**, **III-t**, or **III-u**, respectively:



III-s



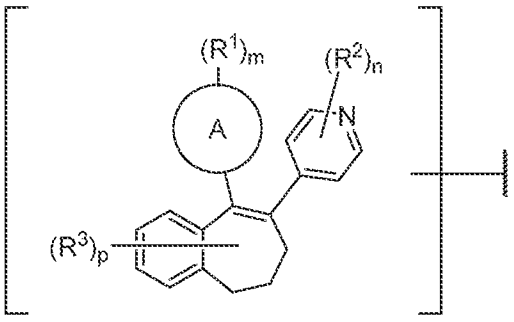
III-t

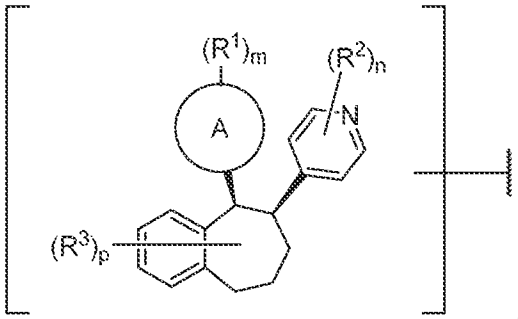
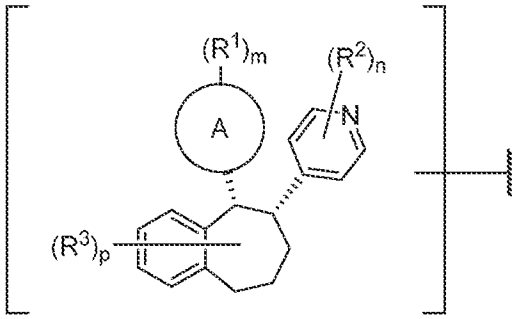


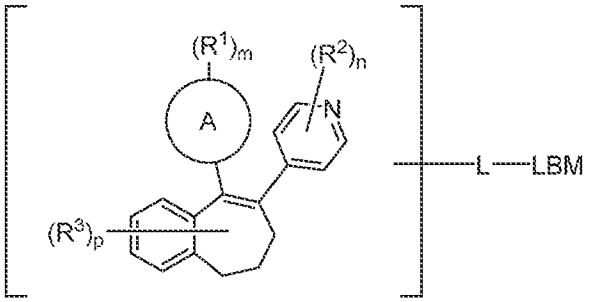
III-u

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

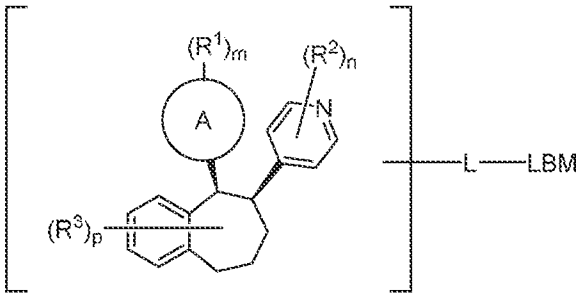
[0330] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

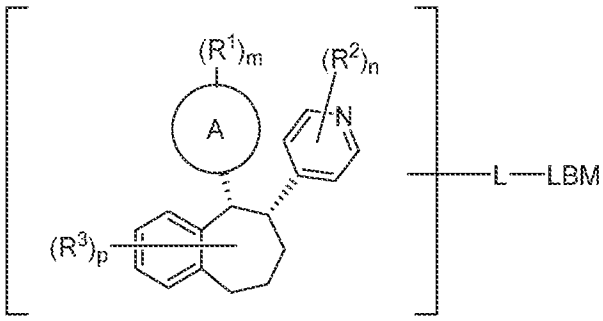
 , or  , thereby forming a compound of one of formulas **III-v**, **III-w**, or **III-x**, respectively:



III-v



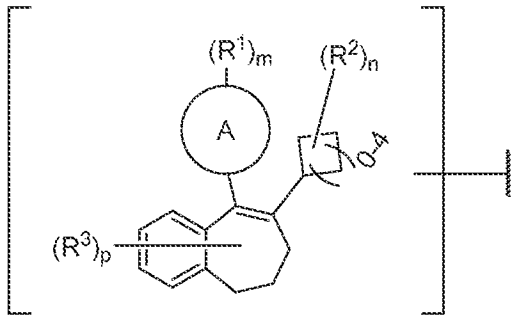
III-w

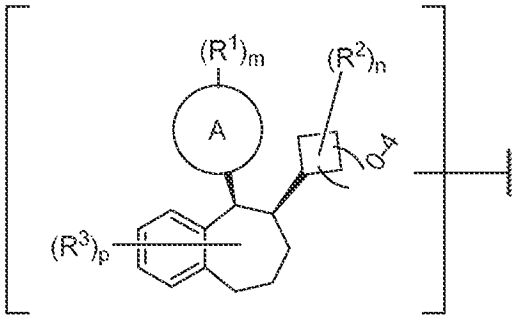
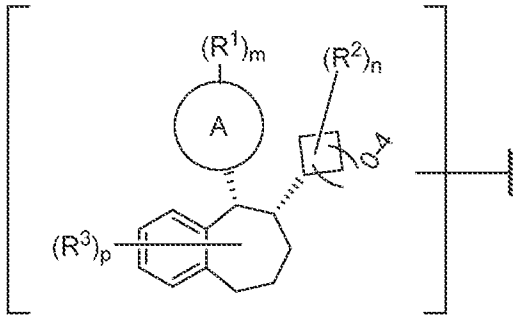


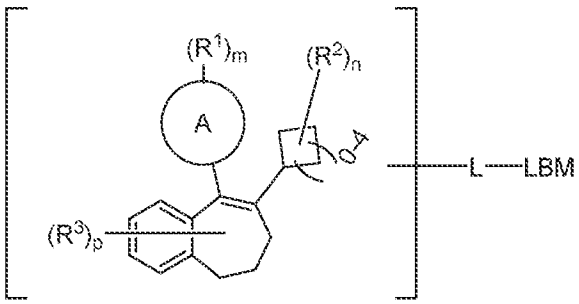
III-x

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

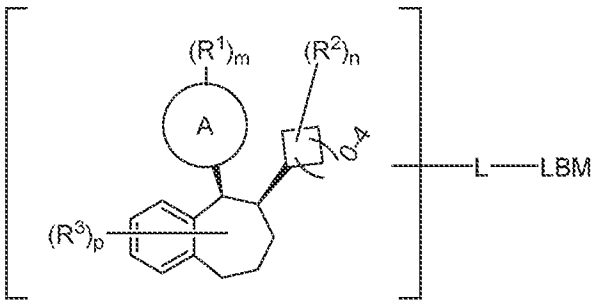
[0331] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

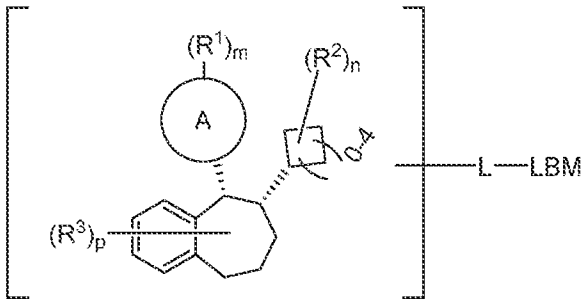
 , or  , thereby forming a compound of one of formulas **III-y**, **III-z**, or **III-aa**, respectively:



III-y



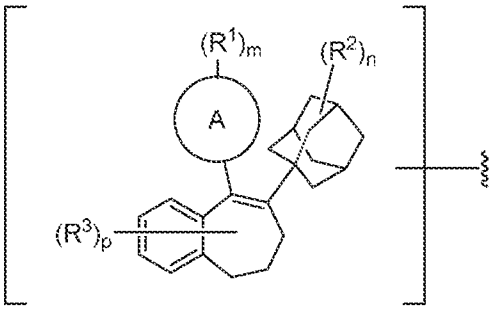
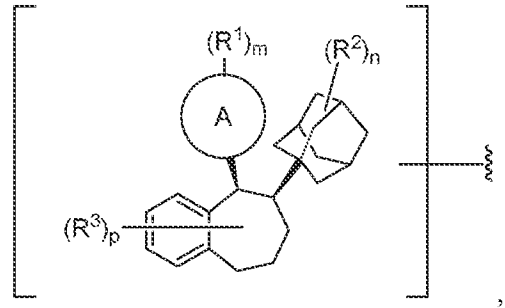
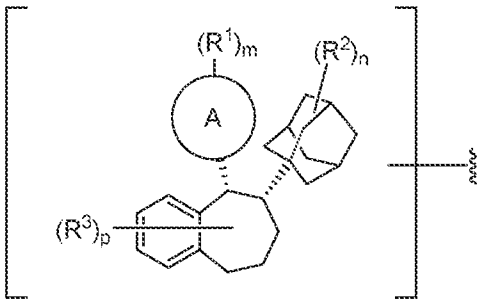
III-z

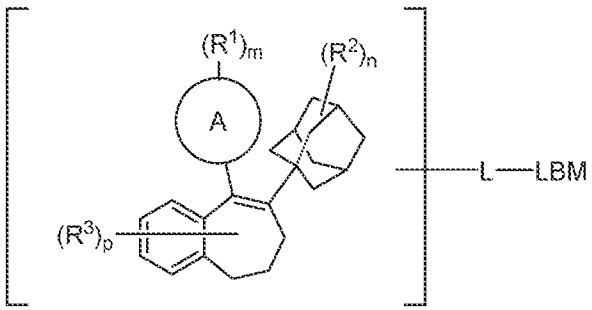


III-aa

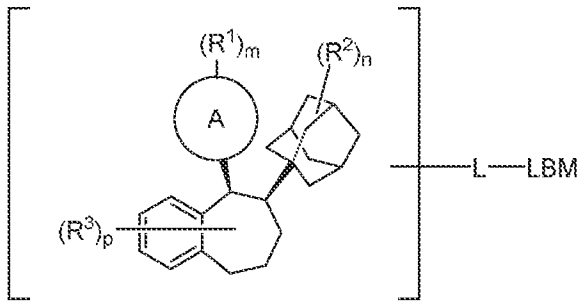
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0332] In certain embodiments, the present invention provides a compound of formula **I-a**,

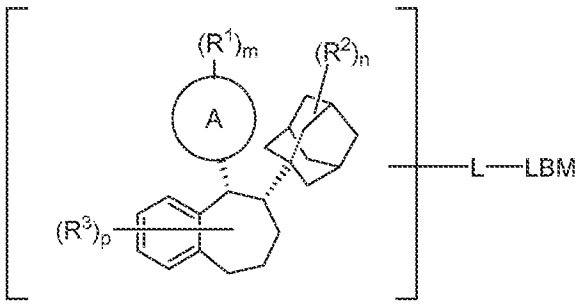
wherein ERBM is  ,  ,  , thereby forming a compound of one of formulas **III-bb**, **III-cc**, or **III-dd**, respectively:



III-bb



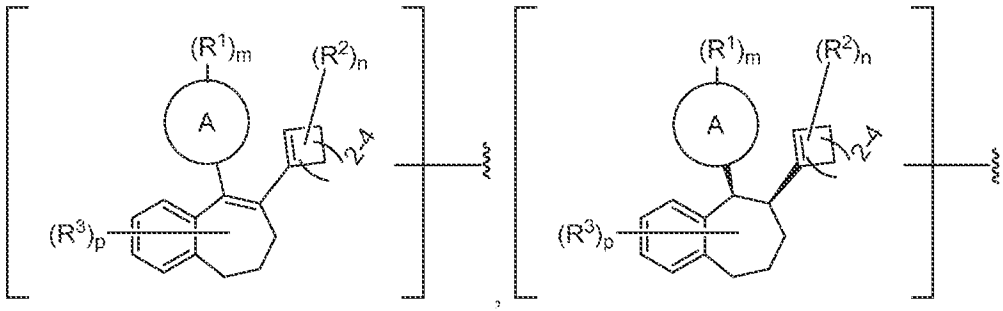
III-cc

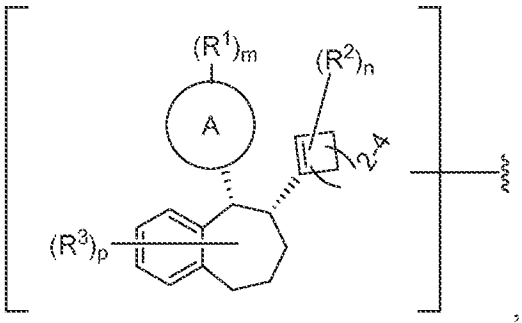


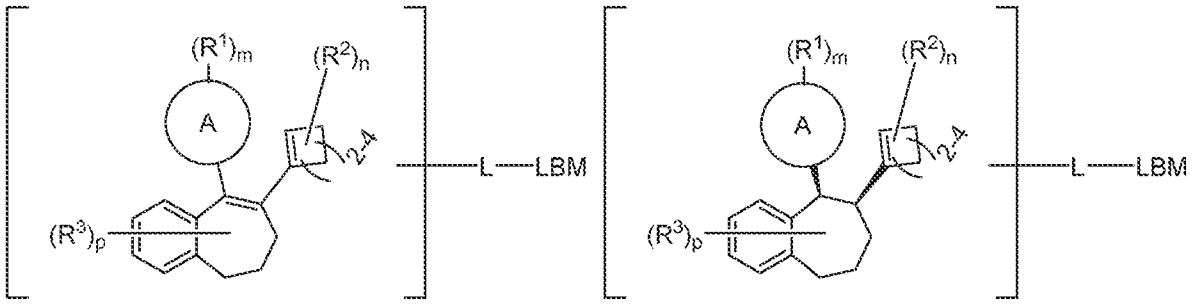
III-dd

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

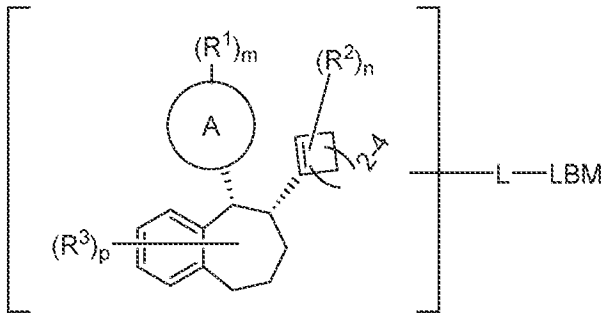
[0333] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is 

, or  , thereby forming a compound of one of formulas **III-ee**, **III-ff**, or **III-gg**, respectively:

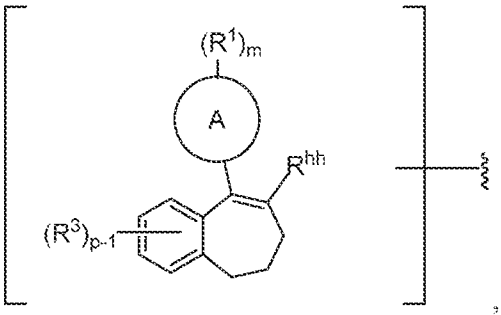


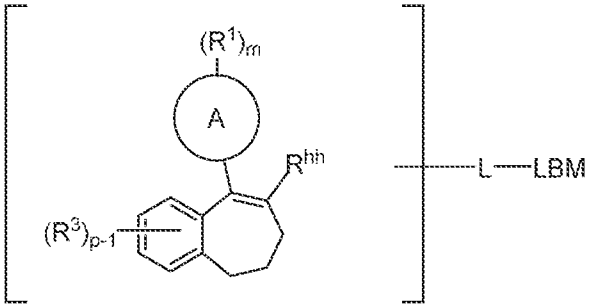
III-ee **III-ff**



III-gg

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

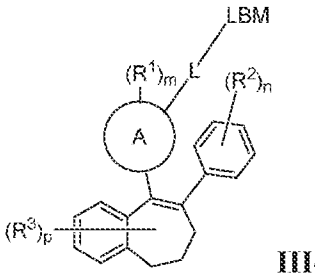
[0334] In certain embodiments, the present invention provides a compound of formula **I-a**, wherein ERBM is  , thereby forming a compound of formula **III-hh**:



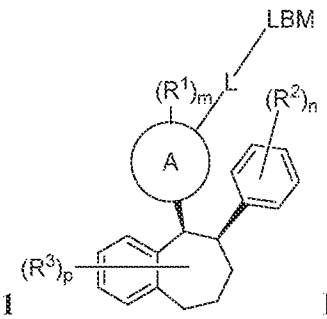
III-hh

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, R^{hh} and LBM is as defined in embodiments and classes and subclasses herein.

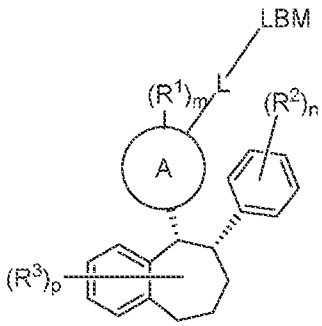
[0335] In some embodiments, the invention provides a compound of one of formulas **III-m-1**, **III-n-1**, **III-o-1**, **III-p-1**, **III-q-1**, **III-r-1**, **III-s-1**, **III-t-1**, **III-u-1**, **III-v-1**, **III-w-1**, **III-x-1**, **III-y-1**, **III-z-1**, or **III-aa-1**:



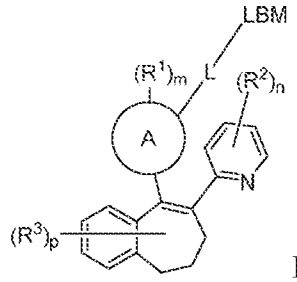
III-m-1



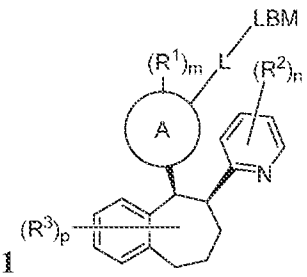
III-n-1



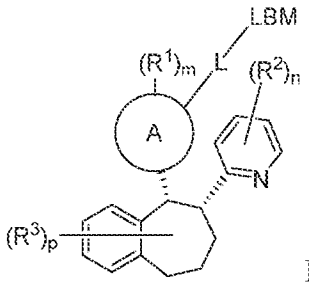
III-o-1



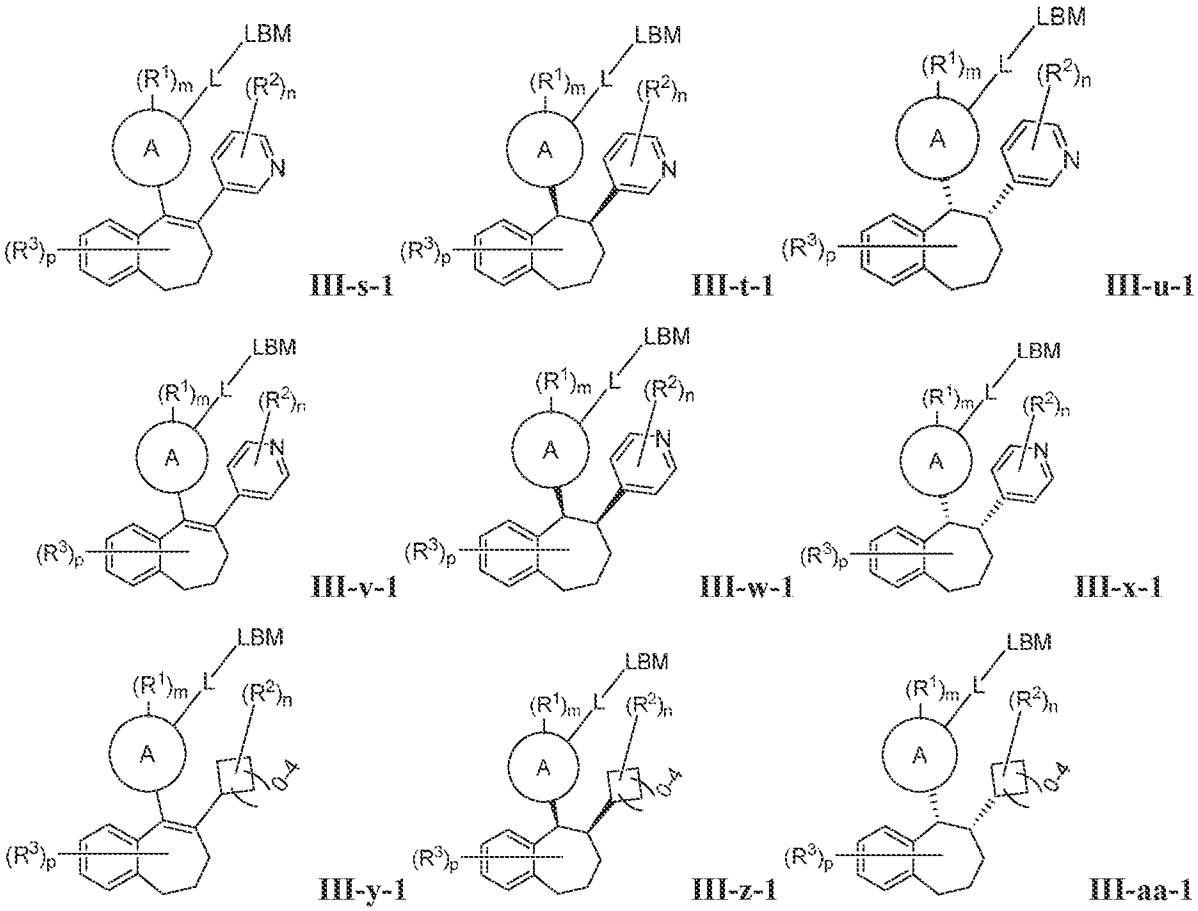
III-p-1



III-q-1



III-r-1



or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0336] In some embodiments, the compound is a compound of formula **III-m-1**, or a pharmaceutically acceptable salt thereof.

[0337] In some embodiments, the compound is a compound of formula **III-n-1**, or a pharmaceutically acceptable salt thereof.

[0338] In some embodiments, the compound is a compound of formula **III-o-1**, or a pharmaceutically acceptable salt thereof.

[0339] In some embodiments, the compound is a compound of formula **III-p-1**, or a pharmaceutically acceptable salt thereof.

[0340] In some embodiments, the compound is a compound of formula **III-q-1**, or a pharmaceutically acceptable salt thereof.

[0341] In some embodiments, the compound is a compound of formula **III-r-1**, or a pharmaceutically acceptable salt thereof.

[0342] In some embodiments, the compound is a compound of formula **III-s-1**, or a pharmaceutically acceptable salt thereof.

[0343] In some embodiments, the compound is a compound of formula **III-t-1**, or a pharmaceutically acceptable salt thereof.

[0344] In some embodiments, the compound is a compound of formula **III-u-1** or a pharmaceutically acceptable salt thereof.

[0345] In some embodiments, the compound is a compound of formula **III-v-1**, or a pharmaceutically acceptable salt thereof.

[0346] In some embodiments, the compound is a compound of formula **III-w-1**, or a pharmaceutically acceptable salt thereof.

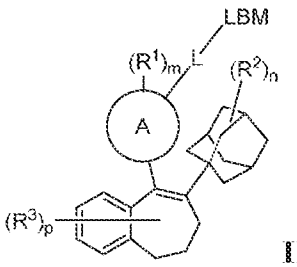
[0347] In some embodiments, the compound is a compound of formula **III-x-1**, or a pharmaceutically acceptable salt thereof.

[0348] In some embodiments, the compound is a compound of formula **III-y-1**, or a pharmaceutically acceptable salt thereof.

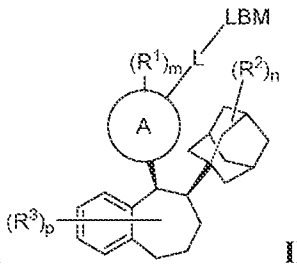
[0349] In some embodiments, the compound is a compound of formula **III-z-1**, or a pharmaceutically acceptable salt thereof.

[0350] In some embodiments, the compound is a compound of formula **III-aa-1**, or a pharmaceutically acceptable salt thereof.

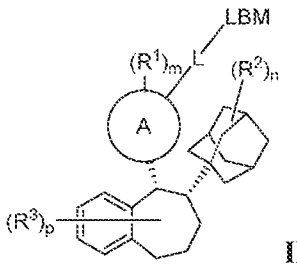
[0351] In some embodiments, the invention provides a compound of one of formulas **III-bb-1**, **III-cc-1**, **III-dd-1**, **III-ee-1**, **III-ff-1** or **III-gg-1**:



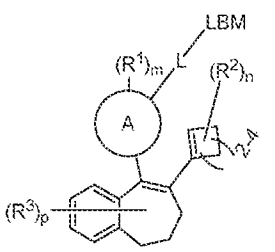
III-bb-1



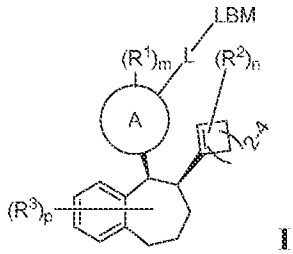
III-cc-1



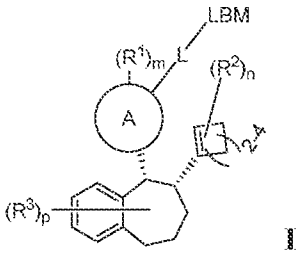
III-dd-1



III-ee-1



III-ff-1



III-gg-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0352] In some embodiments, the compound is a compound of formula **III-bb-1**, or a pharmaceutically acceptable salt thereof.

[0353] In some embodiments, the compound is a compound of formula **III-cc-1**, or a pharmaceutically acceptable salt thereof.

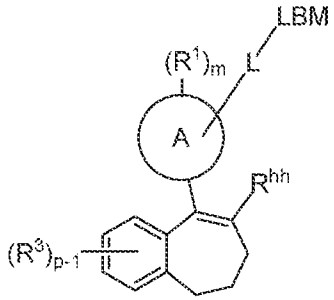
[0354] In some embodiments, the compound is a compound of formula **III-dd-1**, or a pharmaceutically acceptable salt thereof.

[0355] In some embodiments, the compound is a compound of formula **III-ee-1**, or a pharmaceutically acceptable salt thereof.

[0356] In some embodiments, the compound is a compound of formula **III-ff-1**, or a pharmaceutically acceptable salt thereof.

[0357] In some embodiments, the compound is a compound of formula **III-gg-1**, or a pharmaceutically acceptable salt thereof.

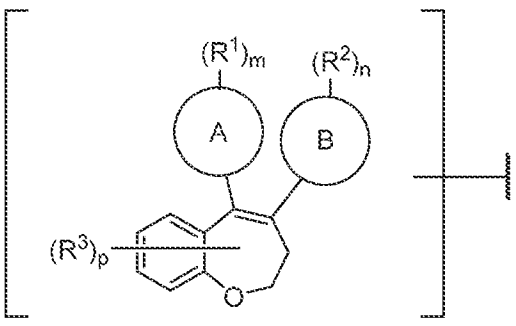
[0358] In some embodiments, invention provides a compound of formula **III-hh-1**:



II-hh-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, R^{hh} and LBM is as defined in embodiments and classes and subclasses herein.

[0359] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is 

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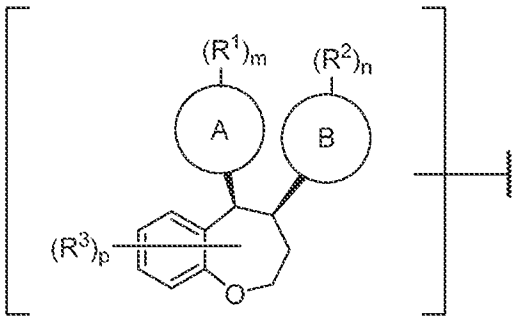

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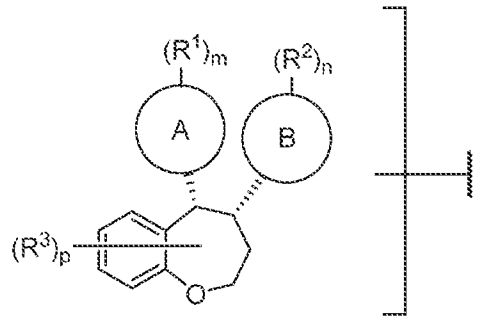

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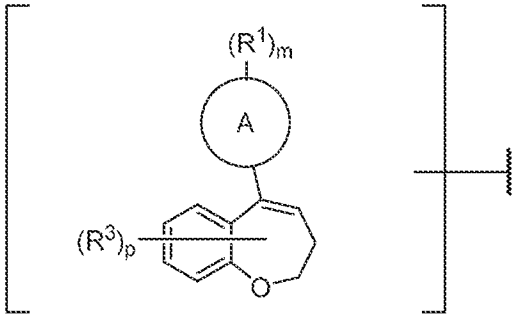

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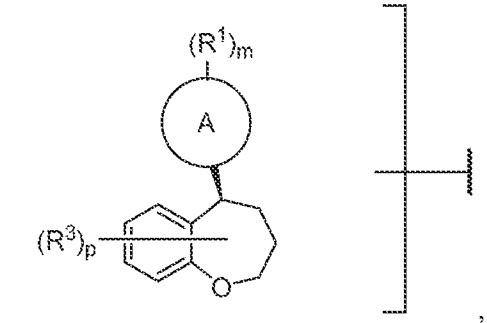

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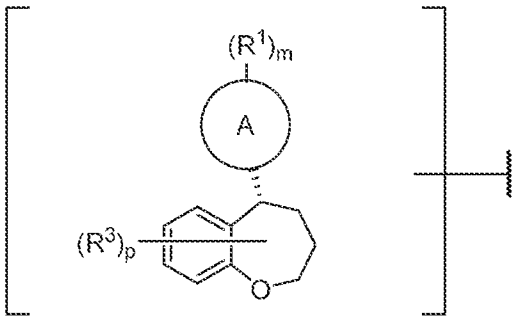
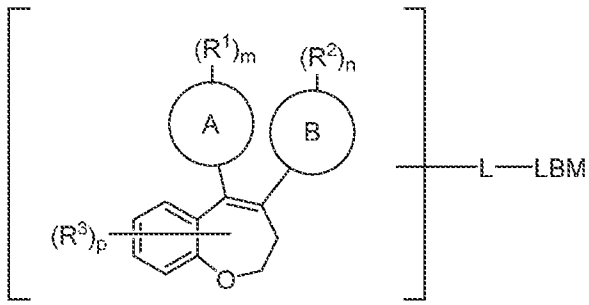
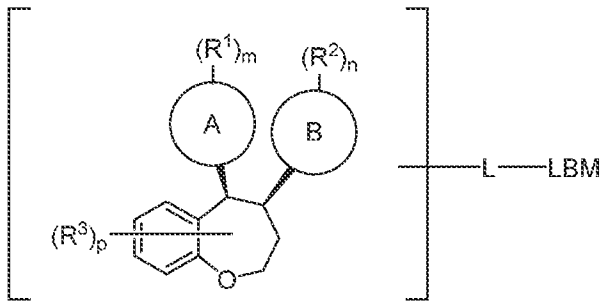


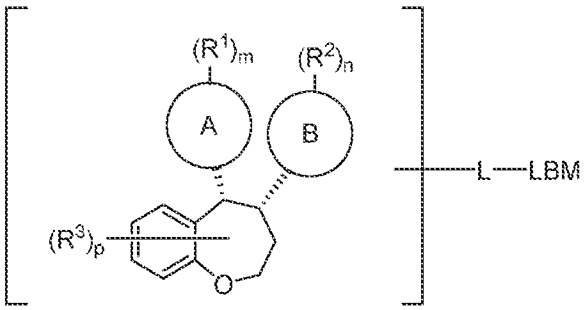
, thereby forming a compound of one of formulas **IV-a**, **IV-b**, **IV-c**, **IV-d**, **IV-e**, or **IV-f**, respectively:



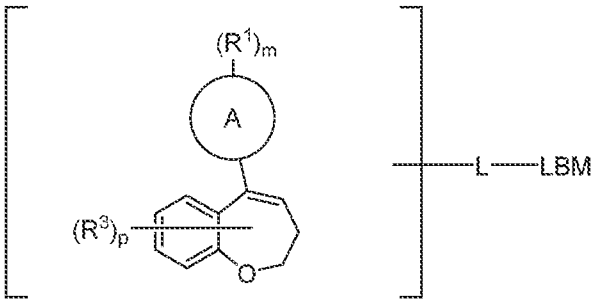
IV-a



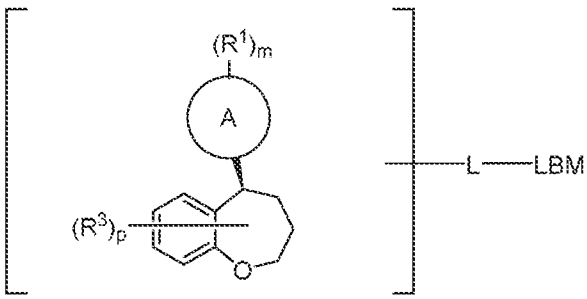
IV-b



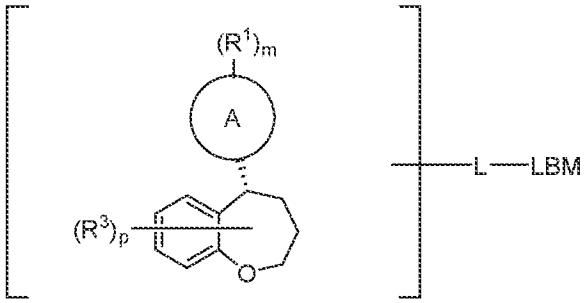
IV-c



IV-d



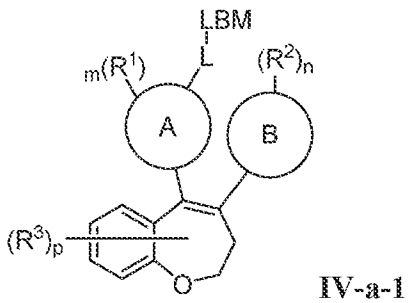
IV-e



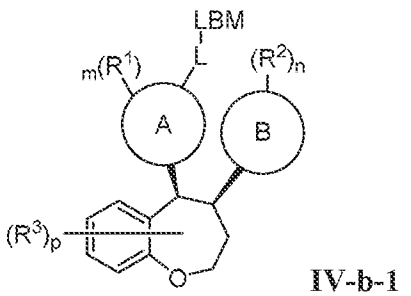
IV-f

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

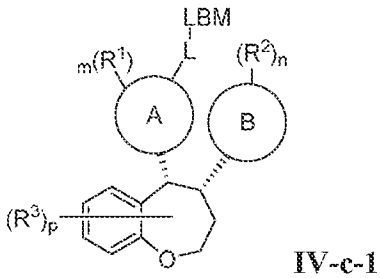
[0360] In some embodiments, the invention provides a compound of one of formulas **IV-a-1**, **IV-b-1**, **IV-c-1**, **IV-d-1**, **IV-e-1**, or **IV-f-1**:



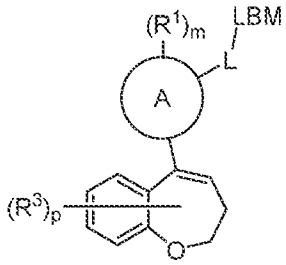
IV-a-1



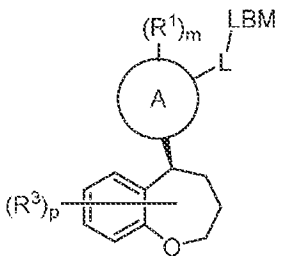
IV-b-1



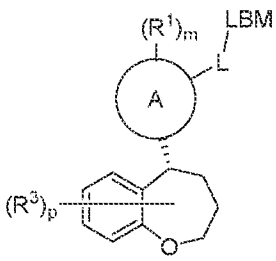
IV-c-1



IV-d-1



IV-e-1



IV-f-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0361] In some embodiments, the compound is a compound of formula **IV-a-1**, or a pharmaceutically acceptable salt thereof.

[0362] In some embodiments, the compound is a compound of formula **IV-b-1**, or a pharmaceutically acceptable salt thereof.

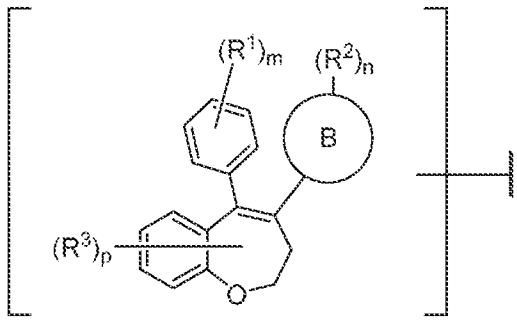
[0363] In some embodiments, the compound is a compound of formula **IV-c-1**, or a pharmaceutically acceptable salt thereof.

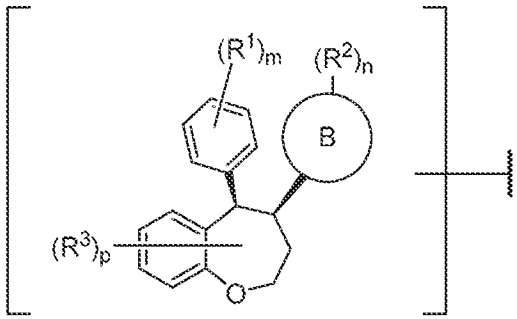
[0364] In some embodiments, the compound is a compound of formula **IV-d-1**, or a pharmaceutically acceptable salt thereof.

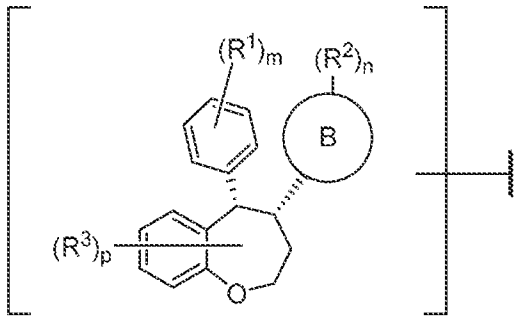
[0365] In some embodiments, the compound is a compound of formula **IV-e-1**, or a pharmaceutically acceptable salt thereof.

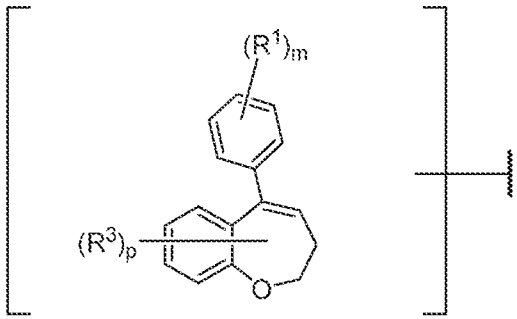
[0366] In some embodiments, the compound is a compound of formula **IV-f-1**, or a pharmaceutically acceptable salt thereof.

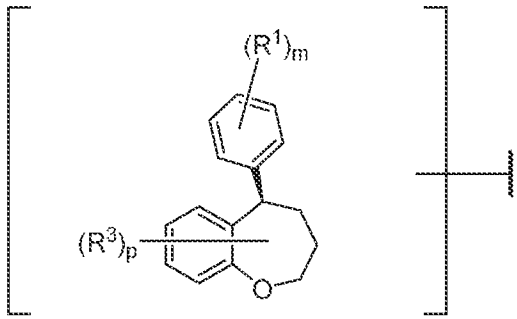
[0367] In certain embodiments, the present invention provides a compound of formula **I-a**,

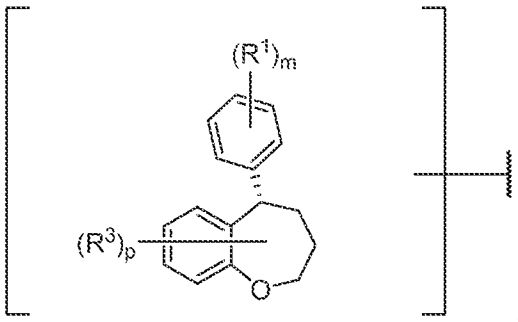
wherein ERBM is  ,

 ,

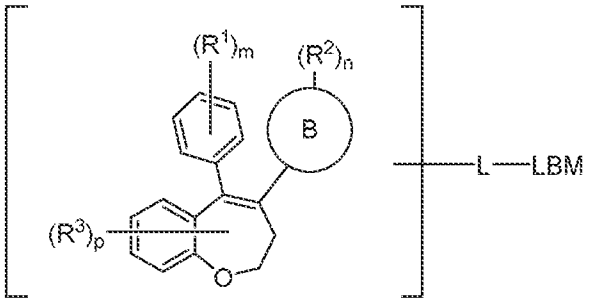
 ,

 ,

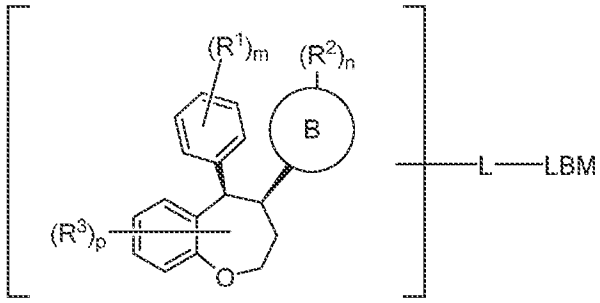
 , or



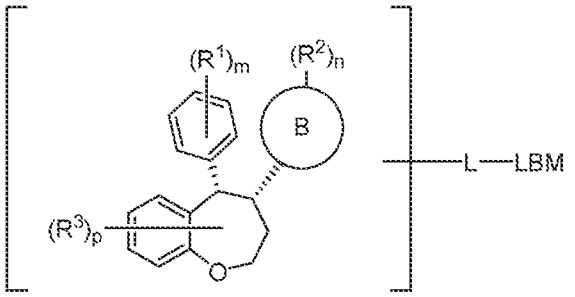
, thereby forming a compound of one of formulas **IV-g**, **IV-h**, **IV-i**, **IV-j**, **IV-k**, or **IV-l**, respectively:



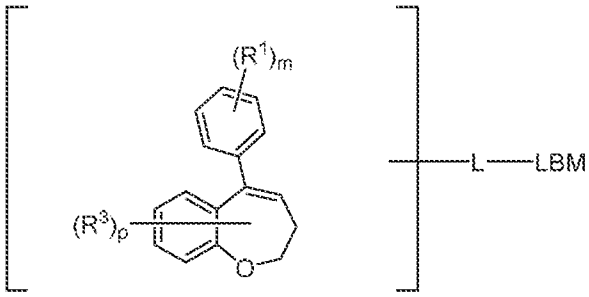
IV-g



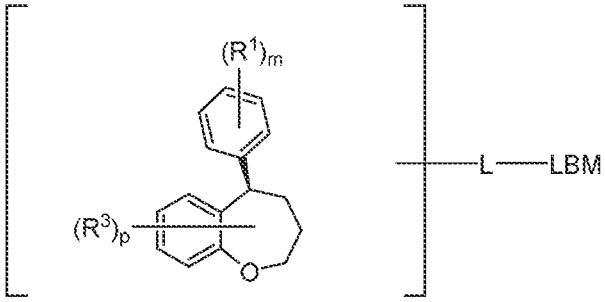
IV-h



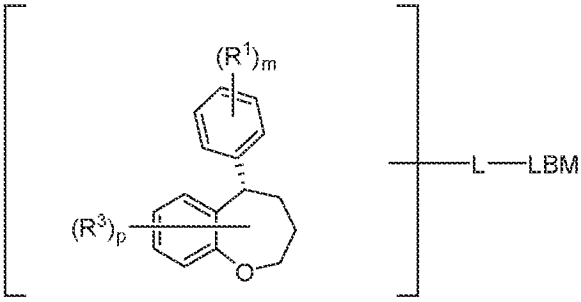
IV-i



IV-j



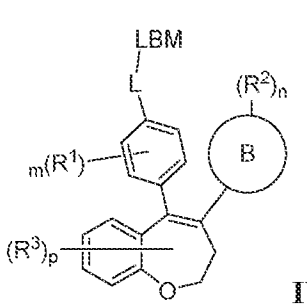
IV-k



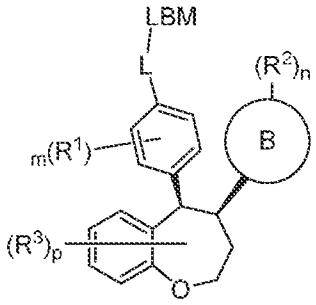
IV-l

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

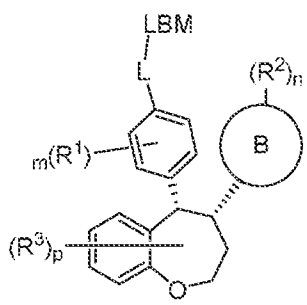
[0368] In some embodiments, the invention provides a compound of one of formulas **IV-g-1**, **IV-h-1**, **IV-i-1**, **IV-j-1**, **V-e**, or **IV-l-1**:



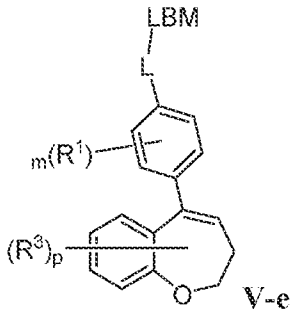
IV-g-1



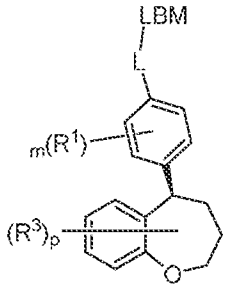
IV-h-1



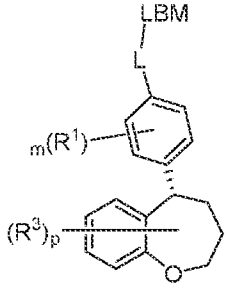
IV-i-1



V-e



IV-k-1



IV-l-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0369] In some embodiments, the compound is a compound of formula **IV-g-1**, or a pharmaceutically acceptable salt thereof.

[0370] In some embodiments, the compound is a compound of formula **IV-h-1**, or a pharmaceutically acceptable salt thereof.

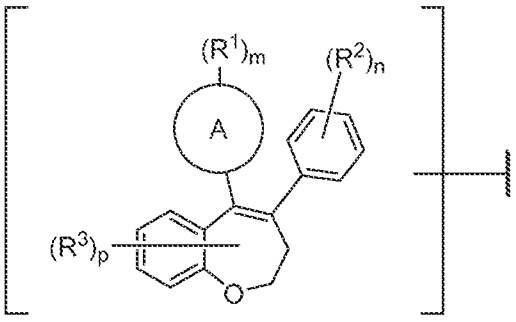
[0371] In some embodiments, the compound is a compound of formula **IV-i-1**, or a pharmaceutically acceptable salt thereof.

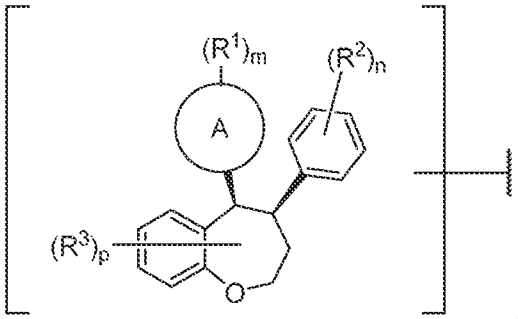
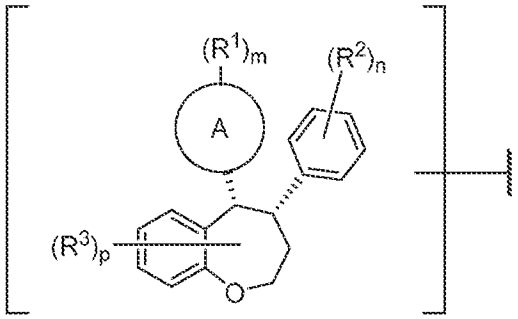
[0372] In some embodiments, the compound is a compound of formula **IV-j-1**, or a pharmaceutically acceptable salt thereof.

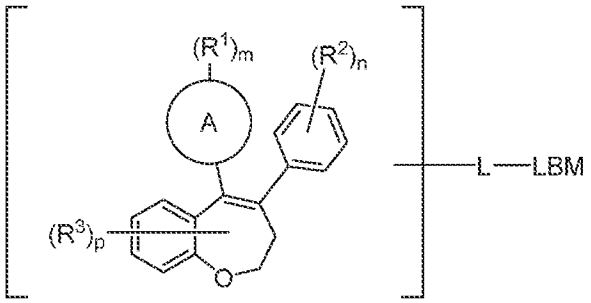
[0373] In some embodiments, the compound is a compound of formula **V-e**, or a pharmaceutically acceptable salt thereof.

[0374] In some embodiments, the compound is a compound of formula **IV-l-1**, or a pharmaceutically acceptable salt thereof.

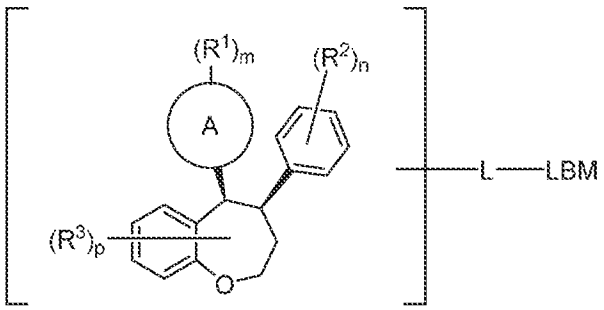
[0375] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

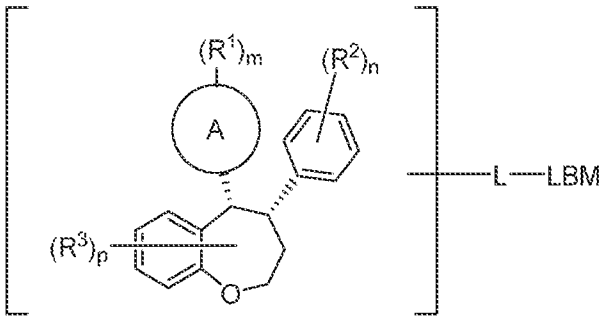
 , or  , thereby forming a compound of one of formulas **IV-m**, **IV-n**, or **IV-o**, respectively:



IV-m



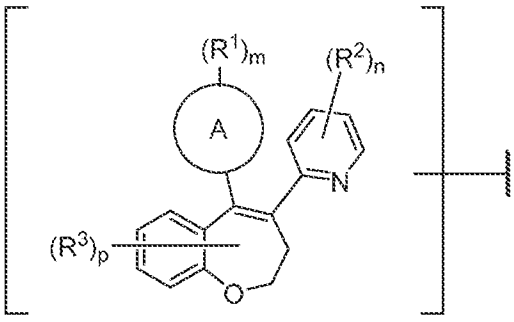
IV-n

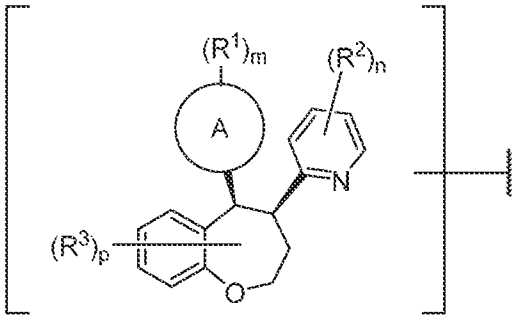
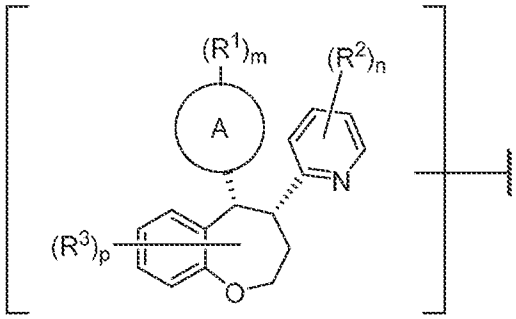


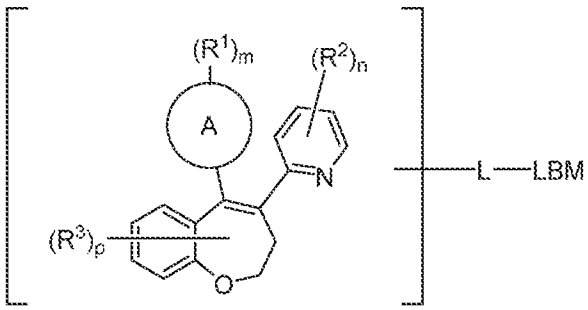
IV-o

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

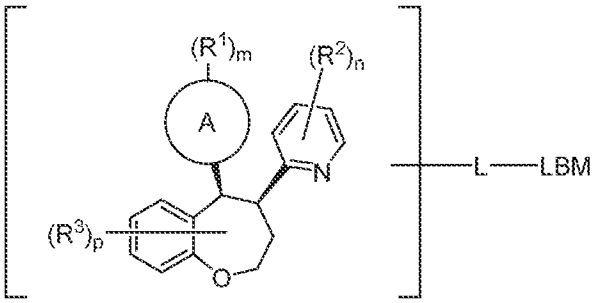
[0376] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

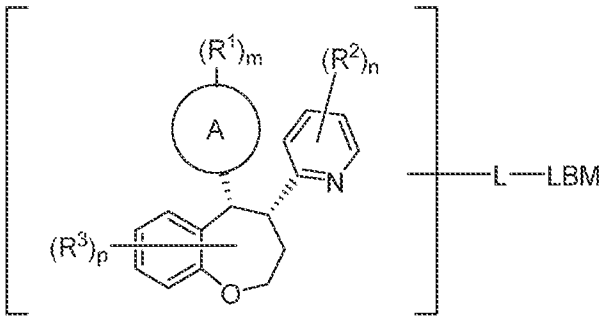
 , or  , thereby forming a compound of one of formulas **IV-p**, **IV-q**, or **IV-r**, respectively:



IV-p



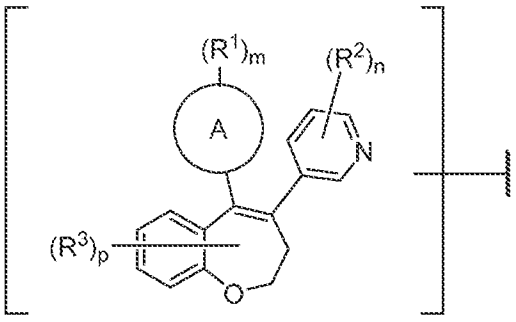
IV-q

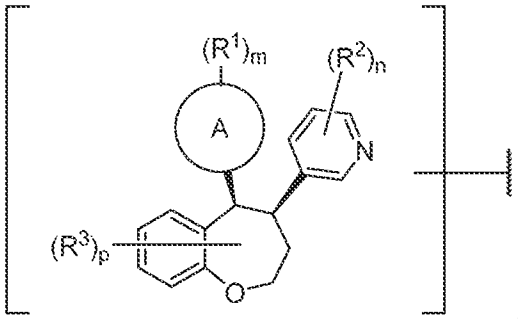
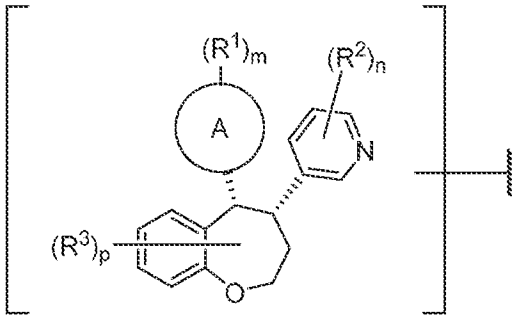


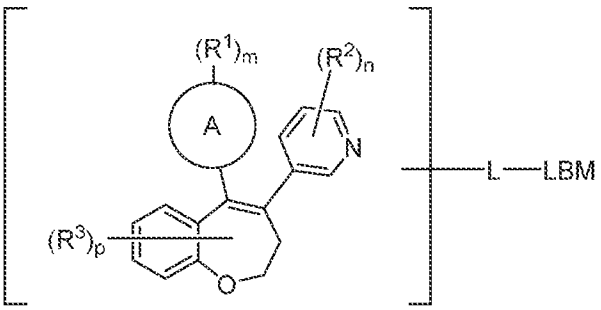
IV-r

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

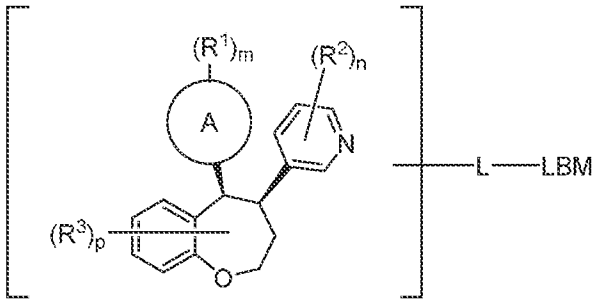
[0377] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

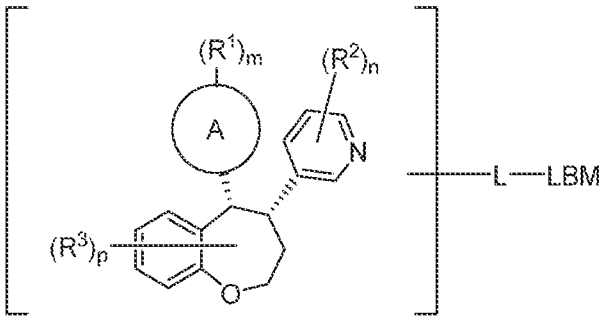
 , or  , thereby forming a compound of one of formulas **IV-s**, **IV-t**, or **IV-u**, respectively:



IV-s



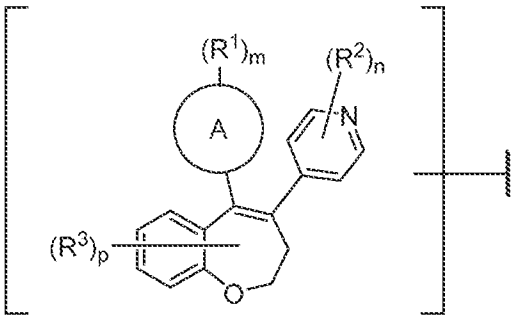
IV-t

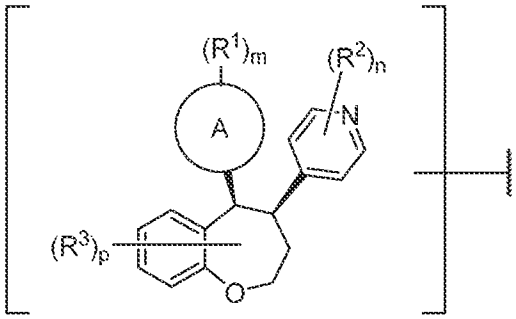
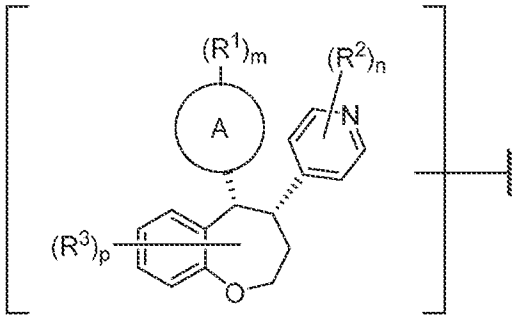


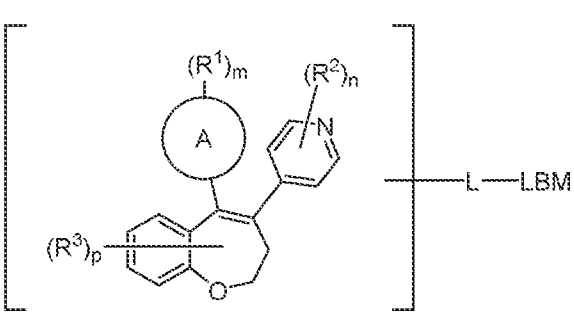
IV-u

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

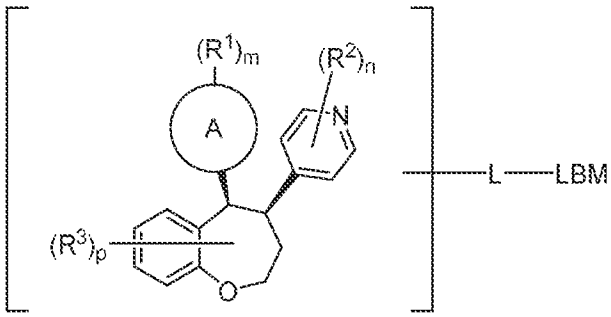
[0378] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

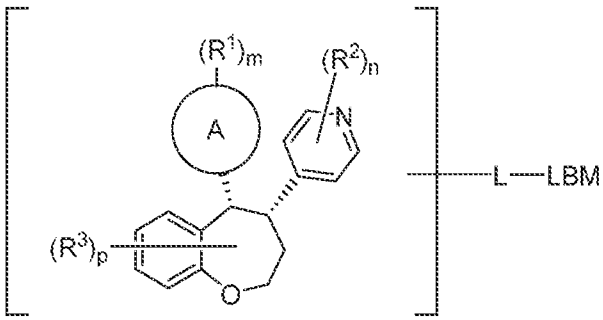
 , or  , thereby forming a compound of one of formulas **IV-v**, **IV-w**, or **IV-x**, respectively:



IV-v



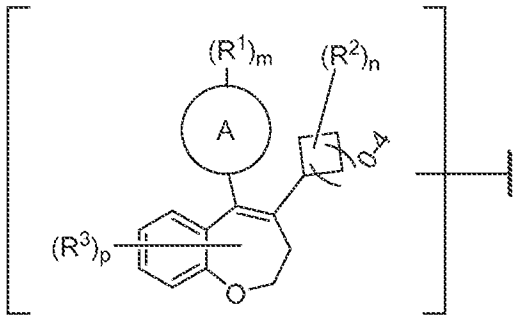
IV-w

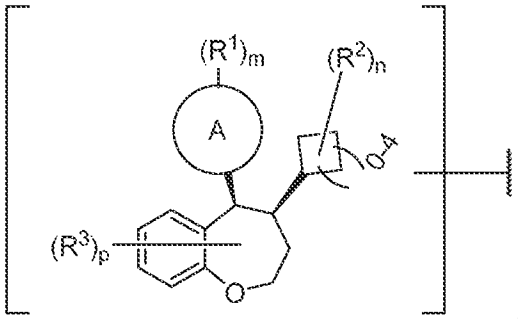
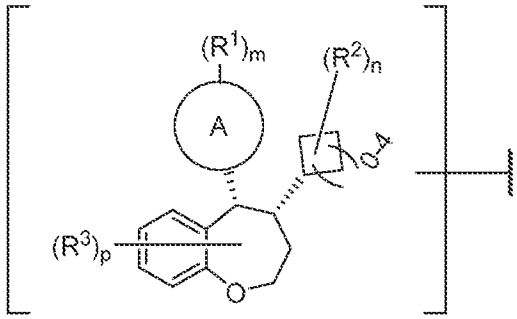


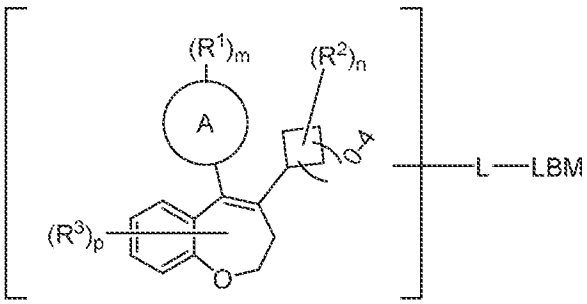
IV-x

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

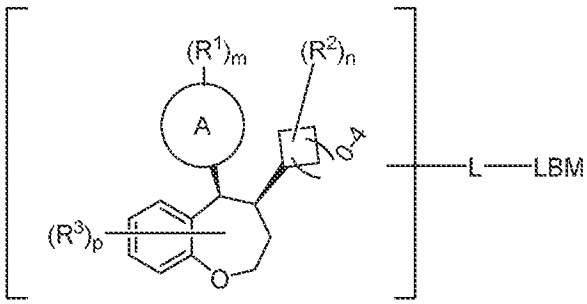
[0379] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

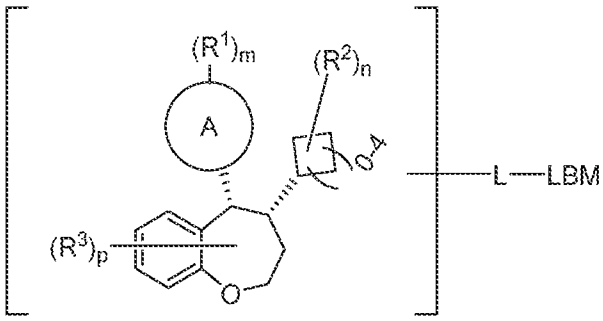
 , or  , thereby forming a compound of one of formulas **IV-y**, **IV-z**, or **IV-aa**, respectively:



IV-y



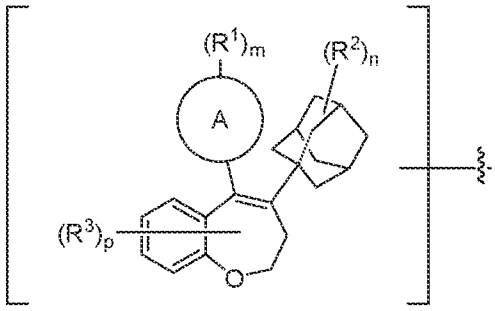
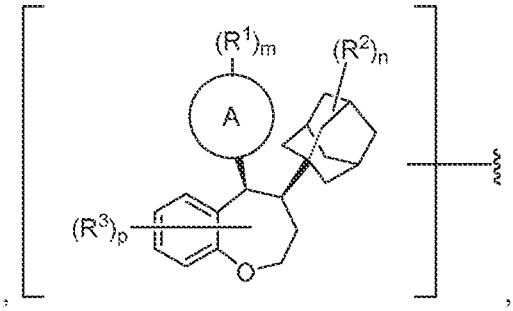
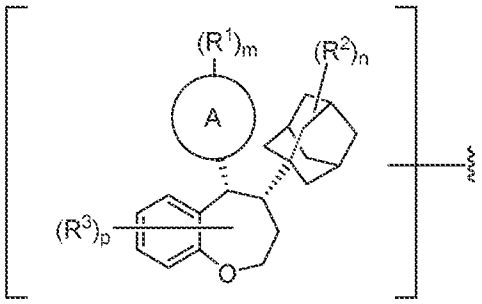
IV-z

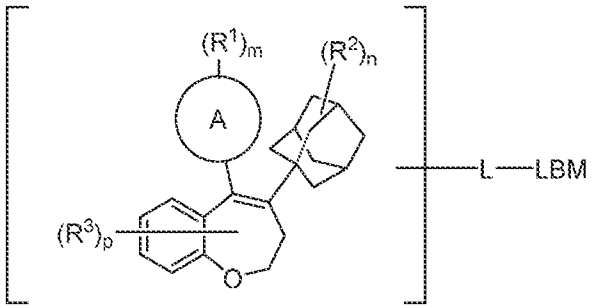


IV-aa

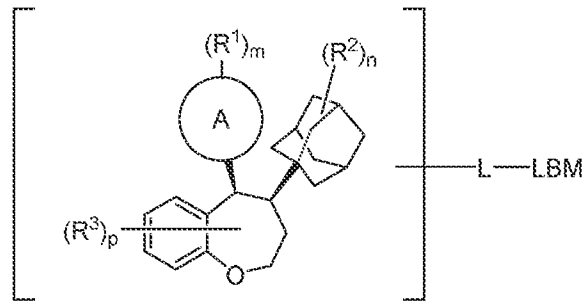
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0380] In certain embodiments, the present invention provides a compound of formula **I-a**,

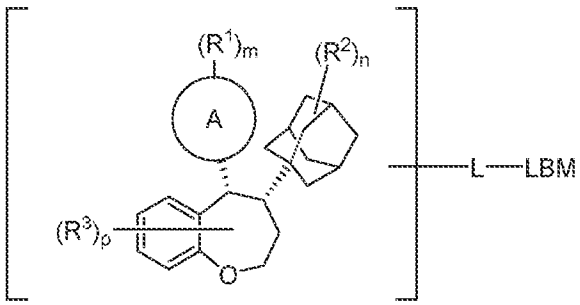
wherein ERBM is  ,  ,  , or , thereby forming a compound of one of formulas **IV-bb**, **IV-cc** or **IV-dd**, respectively:



IV-bb

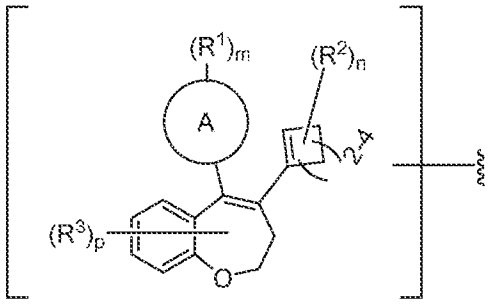
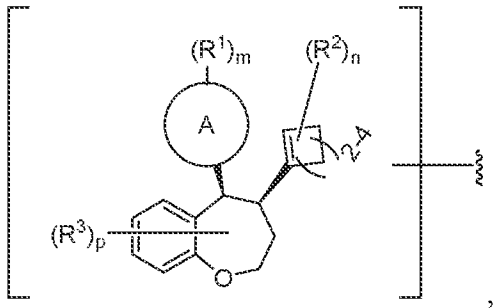
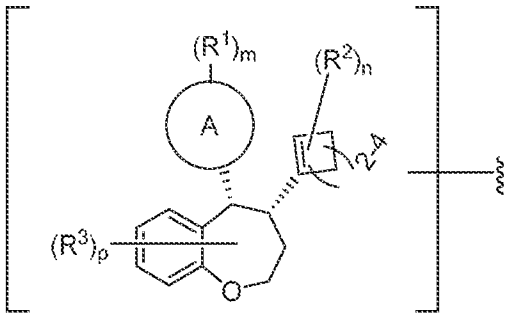


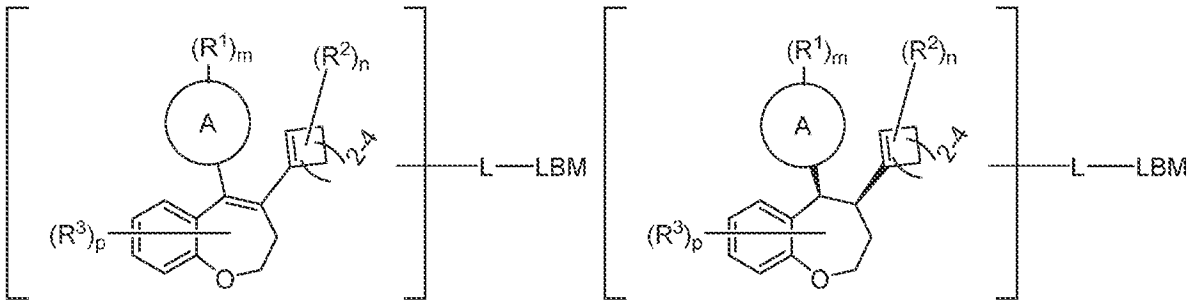
IV-cc



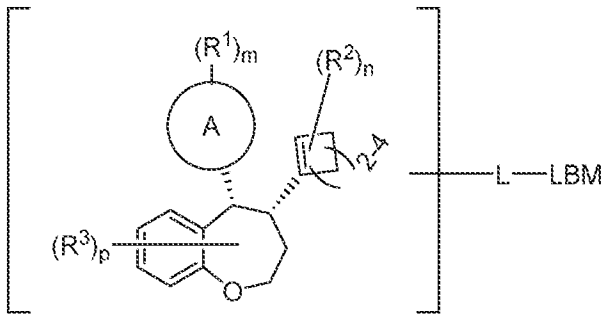
IV-dd

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0381] In certain embodiments, the present invention provides a compound of formula **I-a**, wherein ERBM is  ,  ,  , thereby forming a compound of one of formulas **IV-ee**, **IV-ff**, or **IV-gg**, respectively:



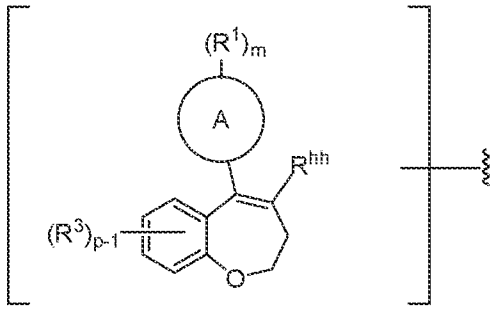
IV-ee **IV-ff**

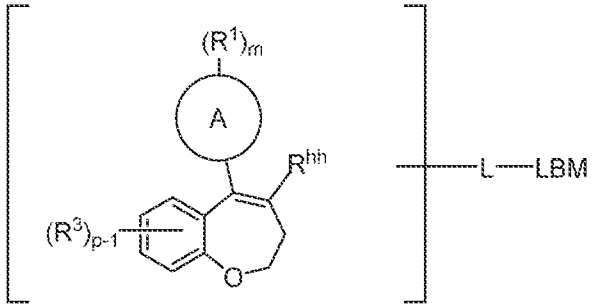


IV-gg

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0382] In certain embodiments, the present invention provides a compound of formula **I-a**,

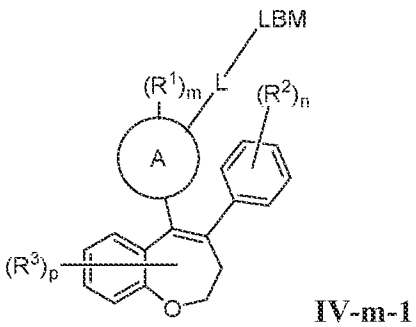
wherein ERBM is  , thereby forming a compound of formula **IV-hh**:



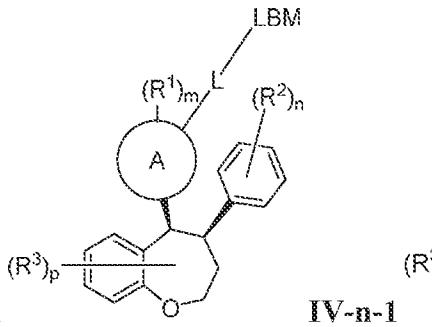
IV-hh

or a pharmaceutically acceptable salt thereof, wherein wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, R^{hh} and LBM is as defined in embodiments and classes and subclasses herein.

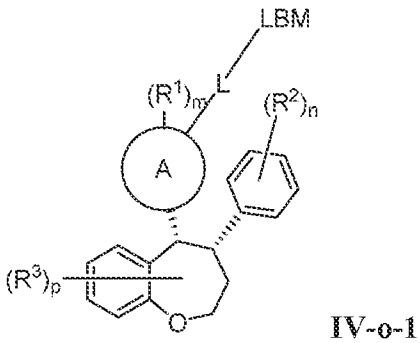
[0383] In some embodiments, the invention provides a compound of one of formulas **IV-m-1**, **IV-n-1**, **IV-o-1**, **IV-p-1**, **IV-q-1**, **IV-r-1**, **IV-s-1**, **IV-t-1**, **IV-u-1**, **IV-v-1**, **IV-w-1**, **IV-x-1**, **IV-y-1**, **IV-z-1**, or **IV-aa-1**:



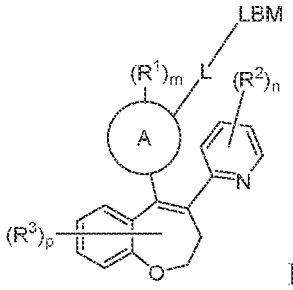
IV-m-1



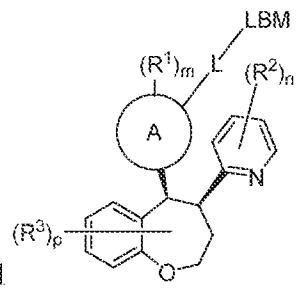
IV-n-1



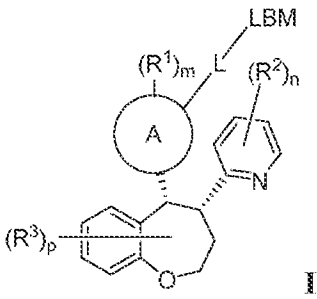
IV-o-1



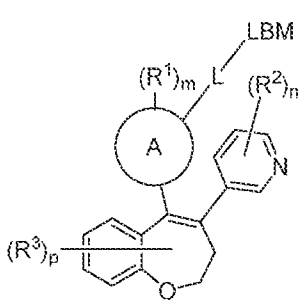
IV-p-1



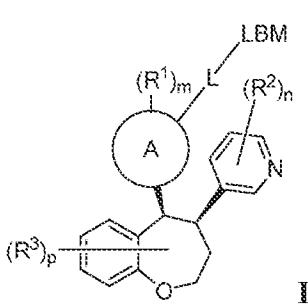
IV-q-1



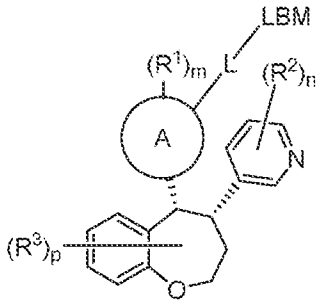
IV-r-1



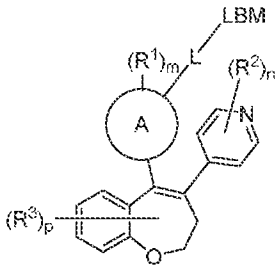
IV-s-1



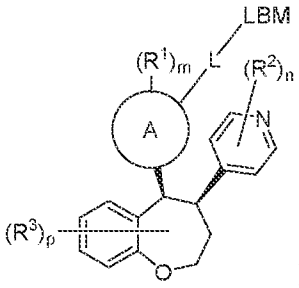
IV-t-1



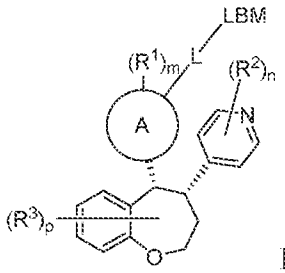
IV-u-1



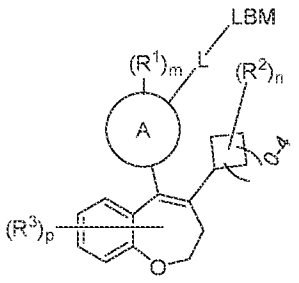
IV-v-1



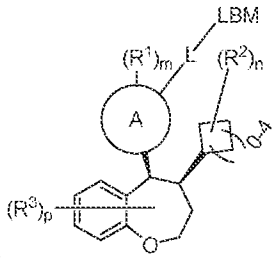
IV-w-1



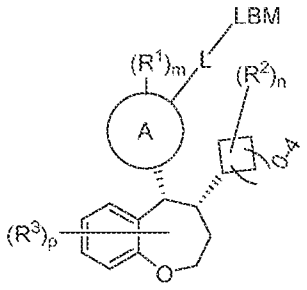
IV-x-1



IV-y-1



IV-z-1



IV-aa-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0384] In some embodiments, the compound is a compound of formula **IV-m-1**, or a pharmaceutically acceptable salt thereof.

[0385] In some embodiments, the compound is a compound of formula **IV-n-1**, or a pharmaceutically acceptable salt thereof.

[0386] In some embodiments, the compound is a compound of formula **IV-o-1**, or a pharmaceutically acceptable salt thereof.

[0387] In some embodiments, the compound is a compound of formula **IV-p-1**, or a pharmaceutically acceptable salt thereof.

[0388] In some embodiments, the compound is a compound of formula **IV-q-1**, or a pharmaceutically acceptable salt thereof.

[0389] In some embodiments, the compound is a compound of formula **IV-r-1**, or a pharmaceutically acceptable salt thereof.

[0390] In some embodiments, the compound is a compound of formula **IV-s-1**, or a pharmaceutically acceptable salt thereof.

[0391] In some embodiments, the compound is a compound of formula **IV-t-1**, or a pharmaceutically acceptable salt thereof.

[0392] In some embodiments, the compound is a compound of formula **IV-u-1** or a pharmaceutically acceptable salt thereof.

[0393] In some embodiments, the compound is a compound of formula **IV-v-1**, or a pharmaceutically acceptable salt thereof.

[0394] In some embodiments, the compound is a compound of formula **IV-w-1**, or a pharmaceutically acceptable salt thereof.

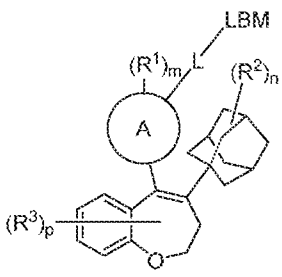
[0395] In some embodiments, the compound is a compound of formula **IV-x-1**, or a pharmaceutically acceptable salt thereof.

[0396] In some embodiments, the compound is a compound of formula **IV-y-1**, or a pharmaceutically acceptable salt thereof.

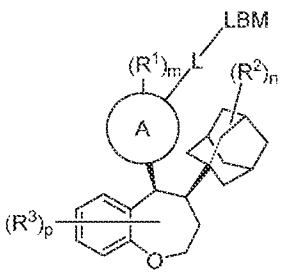
[0397] In some embodiments, the compound is a compound of formula **IV-z-1**, or a pharmaceutically acceptable salt thereof.

[0398] In some embodiments, the compound is a compound of formula **IV-aa-1**, or a pharmaceutically acceptable salt thereof.

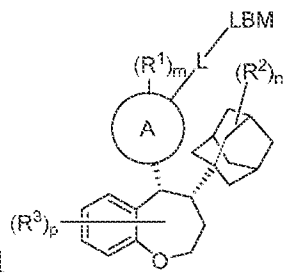
[0399] In some embodiments, the the invention provides a compound of one of formulas **IV-bb-1**, **IV-cc-1**, **IV-dd-1**, **IV-ee-1**, **IV-ff-1** or **IV-gg-1**:



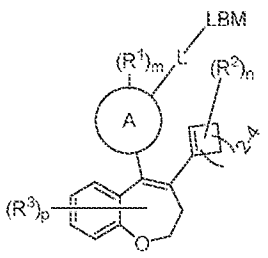
IV-bb-1



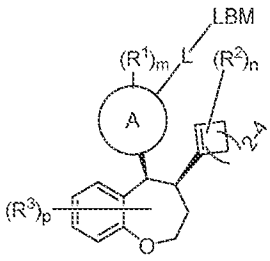
IV-cc-1



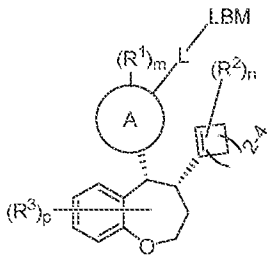
IV-dd-1



IV-ee-1



IV-ff-1



IV-gg-1

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0400] In some embodiments, the compound is a compound of formula **IV-bb-1**, or a pharmaceutically acceptable salt thereof.

[0401] In some embodiments, the compound is a compound of formula **IV-cc-1**, or a pharmaceutically acceptable salt thereof.

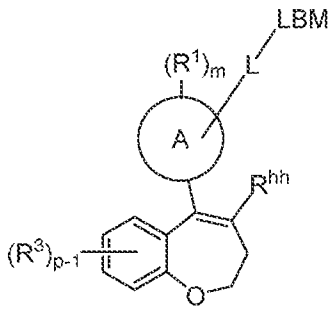
[0402] In some embodiments, the compound is a compound of formula **IV-dd-1**, or a pharmaceutically acceptable salt thereof.

[0403] In some embodiments, the compound is a compound of formula **IV-ee-1**, or a pharmaceutically acceptable salt thereof.

[0404] In some embodiments, the compound is a compound of formula **IV-ff-1**, or a pharmaceutically acceptable salt thereof.

[0405] In some embodiments, the compound is a compound of formula **IV-gg-1**, or a pharmaceutically acceptable salt thereof.

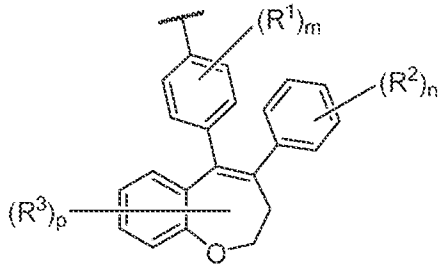
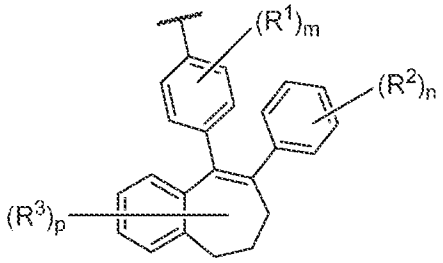
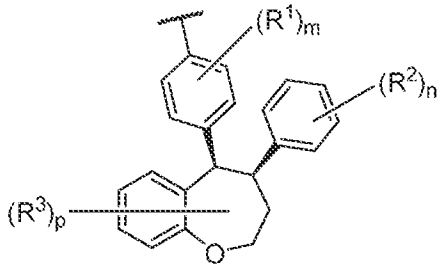
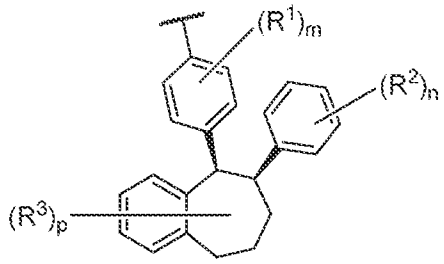
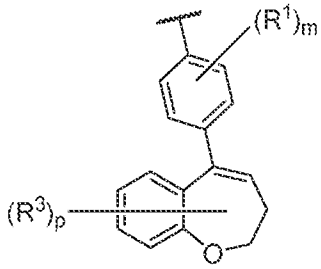
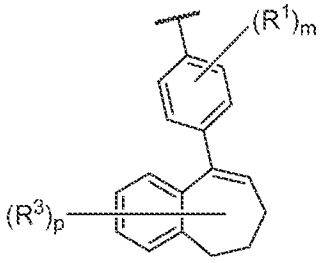
[0406] In some embodiments, the invention provides a compound of formula **IV-hh-1**:

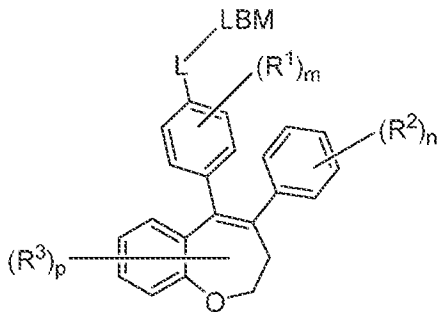


IV-hh-1

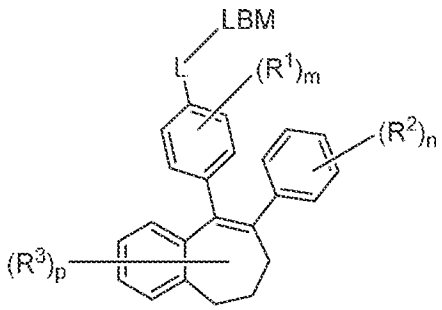
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, m, n, p, L, R^{hh} and LBM is as defined in embodiments and classes and subclasses herein.

[0407] In certain embodiments, the present invention provides a compound of formula **I-a**,

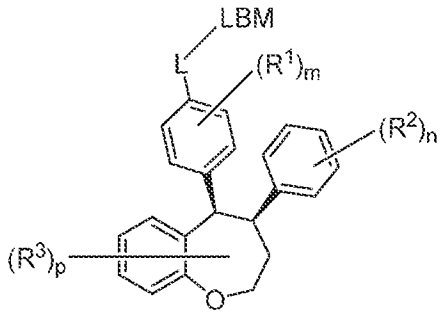
wherein ERBM is  ,  ,  ,  ,  , or  , thereby forming a compound of one of formulas **V-a**, **V-b**, **V-c**, **V-d**, **V-e**, or **V-f**, respectively:



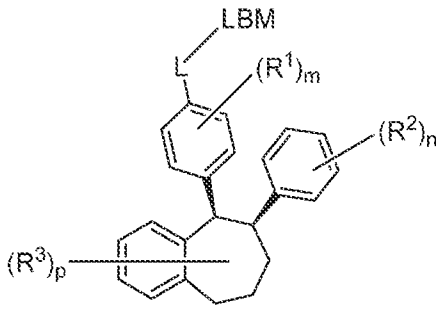
V-a



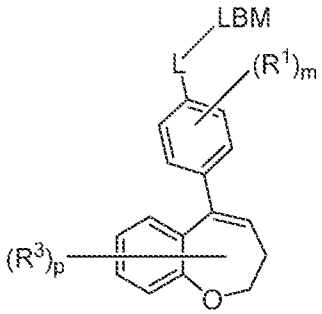
V-b



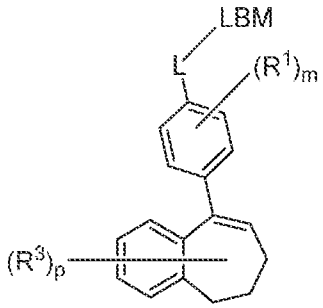
V-c



V-d



V-e



V-f

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

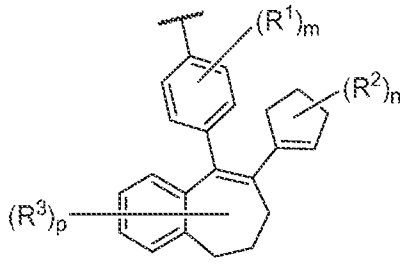
[0408] In some embodiments, the compound is a compound of formula **V-a**, or a pharmaceutically acceptable salt thereof.

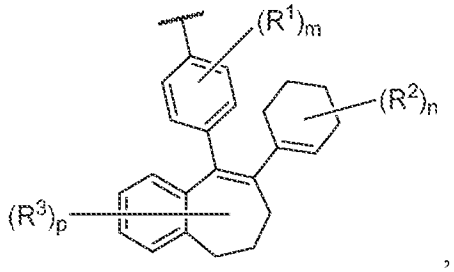
[0409] In some embodiments, the compound is a compound of formula **V-b**, or a pharmaceutically acceptable salt thereof.

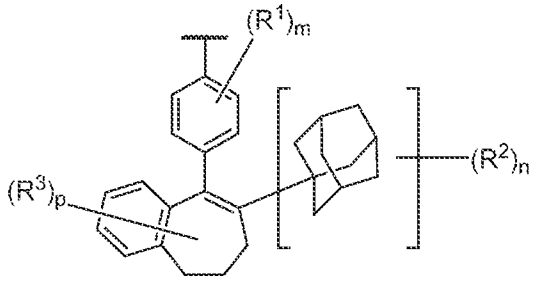
[0410] In some embodiments, the compound is a compound of formula **V-c**, or a pharmaceutically acceptable salt thereof.

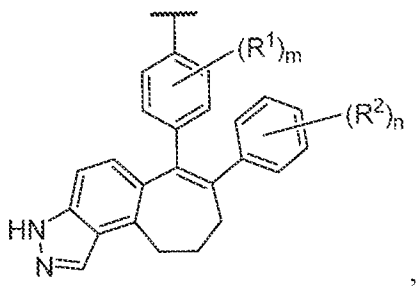
[0411] In some embodiments, the compound is a compound of formula **V-d**, or a pharmaceutically acceptable salt thereof.

[0412] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is 

, 

, 

, 

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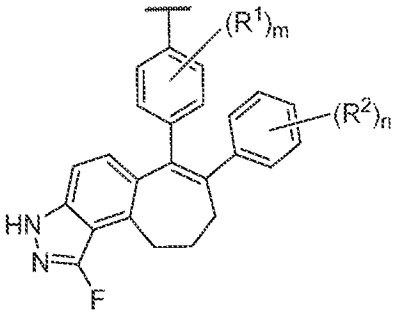

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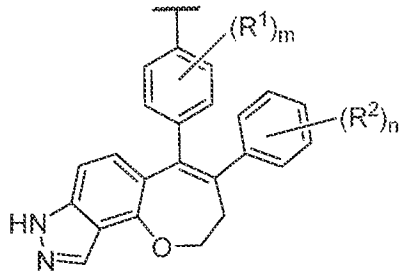

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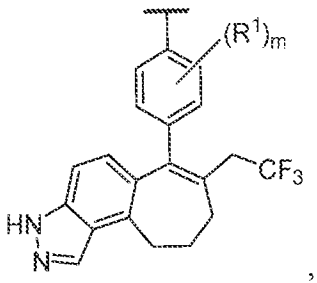
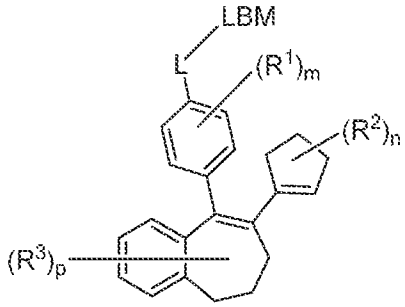
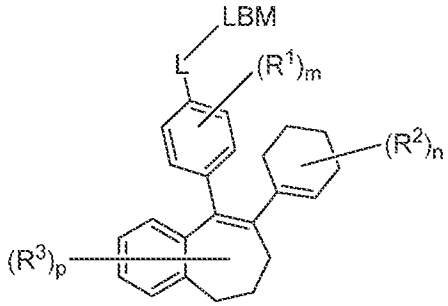


,

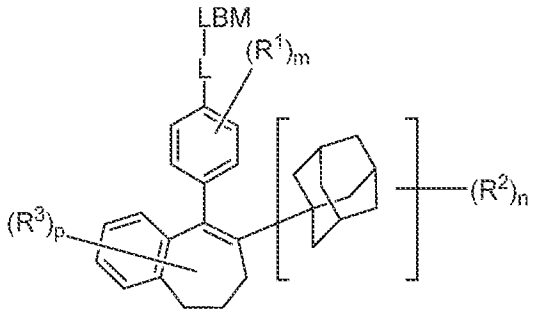
thereby forming a compound of one of formulas **V-g**, **V-h**, **V-i**, **V-j**, **V-k**, **V-l**, or **V-m** respectively:



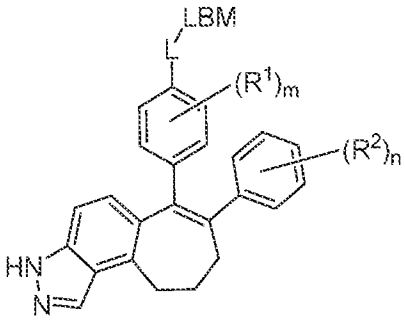
V-g



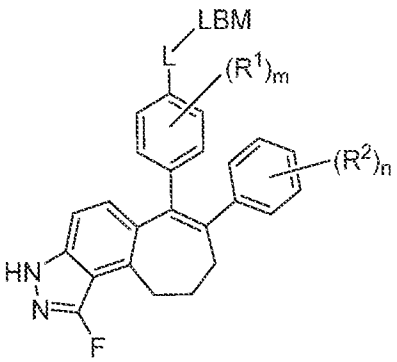
V-h



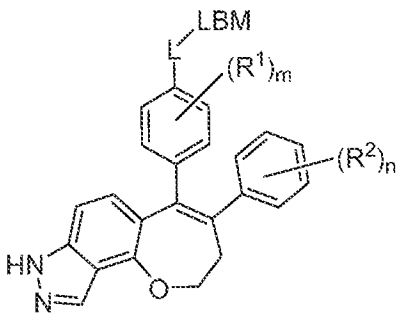
V-i



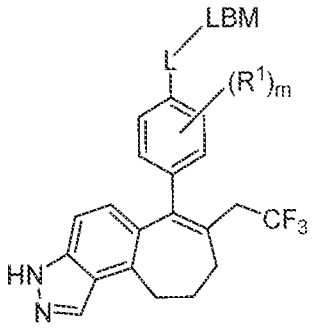
V-j



V-k



V-l



V-m

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0413] In some embodiments, the compound is a compound of formula **V-g**, or a pharmaceutically acceptable salt thereof.

[0414] In some embodiments, the compound is a compound of formula **V-h**, or a pharmaceutically acceptable salt thereof.

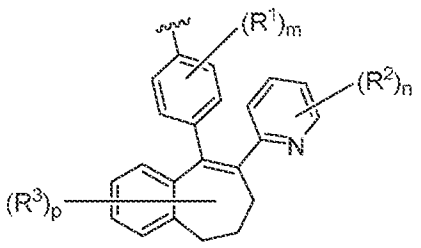
[0415] In some embodiments, the compound is a compound of formula **V-i**, or a pharmaceutically acceptable salt thereof.

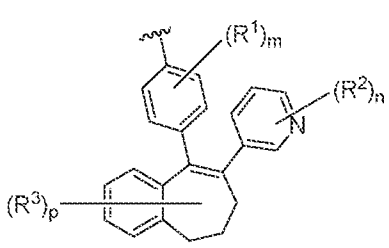
[0416] In some embodiments, the compound is a compound of formula **V-j**, or a pharmaceutically acceptable salt thereof.

[0417] In some embodiments, the compound is a compound of formula **V-k**, or a pharmaceutically acceptable salt thereof.

[0418] In some embodiments, the compound is a compound of formula **V-l**, or a pharmaceutically acceptable salt thereof.

[0419] In certain embodiments, the compound is a compound of formula **V-m**, or a pharmaceutically acceptable salt thereof.

[0420] In certain embodiments, the present invention provides a compound of formula **I-a**, wherein ERBM is 

, 

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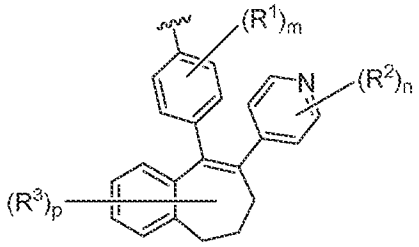
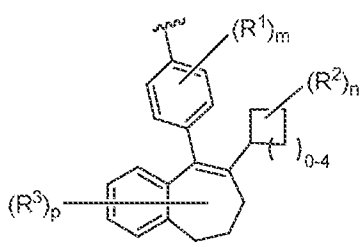
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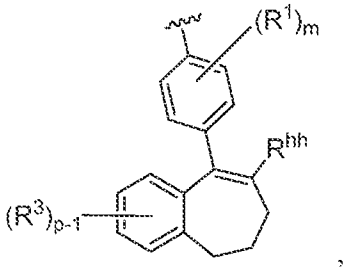
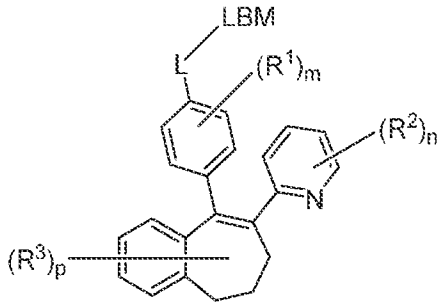
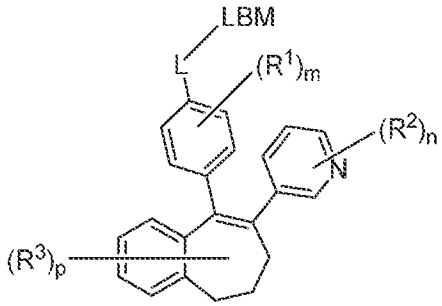


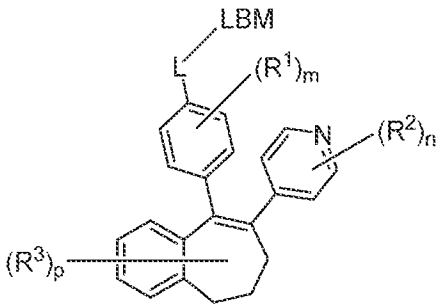
thereby forming a compound of one of formulas **V-n**, **V-o**, **V-p**, **V-q** or **V-r**, respectively:



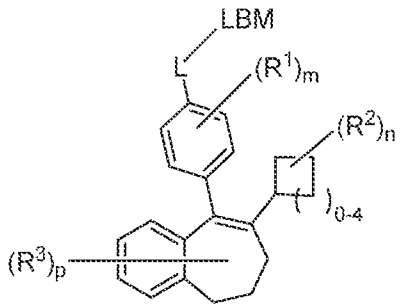
V-n



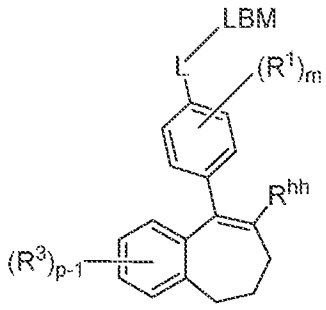
V-o



V-p



V-q



V-r

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, m, n, L, R^{hh}, and LBM is as defined in embodiments and classes and subclasses herein.

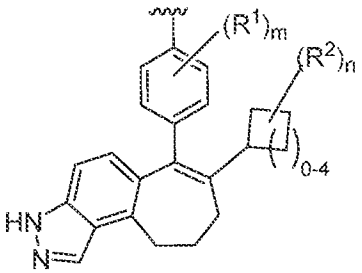
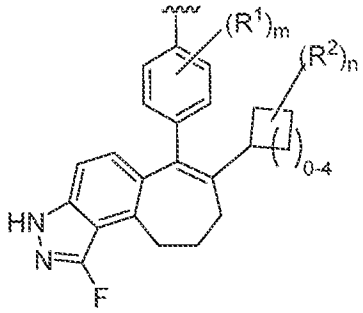
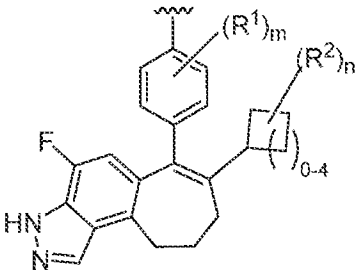
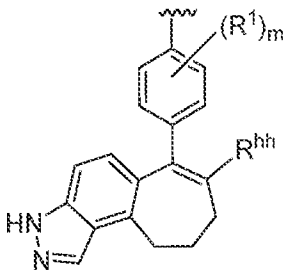
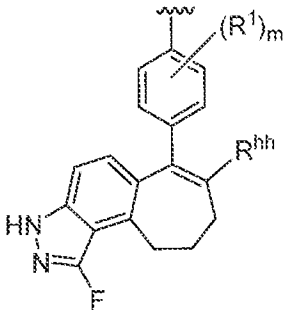
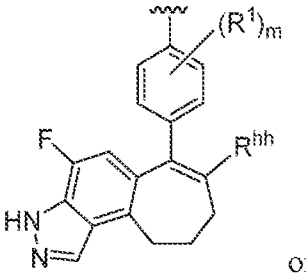
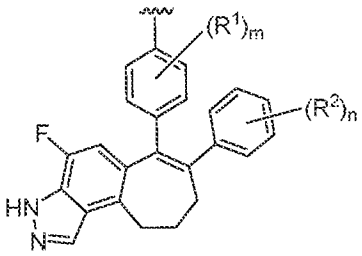
[0421] In some embodiments, the compound is a compound of formula **V-n**, or a pharmaceutically acceptable salt thereof.

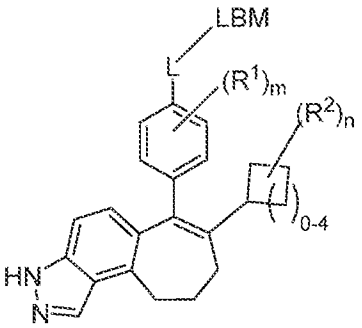
[0422] In some embodiments, the compound is a compound of formula **V-o**, or a pharmaceutically acceptable salt thereof.

[0423] In some embodiments, the compound is a compound of formula **V-p**, or a pharmaceutically acceptable salt thereof.

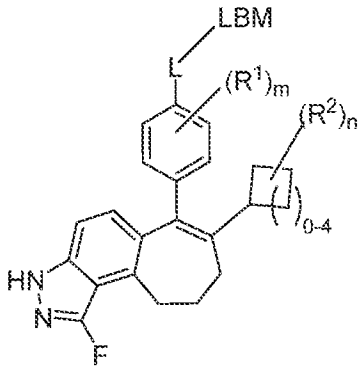
[0424] In some embodiments, the compound is a compound of formula **V-q**, or a pharmaceutically acceptable salt thereof.

[0425] In some embodiments, the compound is a compound of formula **V-r**, or a pharmaceutically acceptable salt thereof.

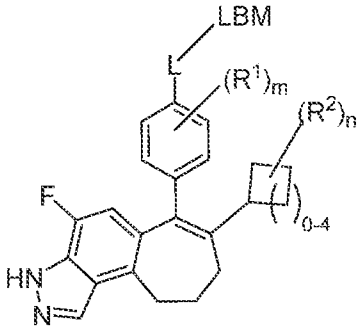
[0426] In certain embodiments, the present invention provides a compound of formula **I-a**, wherein ERBM is  ,  ,  ,  ,  ,  or  , thereby forming a compound of one of formulas **V-s**, **V-t**, **V-u**, **V-v**, **V-w**, **V-x** or **V-y**, respectively:



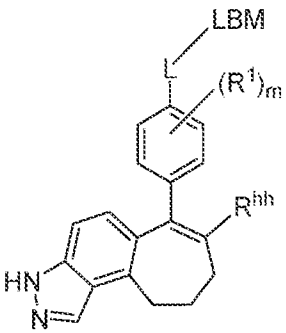
V-s



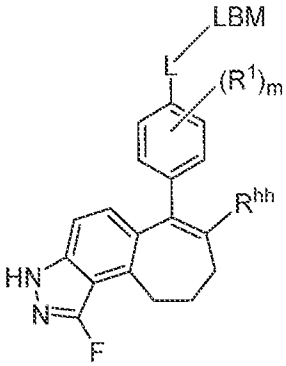
V-t



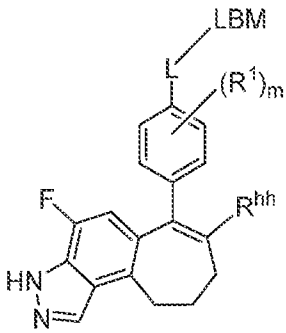
V-u



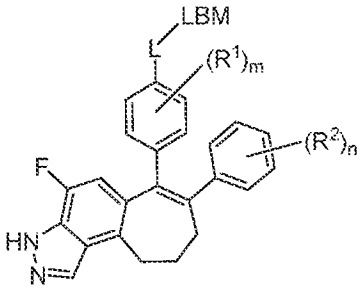
V-v



V-w



V-x



V-y

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, m, n, L, R^{hh}, and LBM is as defined in embodiments and classes and subclasses herein.

[0427] In some embodiments, the compound is a compound of formula **V-s**, or a pharmaceutically acceptable salt thereof.

[0428] In certain embodiments, the compound is a compound of formula **V-t**, or a pharmaceutically acceptable salt thereof.

[0429] In certain embodiments, the compound is a compound of formula **V-u**, or a pharmaceutically acceptable salt thereof.

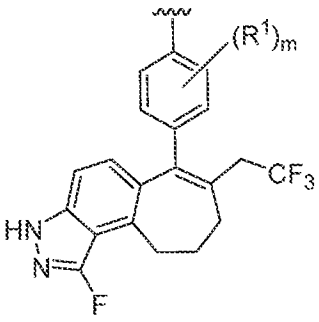
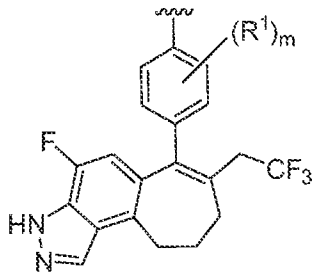
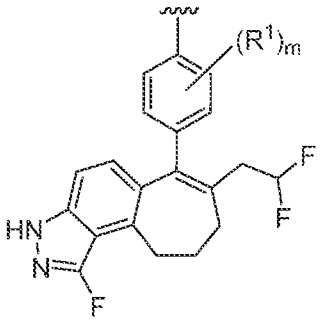
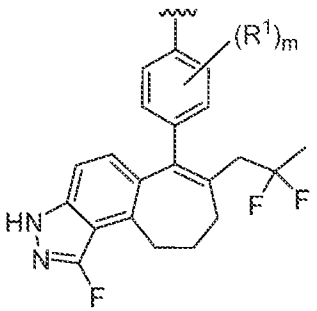
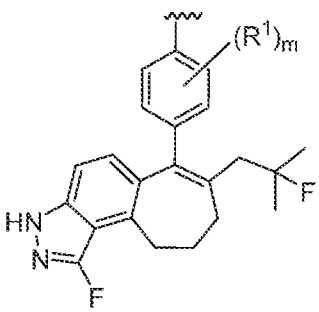
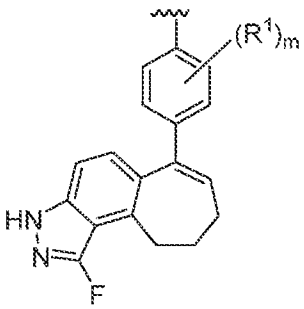
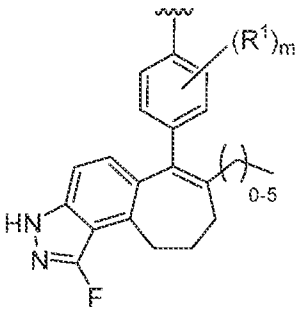
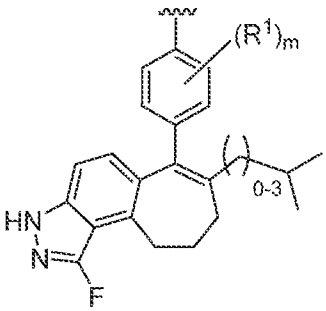
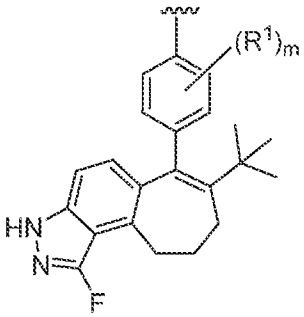
[0430] \In some embodiments, the compound is a compound of formula **V-v**, or a pharmaceutically acceptable salt thereof.

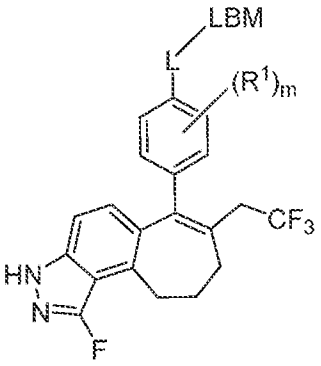
[0431] In certain embodiments, the compound is a compound of formula **V-w**, or a pharmaceutically acceptable salt thereof.

[0432] In certain embodiments, the compound is a compound of formula **V-x**, or a pharmaceutically acceptable salt thereof.

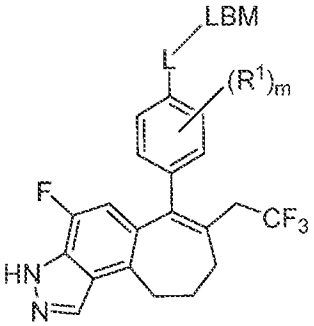
[0433] In certain embodiments, the compound is a compound of formula **V-y**, or a pharmaceutically acceptable salt thereof.

[0434] In certain embodiments, the present invention provides a compound of formula **I-a**,

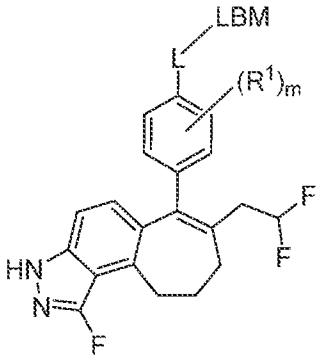
wherein ERBM is  ,  ,  ,  ,  ,  ,  ,  , or  , thereby forming a compound of one of formulas **V-z**, **V-aa**, **V-bb**, **V-cc**, **V-dd**, **V-ee**, **V-ff**, **V-gg** or **V-hh**:



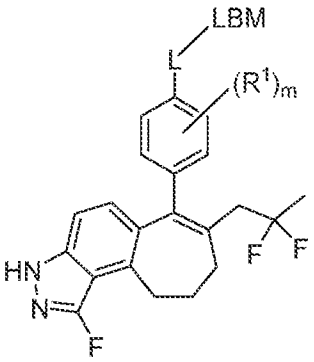
V-z



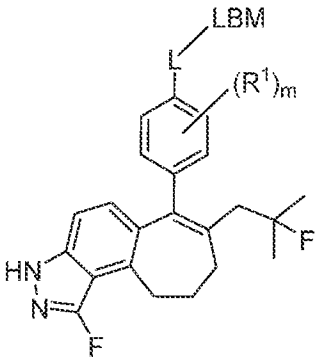
V-aa



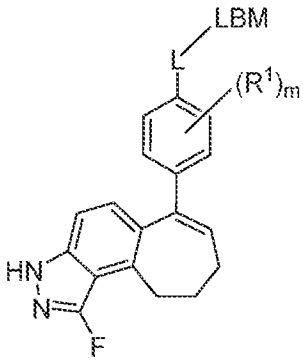
V-bb



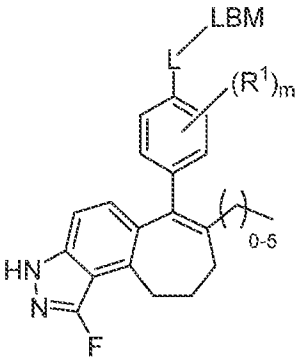
V-cc



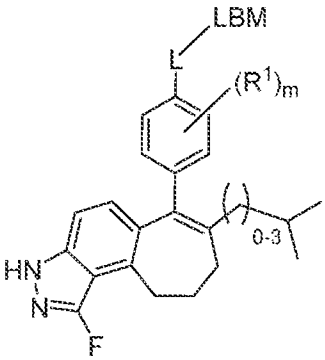
V-dd



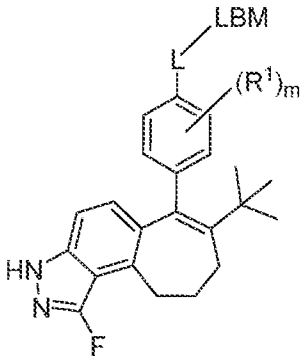
V-ee



V-ff



V-gg



V-hh

or a pharmaceutically acceptable salt thereof, wherein each of R^1, m, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0435] In some embodiments, the compound is a compound of formula **V-z**, or a pharmaceutically acceptable salt thereof.

[0436] In some embodiments, the compound is a compound of formula **V-aa**, or a pharmaceutically acceptable salt thereof.

[0437] In some embodiments, the compound is a compound of formula **V-bb** or a pharmaceutically acceptable salt thereof.

[0438] In some embodiments, the compound is a compound of formula **V-cc**, or a pharmaceutically acceptable salt thereof.

[0439] In some embodiments, the compound is a compound of formula **V-dd**, or a pharmaceutically acceptable salt thereof.

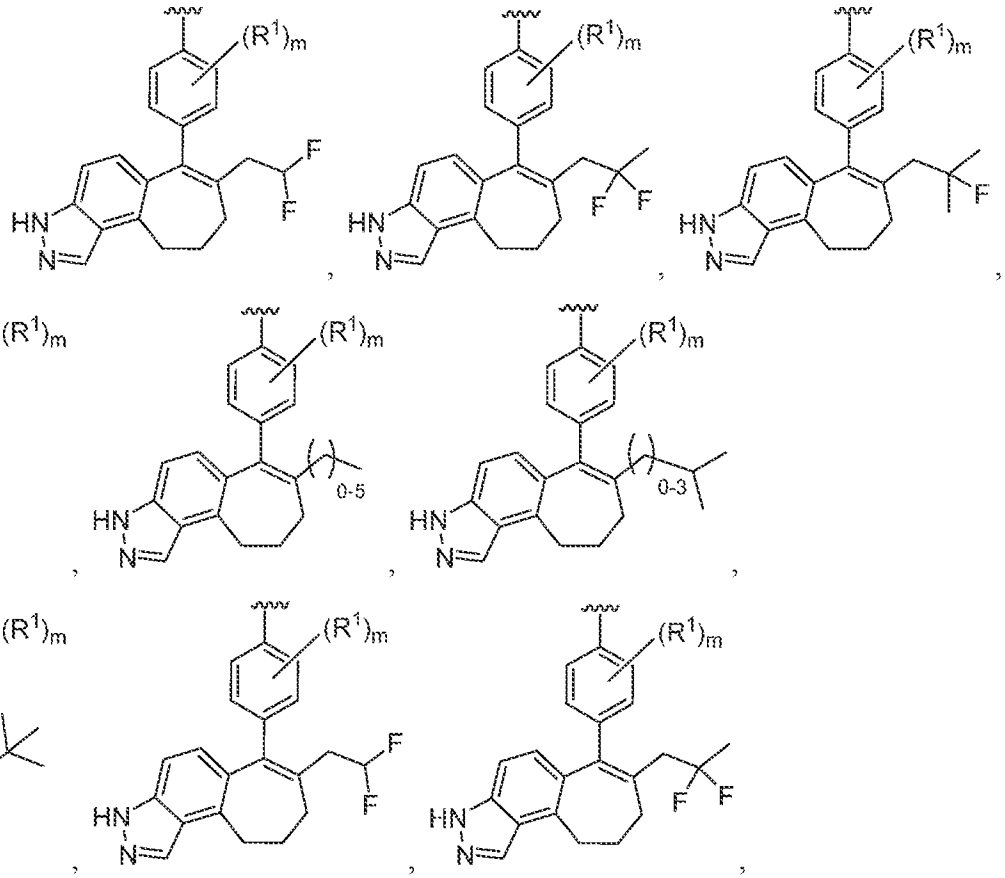
[0440] In some embodiments, the compound is a compound of formula **V-ee**, or a pharmaceutically acceptable salt thereof.

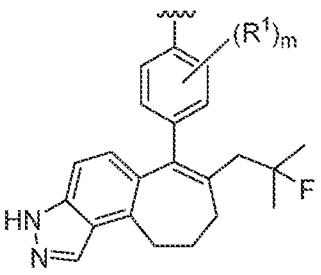
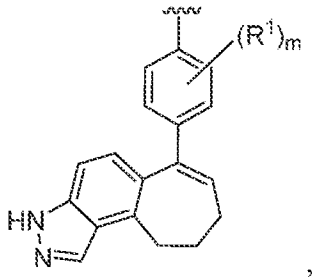
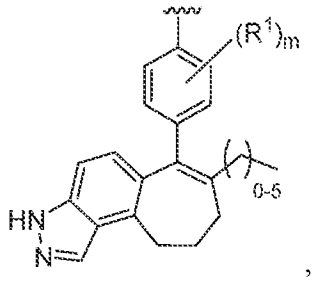
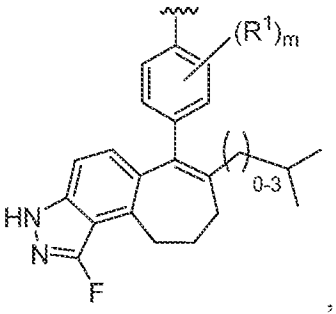
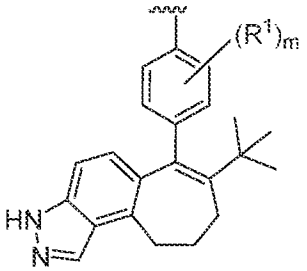
[0441] In some embodiments, the compound is a compound of formula **V-ff** or a pharmaceutically acceptable salt thereof.

[0442] In some embodiments, the compound is a compound of formula **V-gg**, or a pharmaceutically acceptable salt thereof.

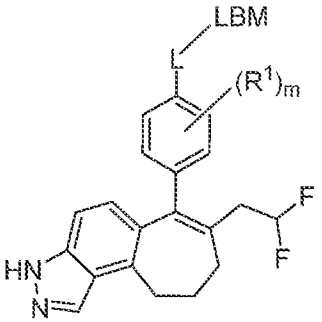
[0443] In some embodiments, the compound is a compound of formula **V-hh**, or a pharmaceutically acceptable salt thereof.

[0444] In certain embodiments, the present invention provides a compound of formula **I-a**,

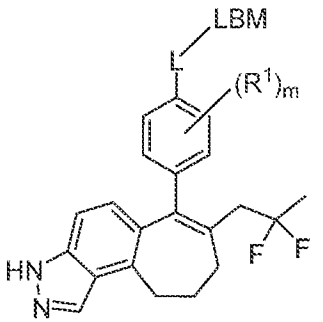
wherein ERBM is 

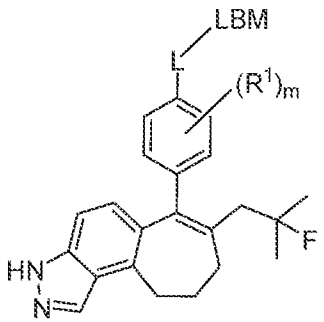
, thereby forming a compound of one of formulas **V-ii**, **V-jj**, **V-kk**, **V-ll**, **V-mm**, **V-nn**, **V-oo**, **V-pp**, **V-qq**, **V-rr**, **V-ss**, **V-tt**, **V-uu**, or **V-vv**:



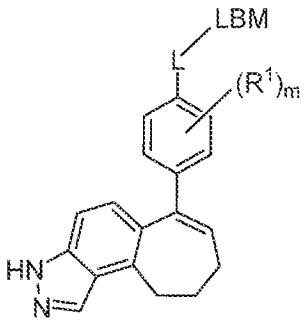
V-ii



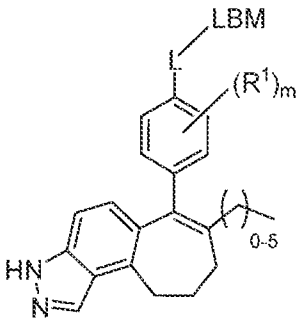
V-jj



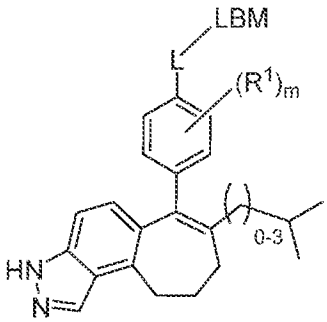
V-kk



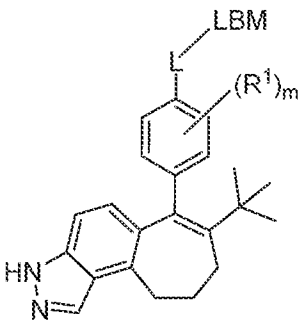
V-ll



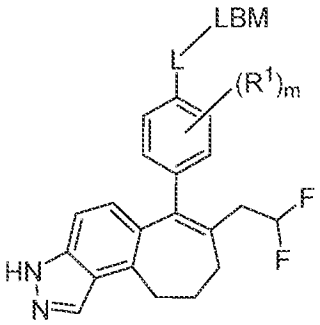
V-mm



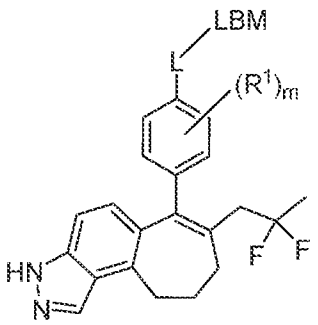
V-nn



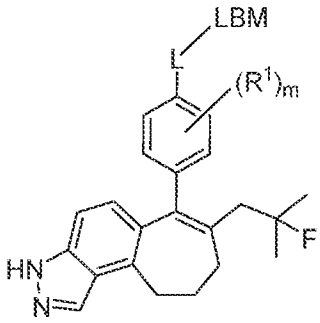
V-oo



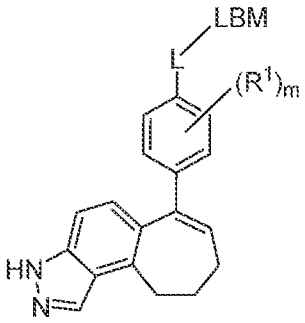
V-pp



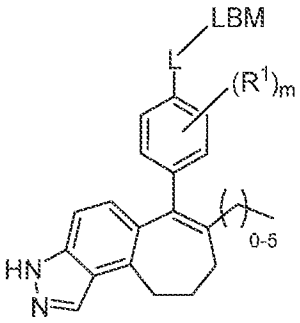
V-qq



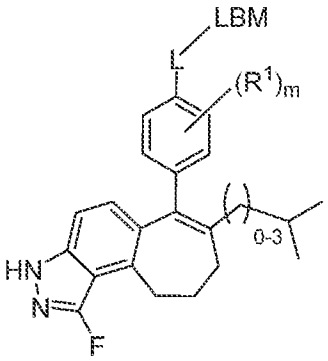
V-rr



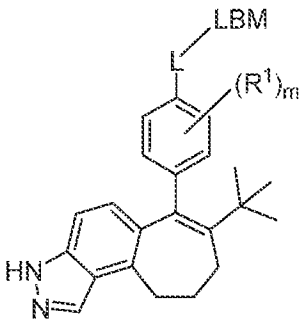
V-ss



V-tt



V-uu



V-vv

or a pharmaceutically acceptable salt thereofwherein each of R^1, m, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0445] In some embodiments, the compound is a compound of formula **V-ii**, or a pharmaceutically acceptable salt thereof.

[0446] In some embodiments, the compound is a compound of formula **V-jj**, or a pharmaceutically acceptable salt thereof.

[0447] In some embodiments, the compound is a compound of formula **V-kk** or a pharmaceutically acceptable salt thereof.

[0448] In some embodiments, the compound is a compound of formula **V-ll**, or a pharmaceutically acceptable salt thereof.

[0449] In some embodiments, the compound is a compound of formula **V-mm**, or a pharmaceutically acceptable salt thereof.

[0450] In some embodiments, the compound is a compound of formula **V-nn**, or a pharmaceutically acceptable salt thereof.

[0451] In some embodiments, the compound is a compound of formula **V-oo** or a pharmaceutically acceptable salt thereof.

[0452] In some embodiments, the compound is a compound of formula **V-pp**, or a pharmaceutically acceptable salt thereof.

[0453] In some embodiments, the compound is a compound of formula **V-qq**, or a pharmaceutically acceptable salt thereof.

[0454] In some embodiments, the compound is a compound of formula **V-rr**, or a pharmaceutically acceptable salt thereof.

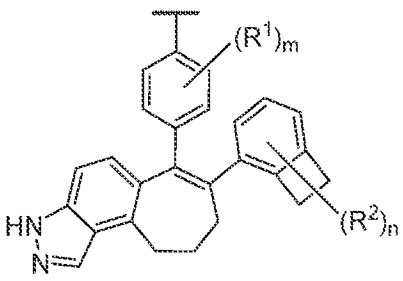
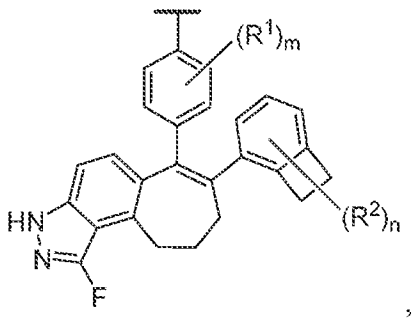
[0455] In some embodiments, the compound is a compound of formula **V-ss**, or a pharmaceutically acceptable salt thereof.

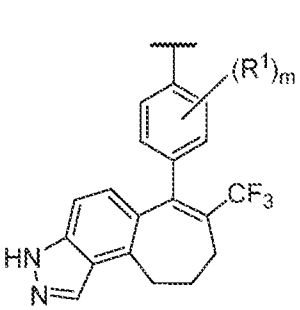
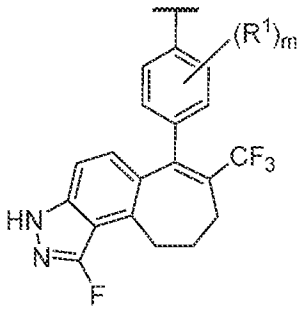
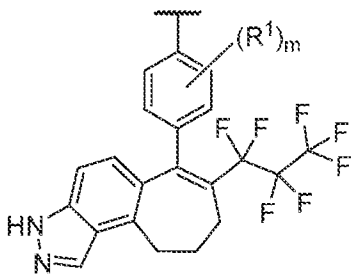
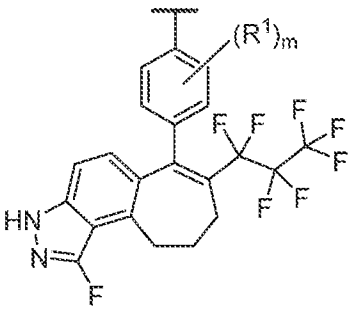
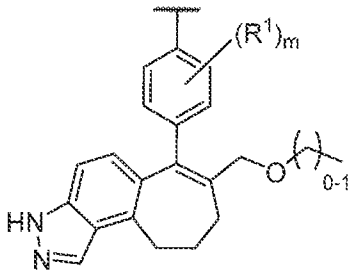
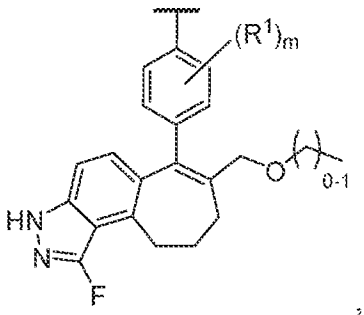
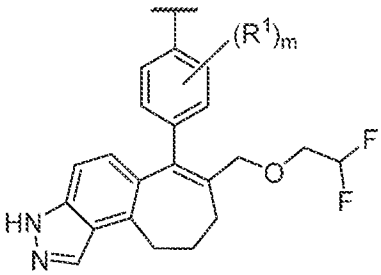
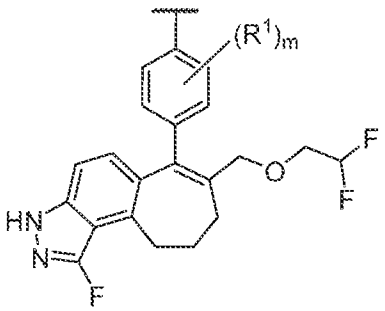
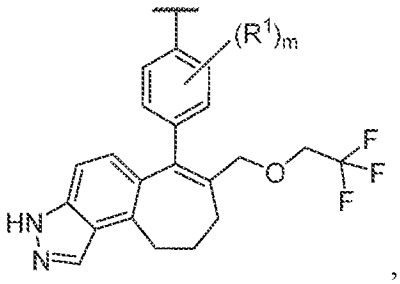
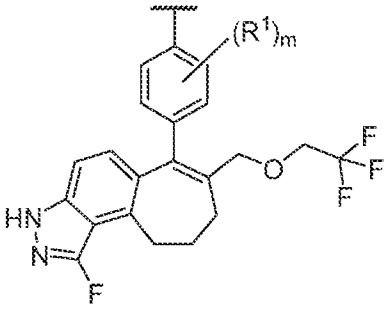
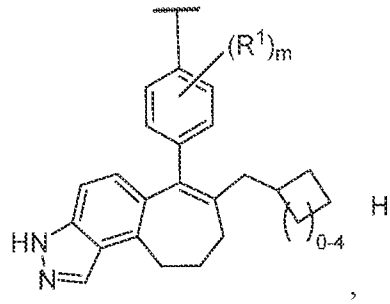
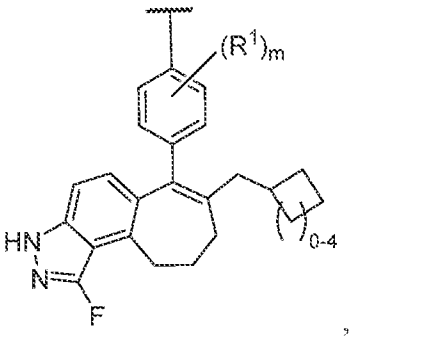
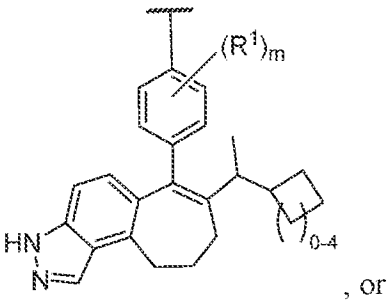
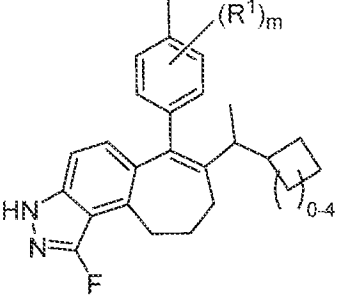
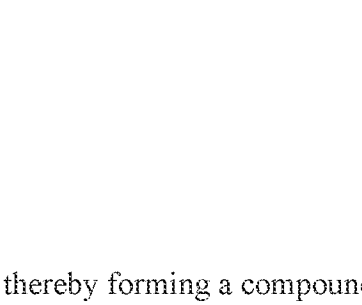
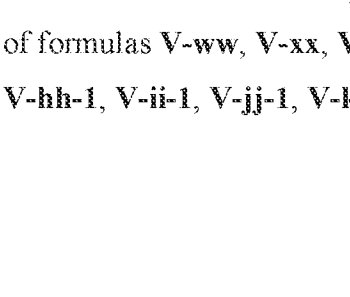
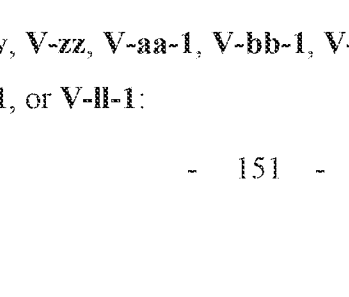
[0456] In some embodiments, the compound is a compound of formula **V-tt** or a pharmaceutically acceptable salt thereof.

[0457] In some embodiments, the compound is a compound of formula **V-uu**, or a pharmaceutically acceptable salt thereof.

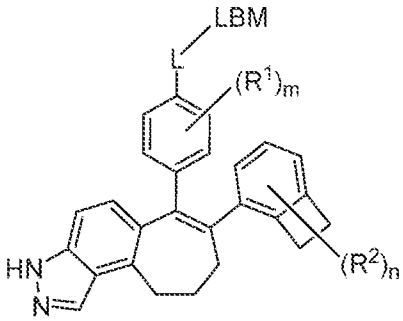
[0458] In some embodiments, the compound is a compound of formula **V-vv**, or a pharmaceutically acceptable salt thereof.

[0459] In certain embodiments, the present invention provides a compound of formula **I-a**,

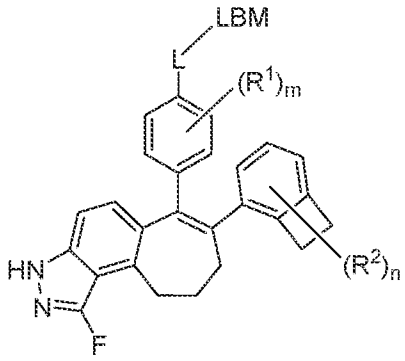
wherein ERBM is  ,  ,

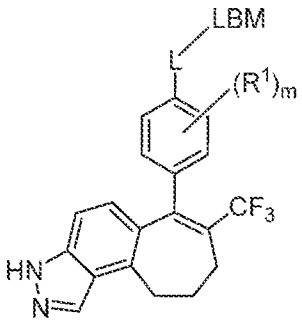
, or , thereby forming a compound of one of formulas **V-ww**, **V-xx**, **V-yy**, **V-zz**, **V-aa-1**, **V-bb-1**, **V-cc-1**, **V-dd-1**, **V-ee-1**, **V-ff-1**, **V-gg-1**, **V-hh-1**, **V-ii-1**, **V-jj-1**, **V-kk-1**, or **V-ll-1**:



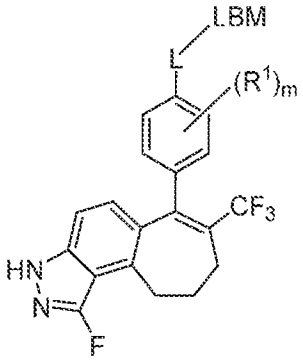
V-ww



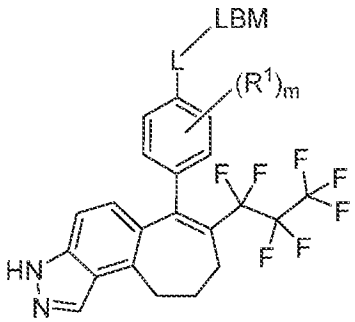
V-xx



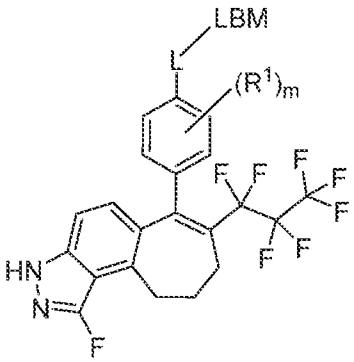
V-yy



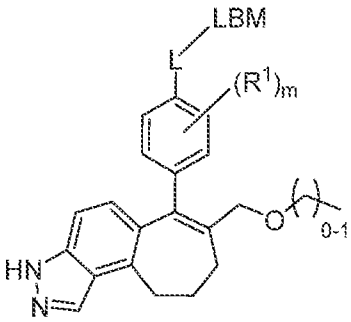
V-zz



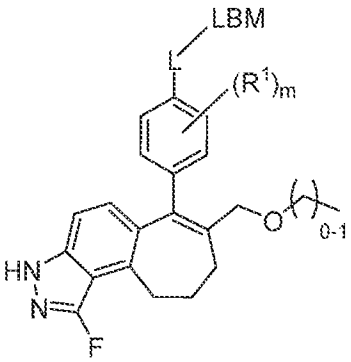
V-aa-1



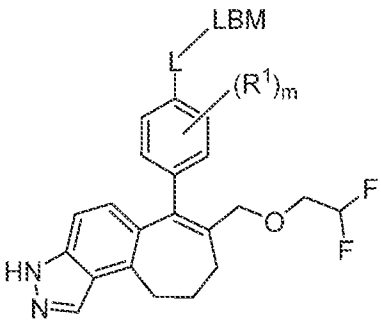
V-bb-1



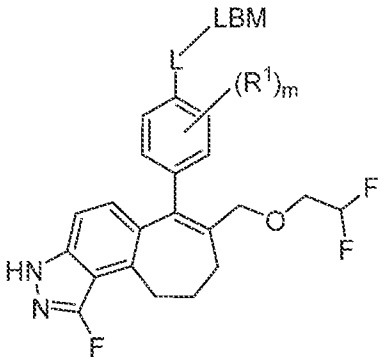
V-cc-1



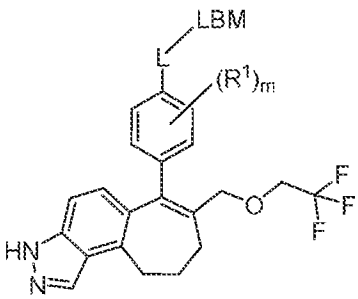
V-dd-1



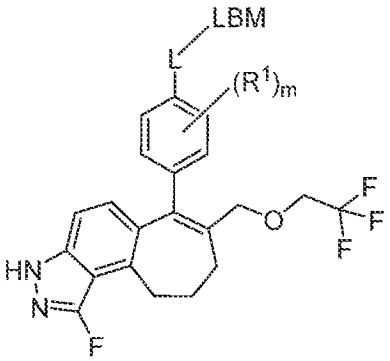
V-ee-1



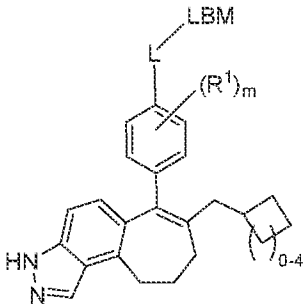
V-ff-1



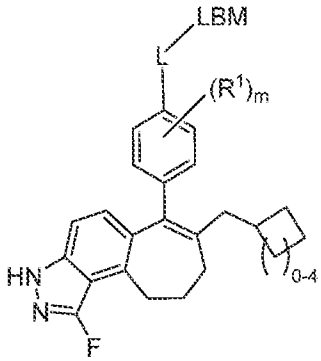
V-gg-1



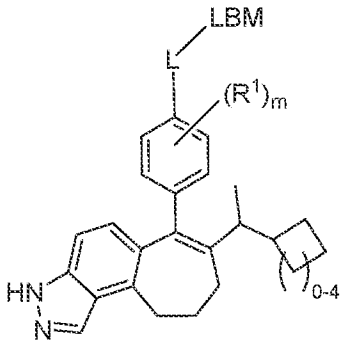
V-hh-1



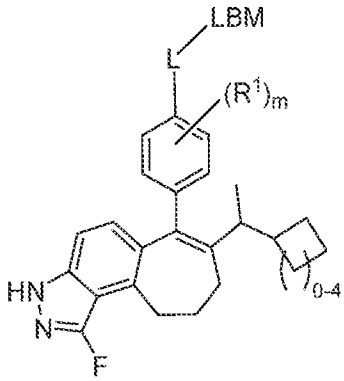
V-ii-1



V-jj-1



V-kk-1



V-ll-1

or a pharmaceutically acceptable salt thereofwherein each of R^1, m, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0460] In some embodiments, the compound is a compound of formula **V-ww**, or a pharmaceutically acceptable salt thereof.

[0461] In some embodiments, the compound is a compound of formula **V-xx**, or a pharmaceutically acceptable salt thereof.

[0462] In some embodiments, the compound is a compound of formula **V-yy** or a pharmaceutically acceptable salt thereof.

[0463] In some embodiments, the compound is a compound of formula **V-zz**, or a pharmaceutically acceptable salt thereof.

[0464] In some embodiments, the compound is a compound of formula **V-aa-1**, or a pharmaceutically acceptable salt thereof.

[0465] In some embodiments, the compound is a compound of formula **V-bb-1**, or a pharmaceutically acceptable salt thereof.

[0466] In some embodiments, the compound is a compound of formula **V-cc-1** or a pharmaceutically acceptable salt thereof.

[0467] In some embodiments, the compound is a compound of formula **V-dd-1**, or a pharmaceutically acceptable salt thereof.

[0468] In some embodiments, the compound is a compound of formula **V-ee-1**, or a pharmaceutically acceptable salt thereof.

[0469] In some embodiments, the compound is a compound of formula **V-ff-1**, or a pharmaceutically acceptable salt thereof.

[0470] In some embodiments, the compound is a compound of formula **V-gg-1**, or a pharmaceutically acceptable salt thereof.

[0471] In some embodiments, the compound is a compound of formula **V-hh-1** or a pharmaceutically acceptable salt thereof.

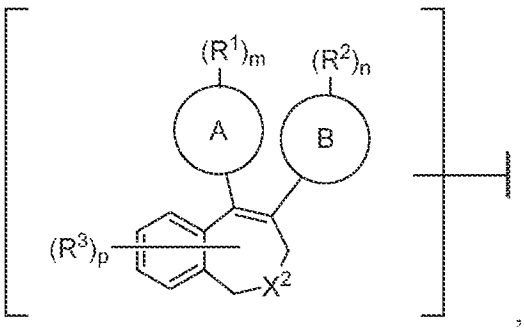
[0472] In some embodiments, the compound is a compound of formula **V-ii-1**, or a pharmaceutically acceptable salt thereof.

[0473] In some embodiments, the compound is a compound of formula **V-jj-1**, or a pharmaceutically acceptable salt thereof.

[0474] In some embodiments, the compound is a compound of formula **V-kk-1**, or a pharmaceutically acceptable salt thereof.

[0475] In some embodiments, the compound is a compound of formula **V-ll-1**, or a pharmaceutically acceptable salt thereof.

[0476] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is 

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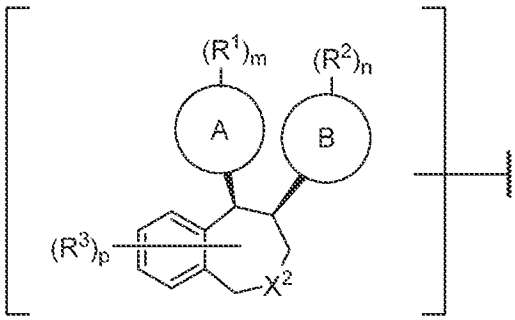

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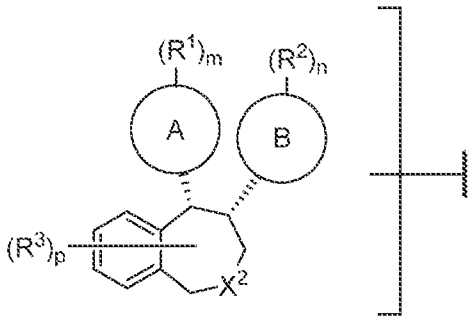

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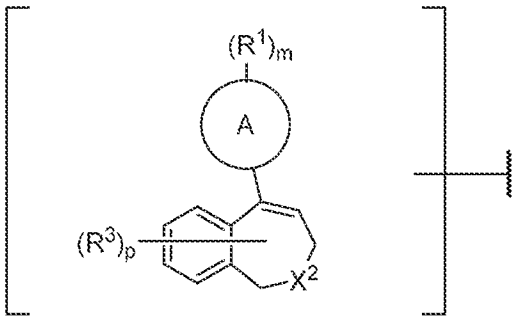

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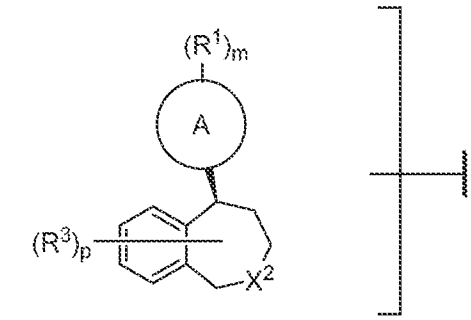

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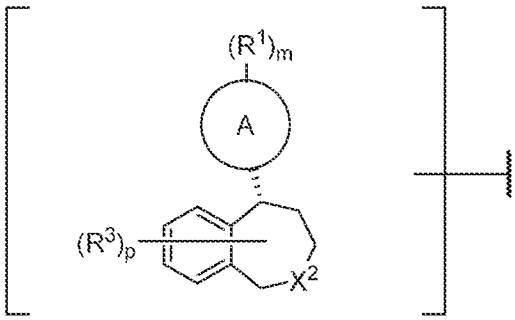
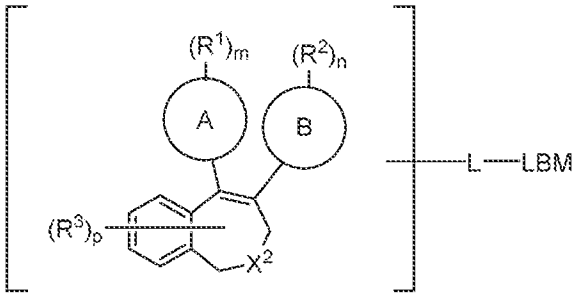
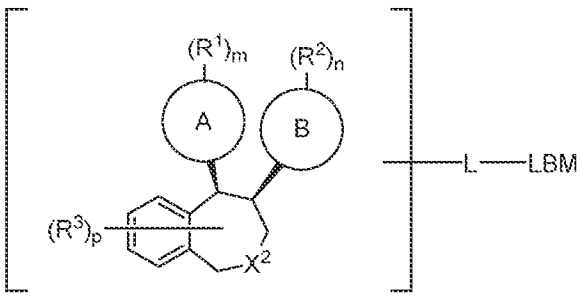


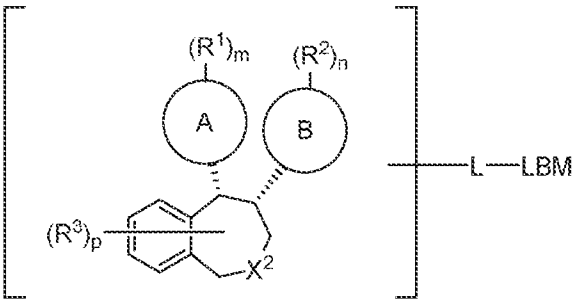
, thereby forming a compound of one of formulas **VI-a**, **VI-b**, **VI-c**, **VI-d**, **VI-e**, or **VI-f**, respectively:



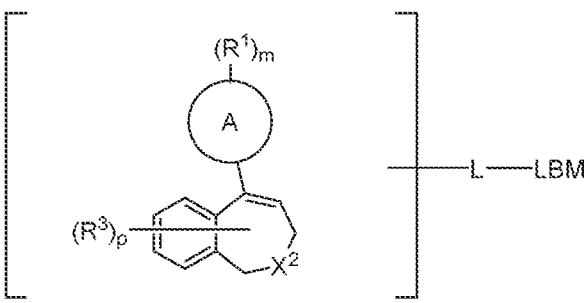
VI-a



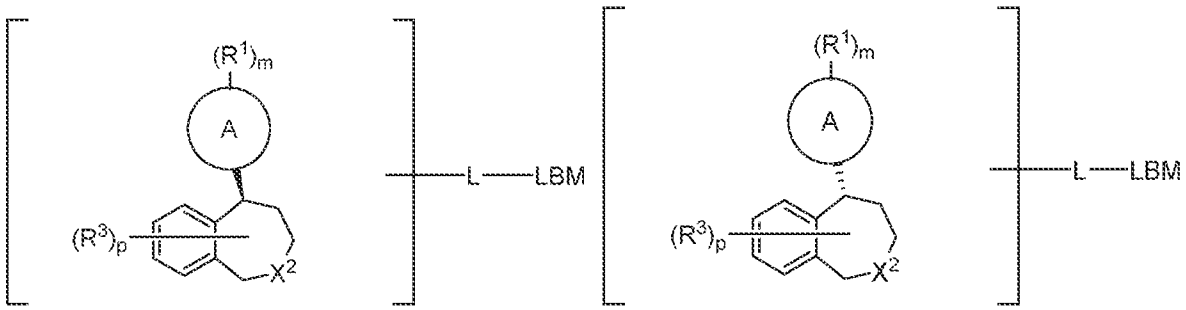
VI-b



VI-c



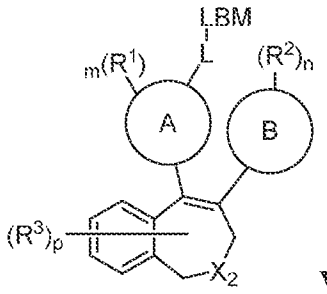
VI-d



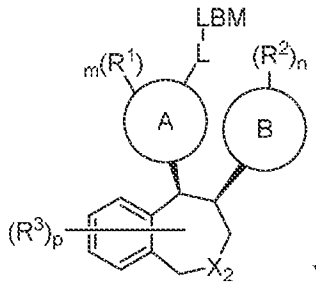
VI-e **VI-f**

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

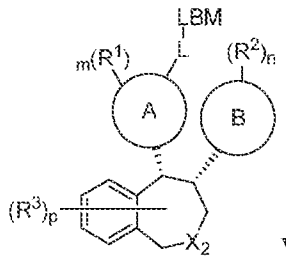
[0477] In some embodiments, the invention provides a compound of one of formulas **VI-a-1**, **VI-b-1**, **VI-c-1**, **VI-d-1**, **VI-e-1**, or **VI-f-1**:



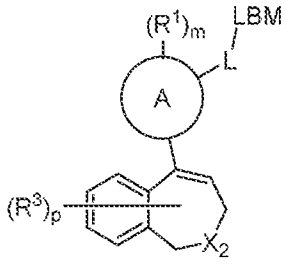
VI-a-1



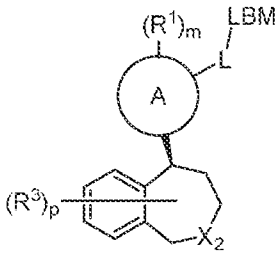
VI-b-1



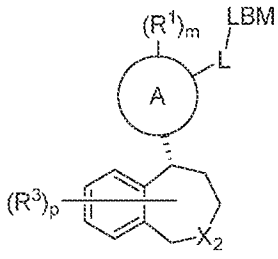
VI-c-1



VI-d-1



VI-e-1



VI-f-1 or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0478] In some embodiments, the compound is a compound of formula **VI-a-1**, or a pharmaceutically acceptable salt thereof.

[0479] In some embodiments, the compound is a compound of formula **VI-b-1**, or a pharmaceutically acceptable salt thereof.

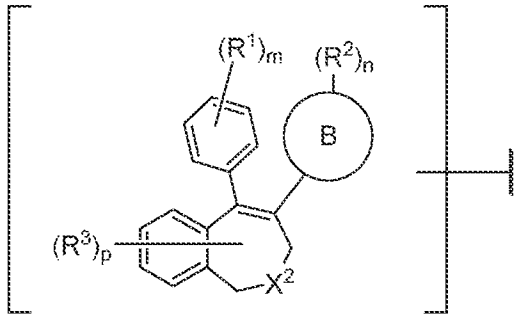
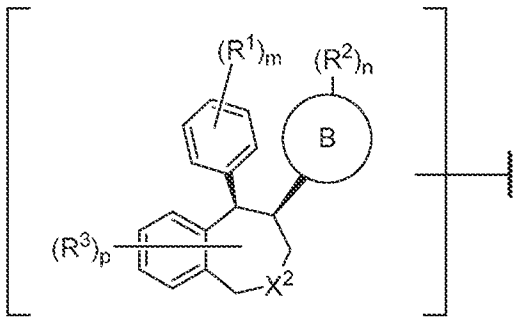
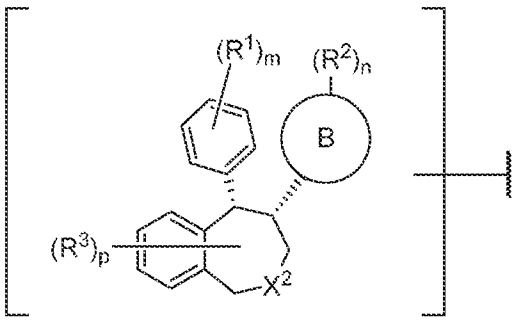
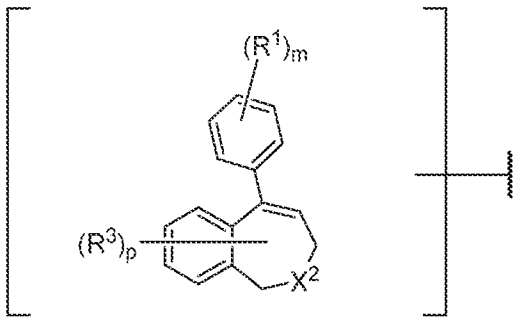
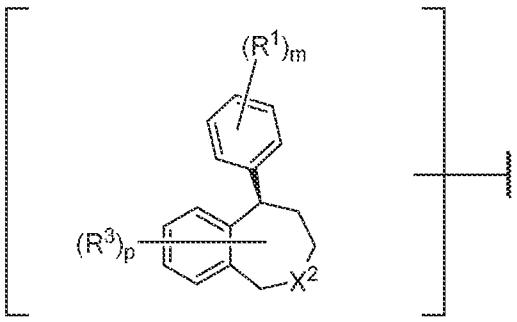
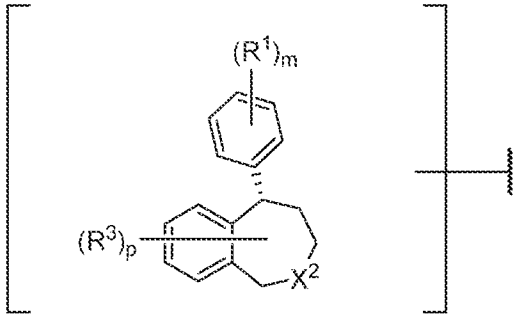
[0480] In some embodiments, the compound is a compound of formula **VI-c-1**, or a pharmaceutically acceptable salt thereof.

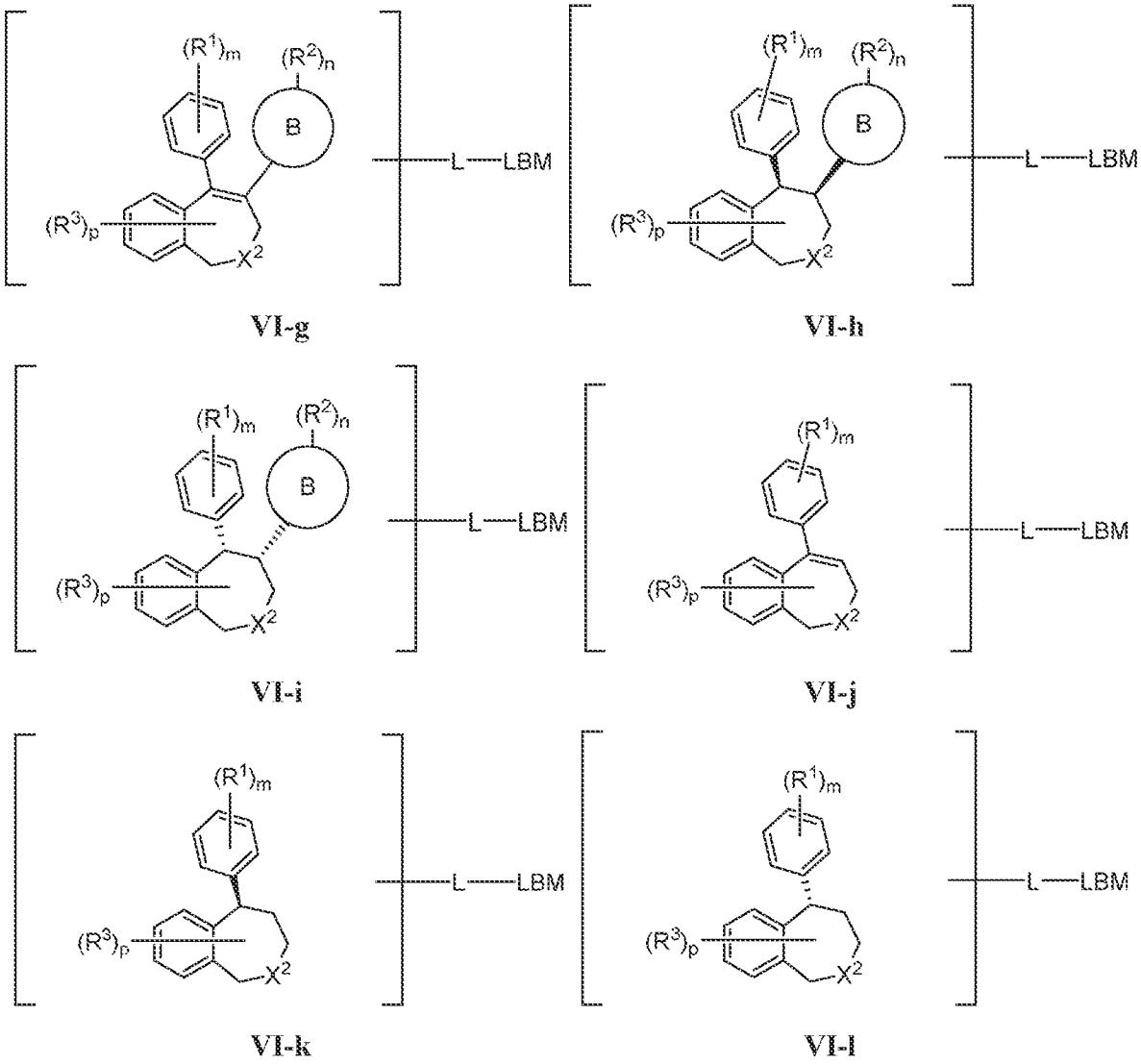
[0481] In some embodiments, the compound is a compound of formula **VI-d-1**, or a pharmaceutically acceptable salt thereof.

[0482] In some embodiments, the compound is a compound of formula **VI-e-1**, or a pharmaceutically acceptable salt thereof.

[0483] In some embodiments, the compound is a compound of formula **VI-f-1**, or a pharmaceutically acceptable salt thereof.

[0484] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,  ,  ,  ,  , or  , thereby forming a compound of one of formulas **VI-g**, **VI-h**, **VI-i**, **VI-j**, **VI-k**, or **VI-l**, respectively:



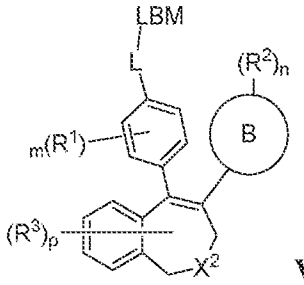
VI-g **VI-h**

VI-i **VI-j**

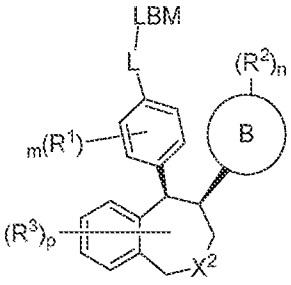
VI-k **VI-l**

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

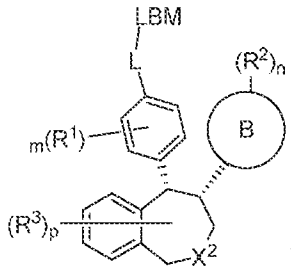
[0485] In some embodiments, the invention provides a compound of one of formulas **VI-g-1**, **VI-h-1**, **VI-i-1**, **VI-j-1**, **VI-k-1**, or **IV-l-1**:



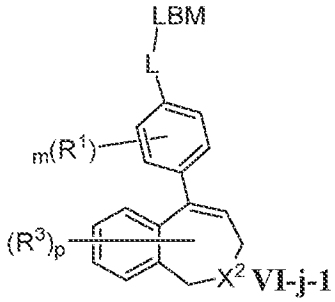
VI-g-1



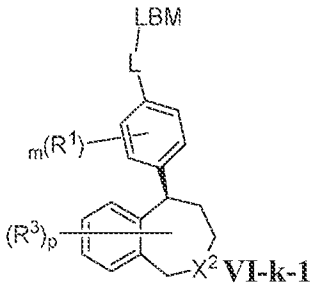
VI-h-1



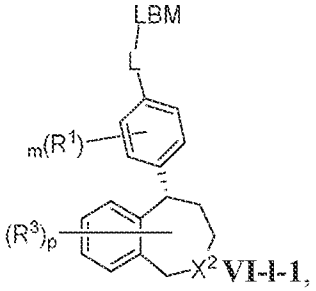
VI-i-1



VI-j-1



VI-k-1



VI-l-1, or a pharmaceutically acceptable salt thereof wherein each of Ring B, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0486] In some embodiments, the compound is a compound of formula **VI-g-1**, or a pharmaceutically acceptable salt thereof.

[0487] In some embodiments, the compound is a compound of formula **VI-h-1**, or a pharmaceutically acceptable salt thereof.

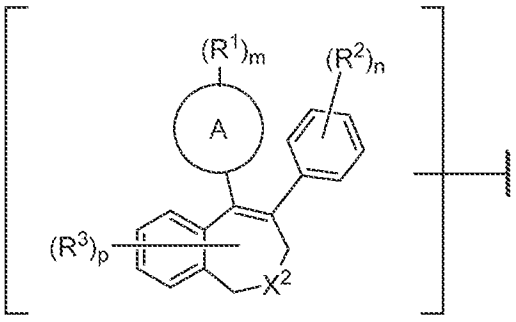
[0488] In some embodiments, the compound is a compound of formula **VI-i-1**, or a pharmaceutically acceptable salt thereof.

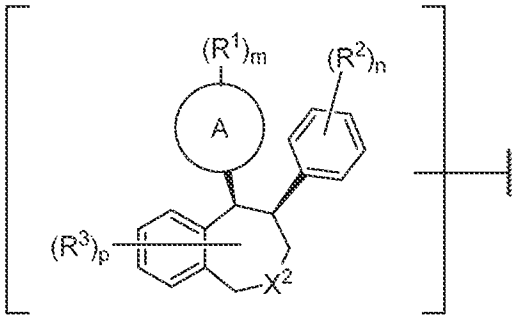
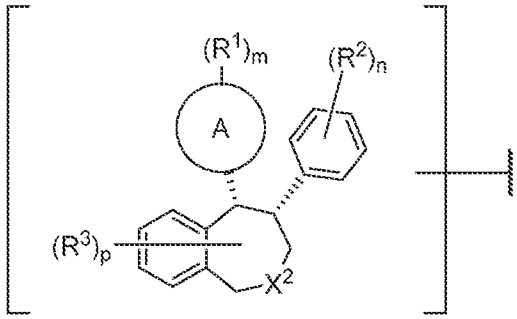
[0489] In some embodiments, the compound is a compound of formula **VI-j-1**, or a pharmaceutically acceptable salt thereof.

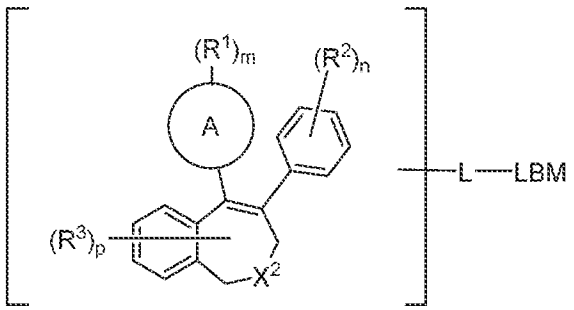
[0490] In some embodiments, the compound is a compound of formula **VI-k-1**, or a pharmaceutically acceptable salt thereof.

[0491] In some embodiments, the compound is a compound of formula **VI-l-1**, or a pharmaceutically acceptable salt thereof.

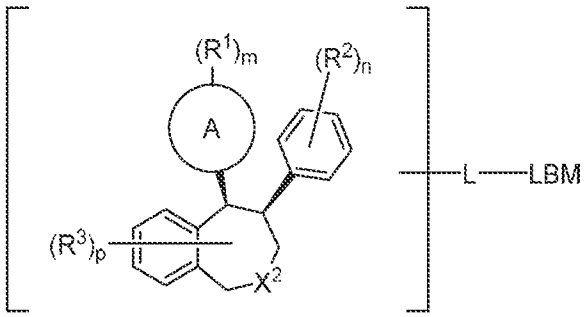
[0492] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

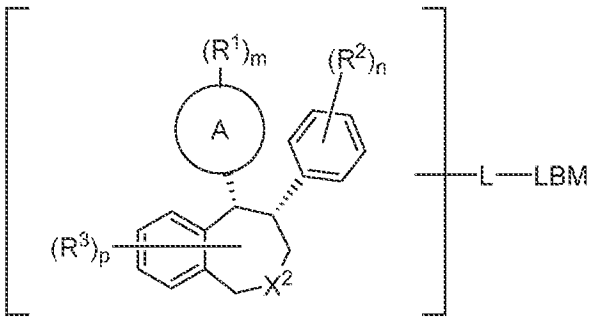
 , or  , thereby forming a compound of one of formulas **VI-m**, **VI-n**, or **VI-o**, respectively:



VI-m



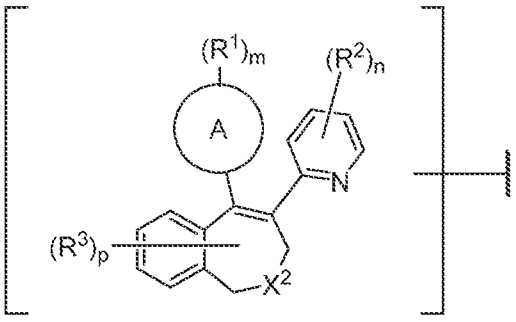
VI-n

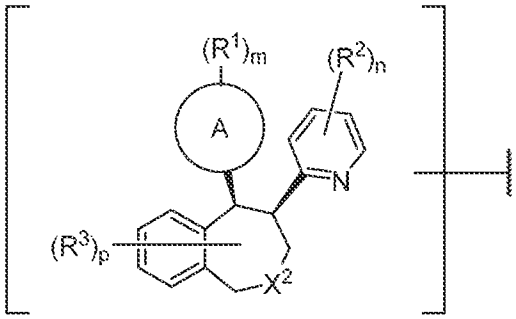
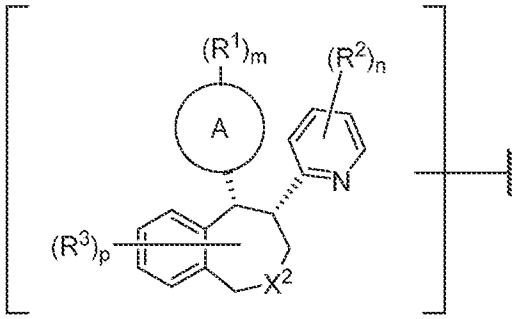


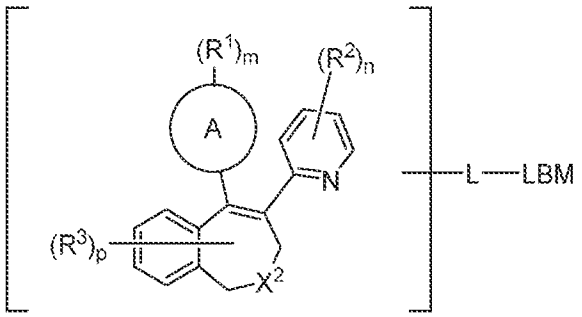
VI-o

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

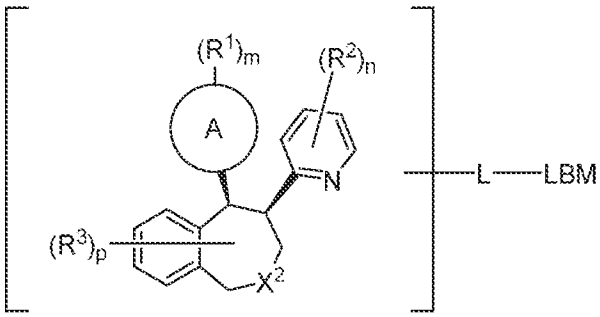
[0493] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

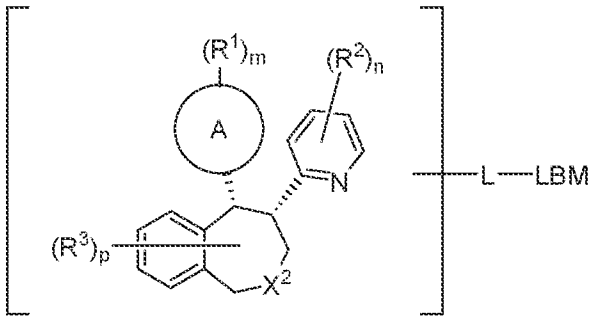
 , or  , thereby forming a compound of one of formulas **VI-p**, **VI-q**, or **VI-r**, respectively:



VI-p



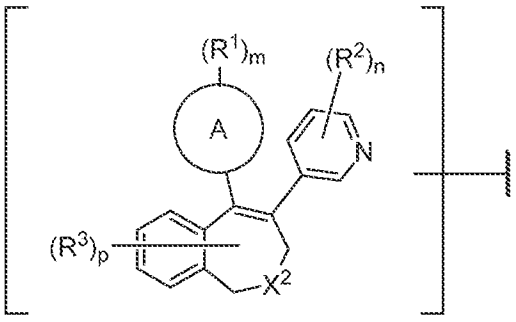
VI-q

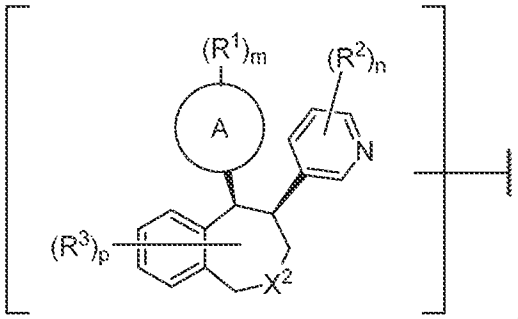
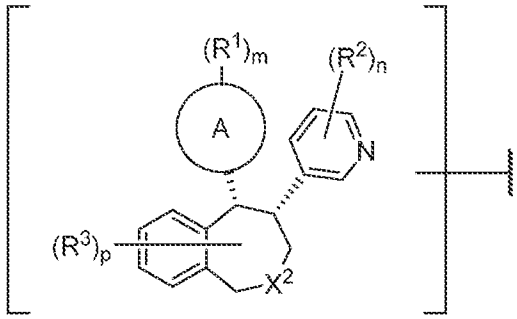


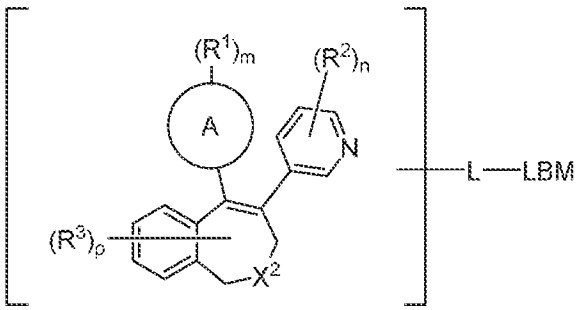
VI-r

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

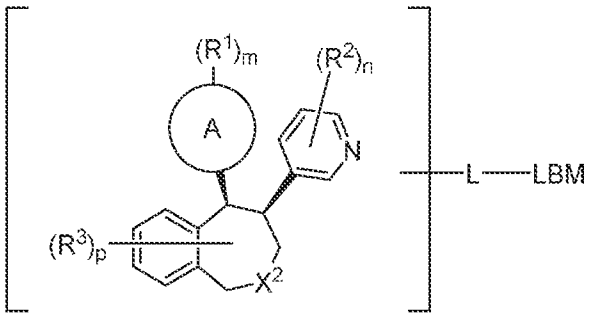
[0494] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

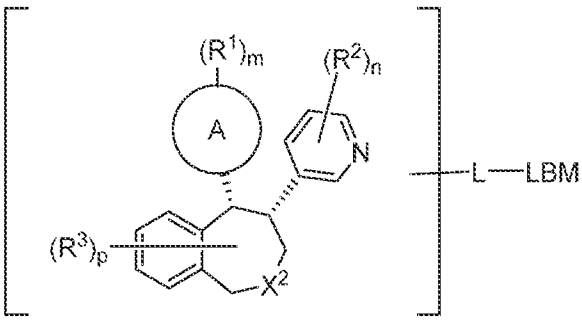
 , or  , thereby forming a compound of one of formulas **VI-s**, **VI-t**, or **VI-u**, respectively:



VI-s



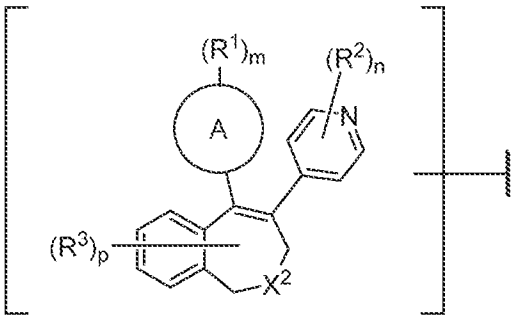
VI-t

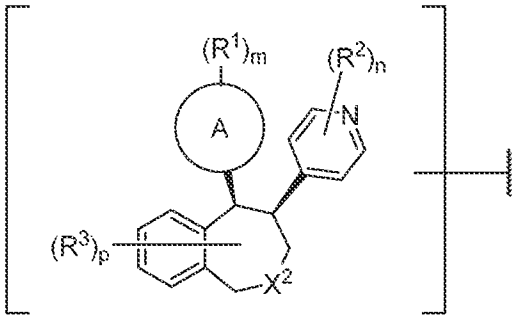
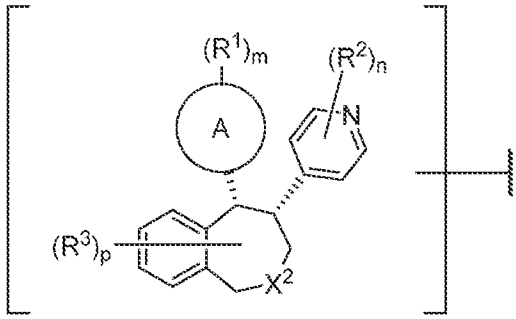


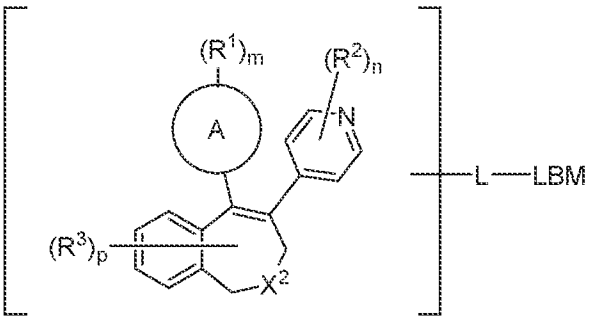
VI-u

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

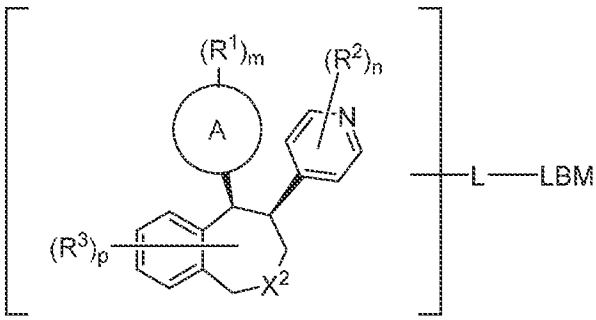
[0495] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

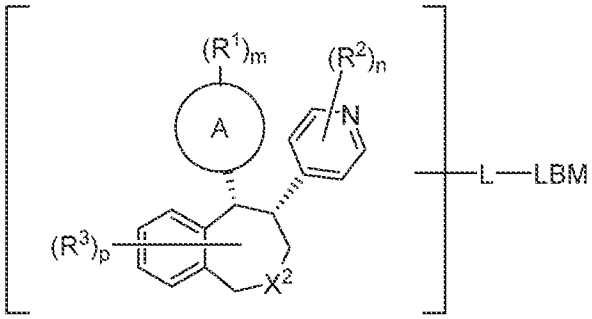
 , or  , thereby forming a compound of one of formulas **VI-v**, **VI-w**, or **VI-x**, respectively:



VI-v



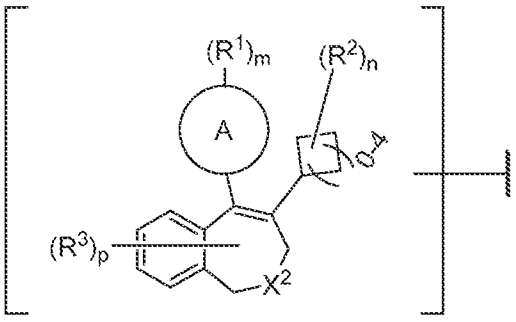
VI-w

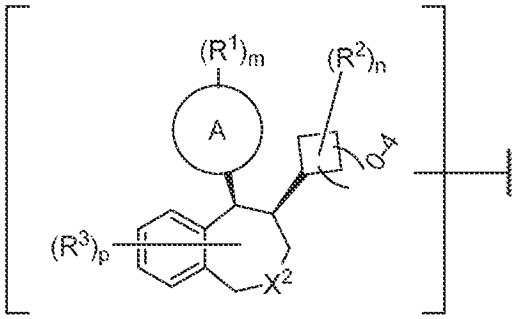
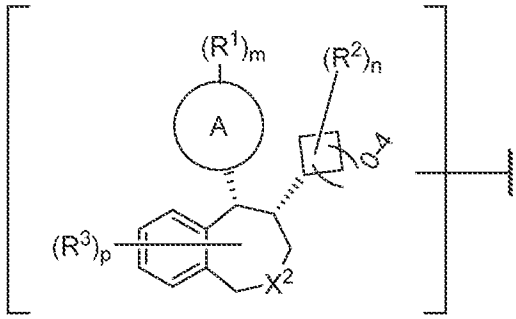


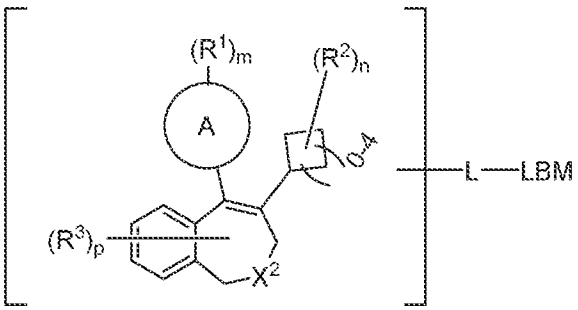
VI-x

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

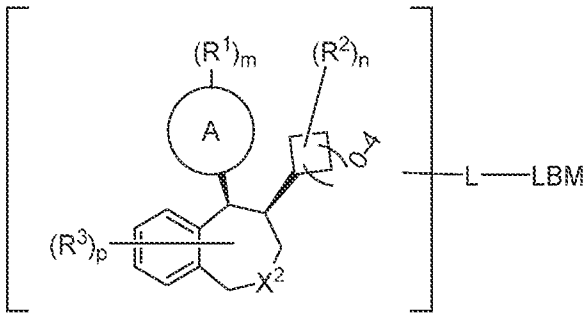
[0496] In certain embodiments, the present invention provides a compound of formula **I-a**,

wherein ERBM is  ,

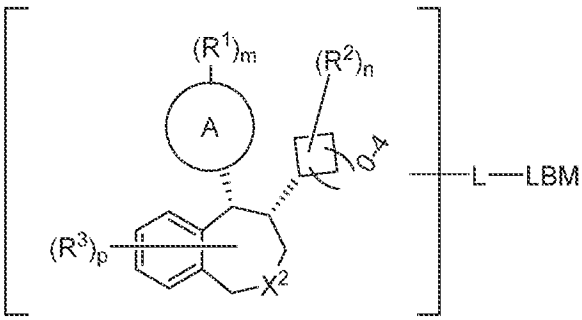
 , or  , thereby forming a compound of one of formulas **VI-y**, **VI-z**, or **VI-aa**, respectively:



VI-y



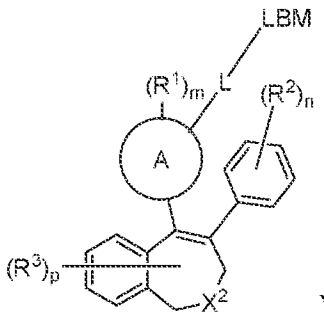
VI-z



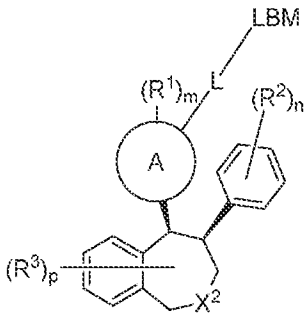
VI-aa

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

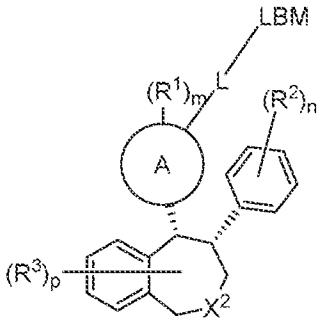
[0497] In some embodiments, the invention provides a compound of one of formulas **VI-m-1**, **VI-n-1**, **VI-o-1**, **VI-p-1**, **VI-q-1**, **VI-r-1**, **VI-s-1**, **VI-t-1**, **VI-u-1**, **VI-v-1**, **VI-w-1**, **VI-x-1**, **VI-y-1**, **VI-z-1**, or **VI-aa-1**:



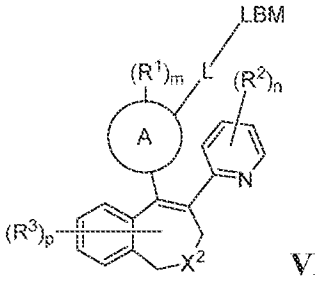
VI-m-1



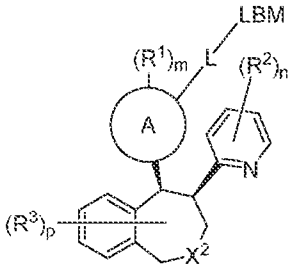
VI-n-1



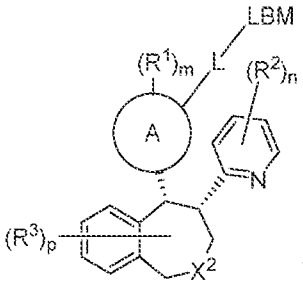
VI-o-1



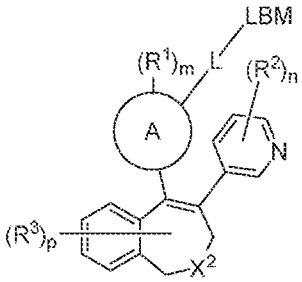
VI-p-1



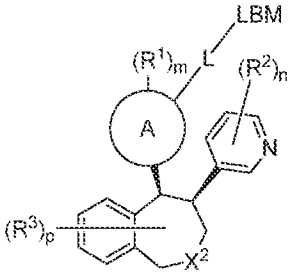
VI-q-1



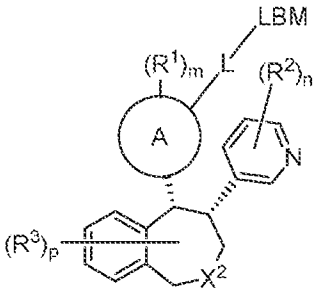
VI-r-1



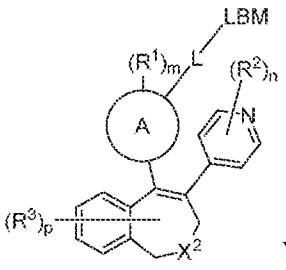
VI-s-1



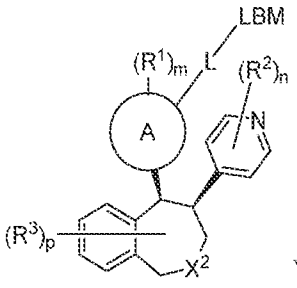
VI-t-1



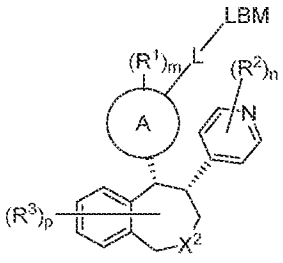
VI-u-1



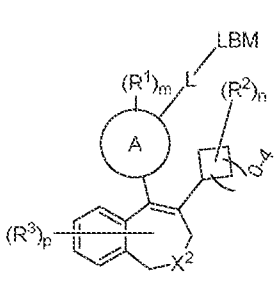
VI-v-1



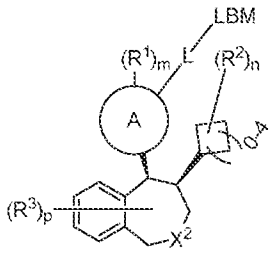
VI-w-1



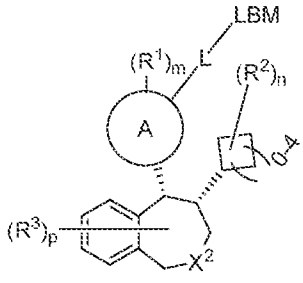
VI-x-1



VI-y-1



VI-z-1



VI-aa-1, or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^2, R^3, X^2, m, n, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0498] In some embodiments ,the compound is a compound of formula **VI-m-1**, or a pharmaceutically acceptable salt thereof.

[0499] In some embodiments, the compound is a compound of formula **VI-n-1**, or a pharmaceutically acceptable salt thereof.

[0500] In some embodiments ,the compound is a compound of formula **VI-o-1**, or a pharmaceutically acceptable salt thereof.

[0501] In some embodiments, the compound is a compound of formula **VI-p-1**, or a pharmaceutically acceptable salt thereof.

[0502] In some embodiments, the compound is a compound of formula **VI-q-1**, or a pharmaceutically acceptable salt thereof.

[0503] In some embodiments, the compound is a compound of formula **VI-r-1**, or a pharmaceutically acceptable salt thereof.

[0504] In some embodiments, the compound is a compound of formula **VI-s-1**, or a pharmaceutically acceptable salt thereof.

[0505] In some embodiments, the compound is a compound of formula **VI-t-1**, or a pharmaceutically acceptable salt thereof.

[0506] In some embodiments, the compound is a compound of formula **VI-u-1** or a pharmaceutically acceptable salt thereof.

[0507] In some embodiments, the compound is a compound of formula **VI-v-1**, or a pharmaceutically acceptable salt thereof.

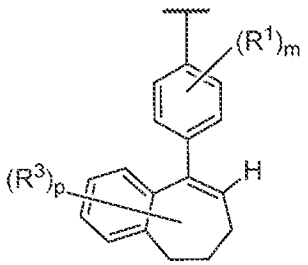
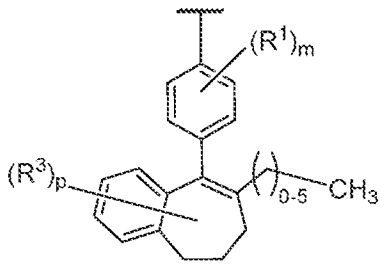
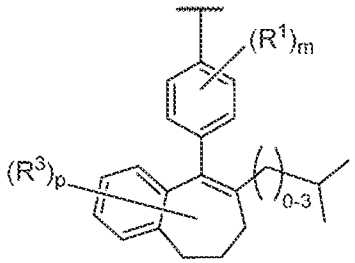
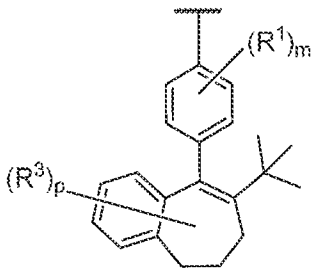
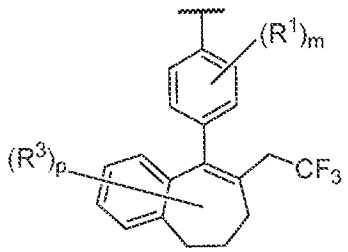
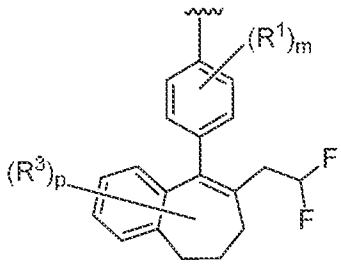
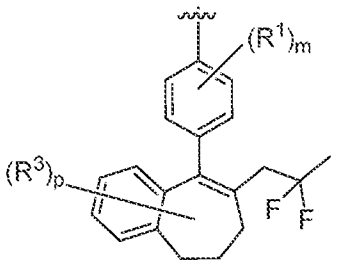
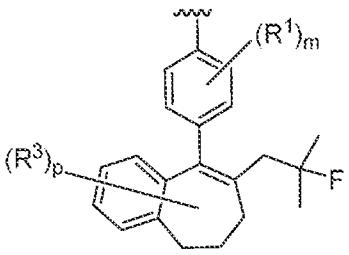
[0508] In some embodiments, the compound is a compound of formula **VI-w-1**, or a pharmaceutically acceptable salt thereof.

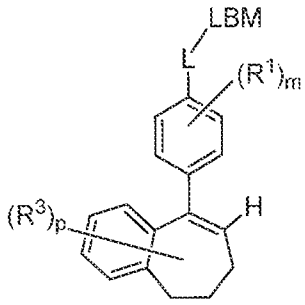
[0509] In some embodiments, the compound is a compound of formula **VI-x-1**, or a pharmaceutically acceptable salt thereof.

[0510] In some embodiments, the compound is a compound of formula **VI-y-1**, or a pharmaceutically acceptable salt thereof.

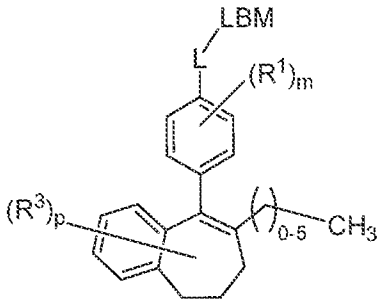
[0511] In some embodiments, the compound is a compound of formula **VI-z-1**, or a pharmaceutically acceptable salt thereof.

[0512] In some embodiments, the compound is a compound of formula **VI-aa-1**, or a pharmaceutically acceptable salt thereof.

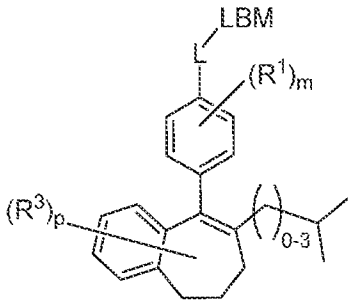
[0513] In certain embodiments, the present invention provides a compound of formula **I-a**, wherein ERBM is  ,  ,  ,  ,  ,  ,  ,  , or thereby forming a compound of one of formulas **VII-a**, **VII-b**, **VII-c**, **VII-d**, **VII-e**, **VII-f**, **VII-g**,or **VII-h**, respectively:



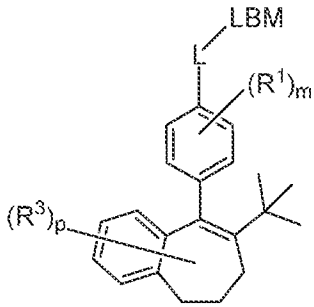
VII-a



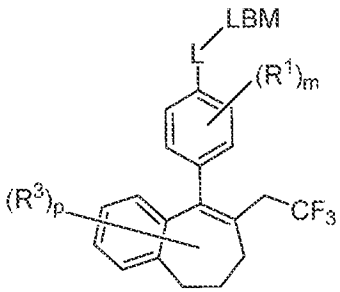
VII-b



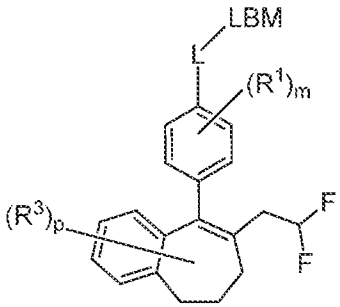
VII-c



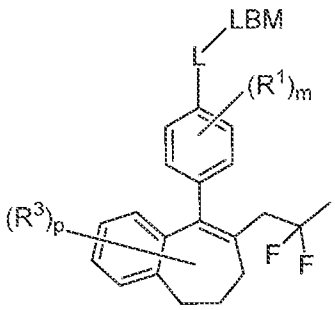
VII-d



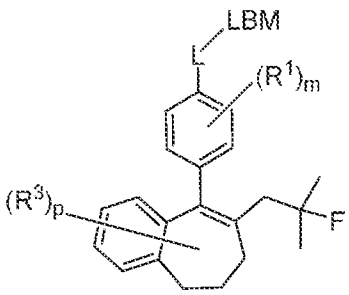
VII-e



VII-f



VII-g



VII-h

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^3, m, p, L, and LBM is as defined in embodiments and classes and subclasses herein.

[0514] In some embodiments, the compound is a compound of formula **VII-a**, or a pharmaceutically acceptable salt thereof.

[0515] In some embodiments, the compound is a compound of formula **VII-b**, or a pharmaceutically acceptable salt thereof.

[0516] In some embodiments, the compound is a compound of formula **VII-c**, or a pharmaceutically acceptable salt thereof.

[0517] In some embodiments, the compound is a compound of formula **VII-d**, or a pharmaceutically acceptable salt thereof.

[0518] In some embodiments, the compound is a compound of formula **VII-e**, or a pharmaceutically acceptable salt thereof.

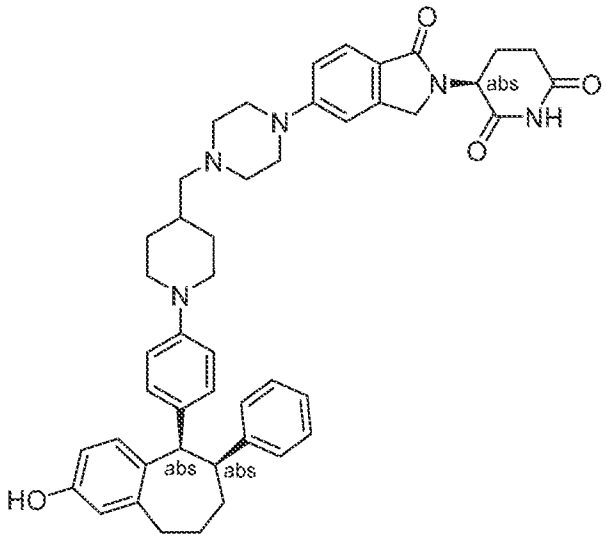
[0519] In some embodiments, the compound is a compound of formula **VII-f**, or a pharmaceutically acceptable salt thereof.

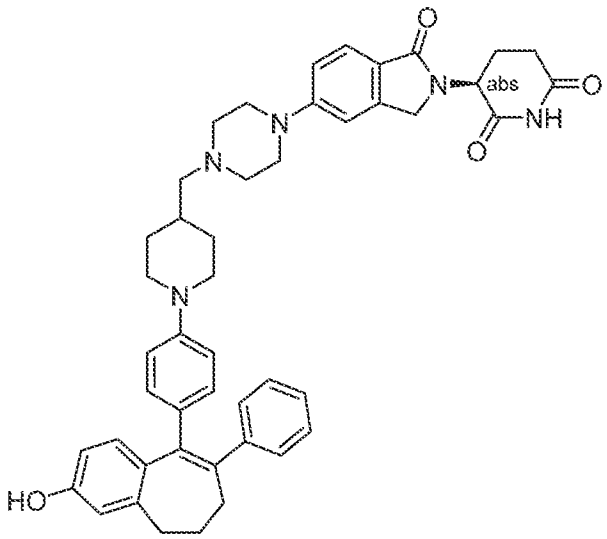
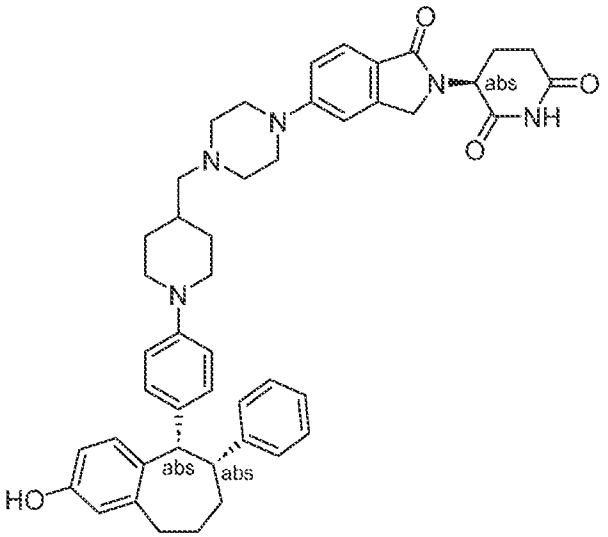
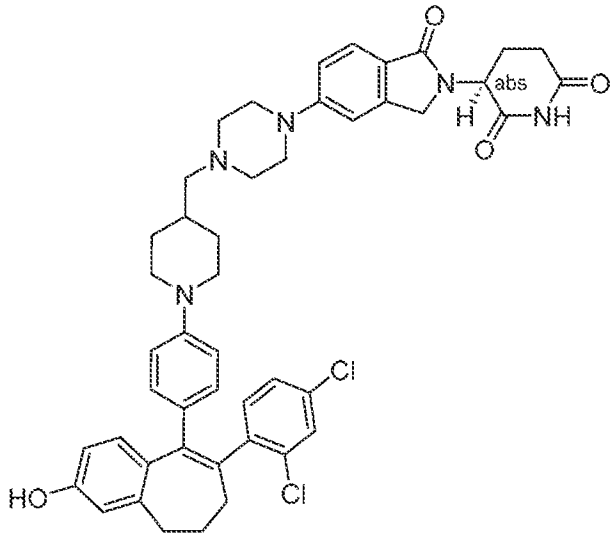
[0520] In some embodiments, the compound is a compound of formula **VII-g**, or a pharmaceutically acceptable salt thereof.

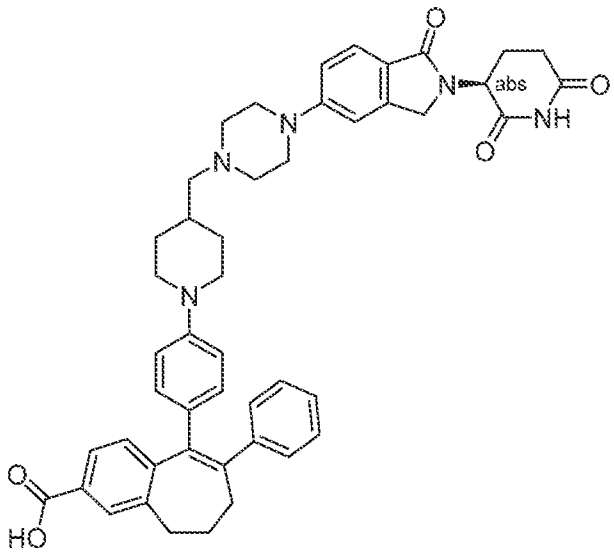
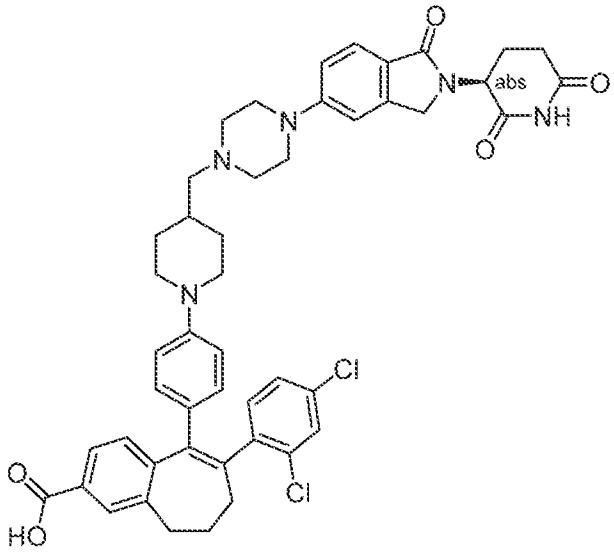
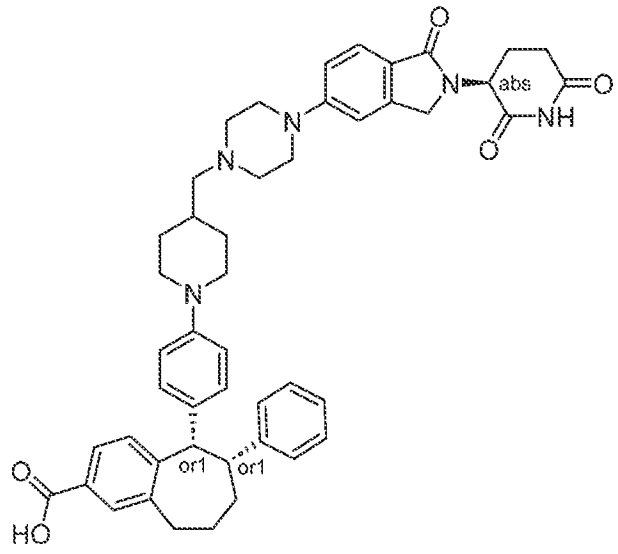
[0521] In some embodiments, the compound is a compound of formula **VII-h**, or a pharmaceutically acceptable salt thereof.

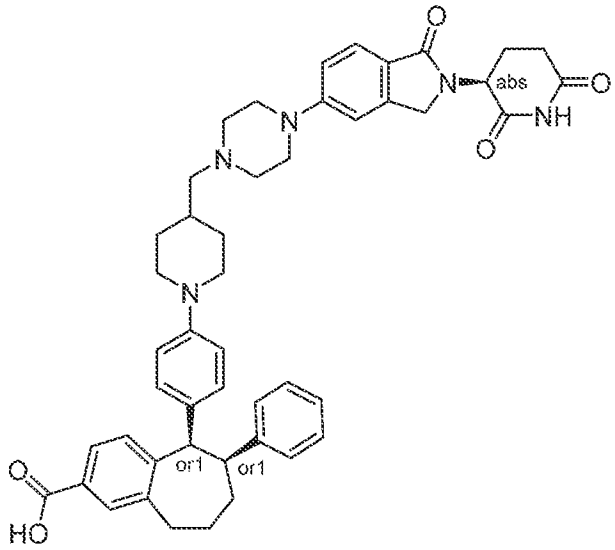
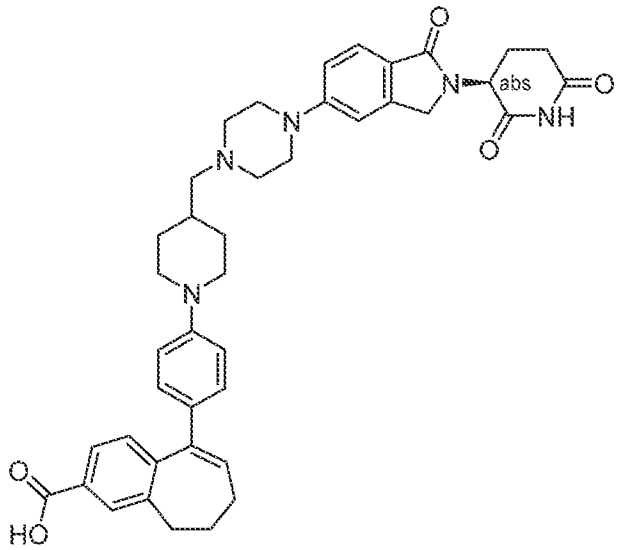
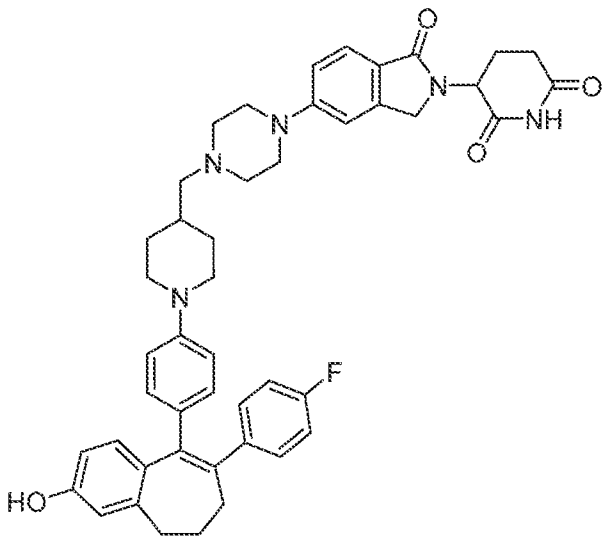
[0522] Examples of compounds of the present disclosure include those listed in the Tables and exemplification herein, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof. In some embodiments, the present disclosure provides a compound selected from those depicted in **Table 1**, below, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof. In some embodiments, the present disclosure provides a compound set forth in **Table 1**, below, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound set forth in **Table 1**, below.

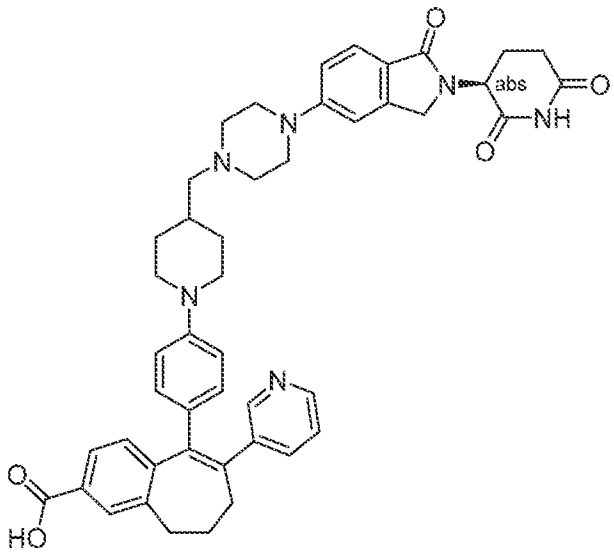
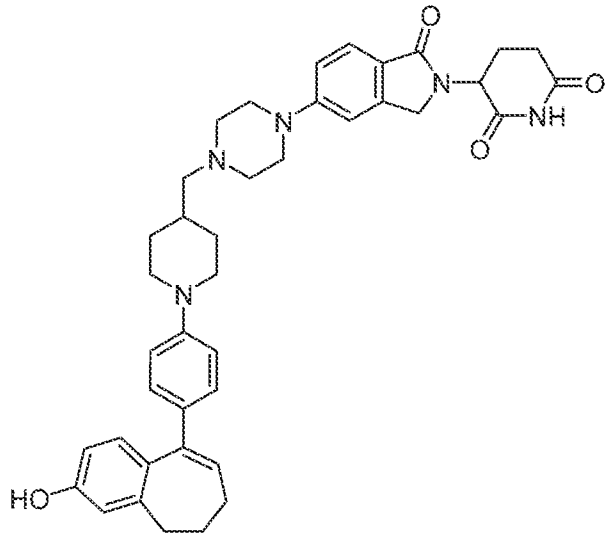
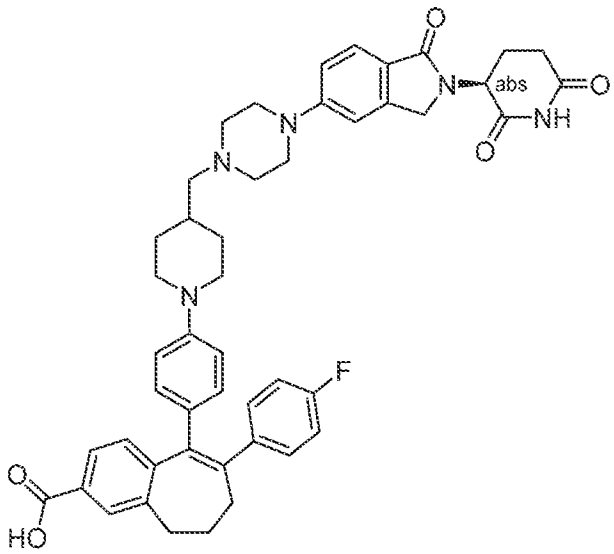
Table 1. Representative Compounds of the Disclosure.

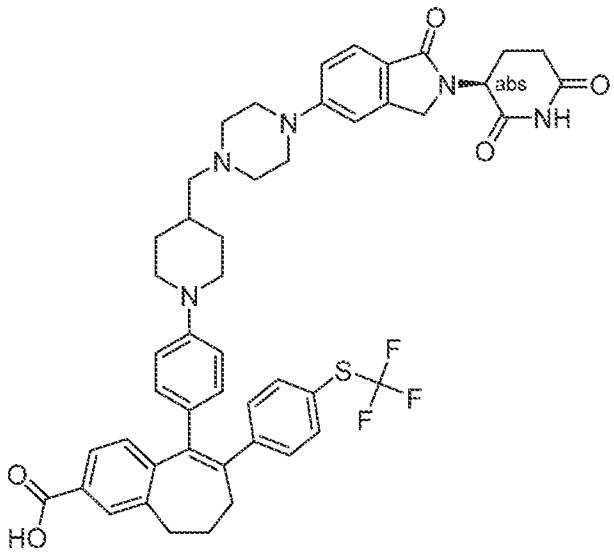
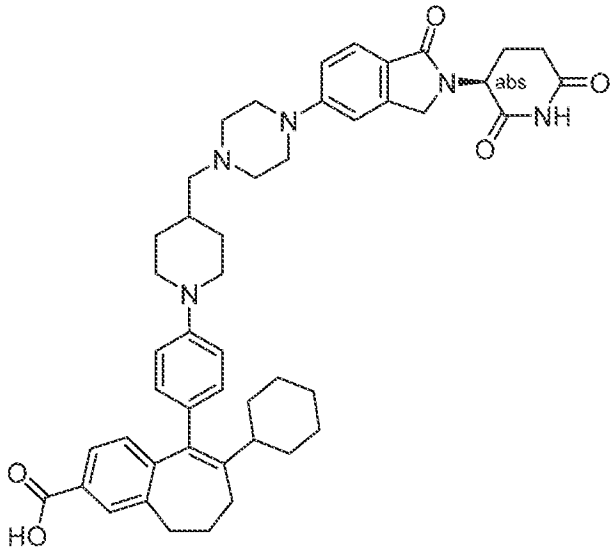
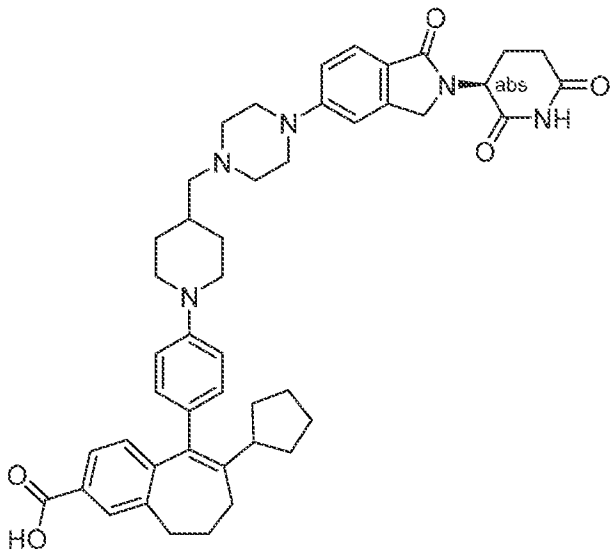
Compound No.	Structure
I-1‡	

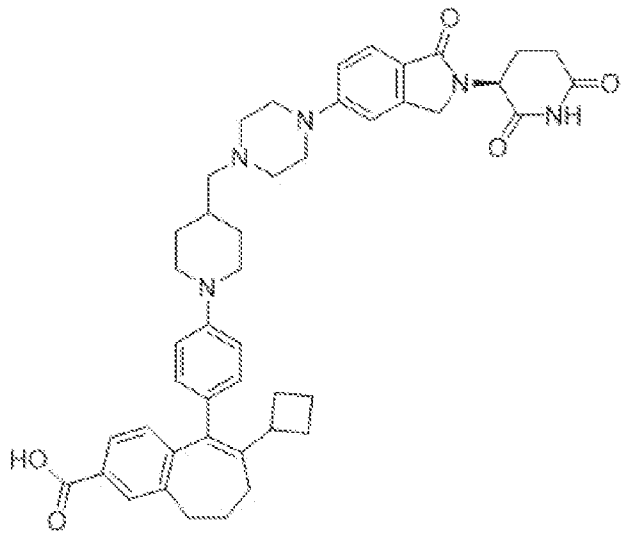
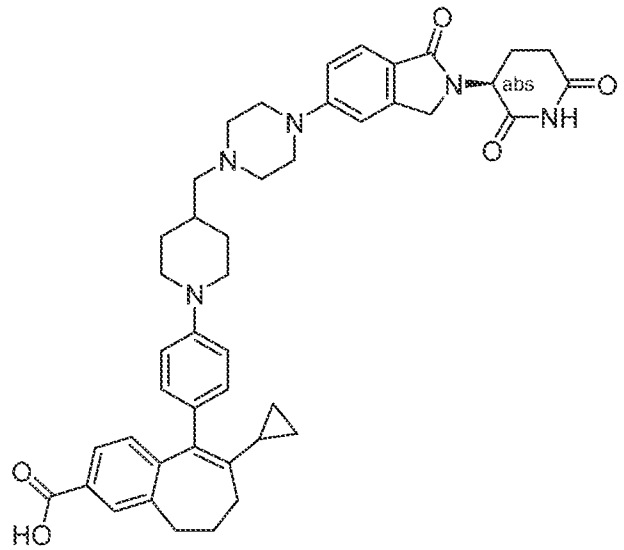
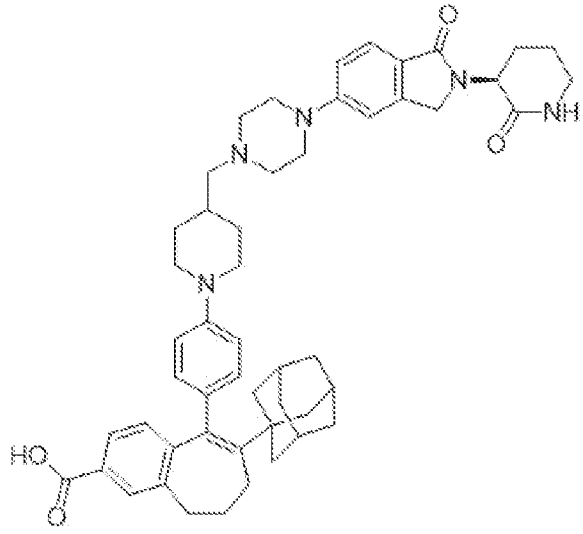
I-2	
I-3‡	
I-4	

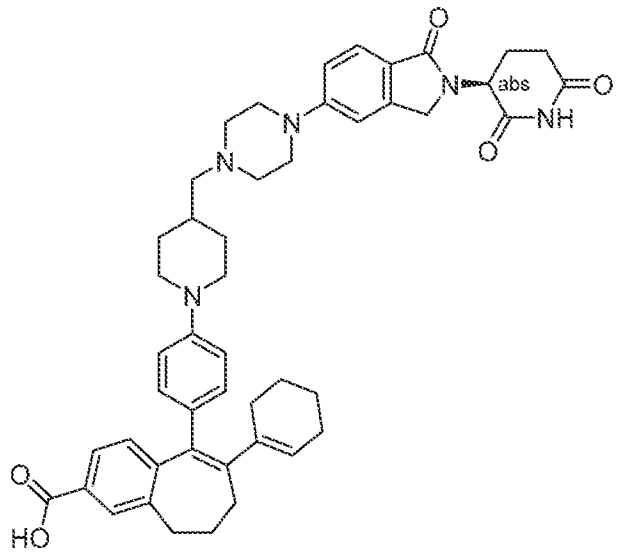
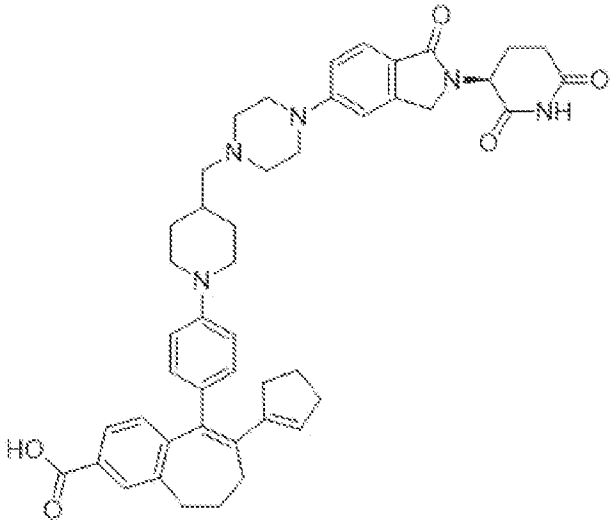
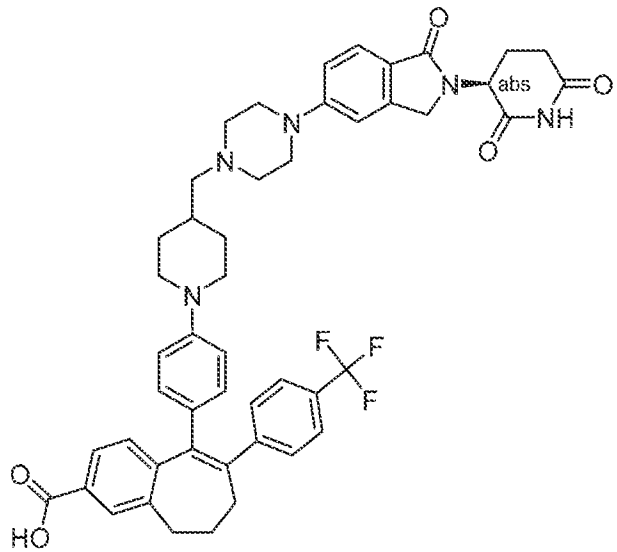
I-5	
I-6	
I-7	

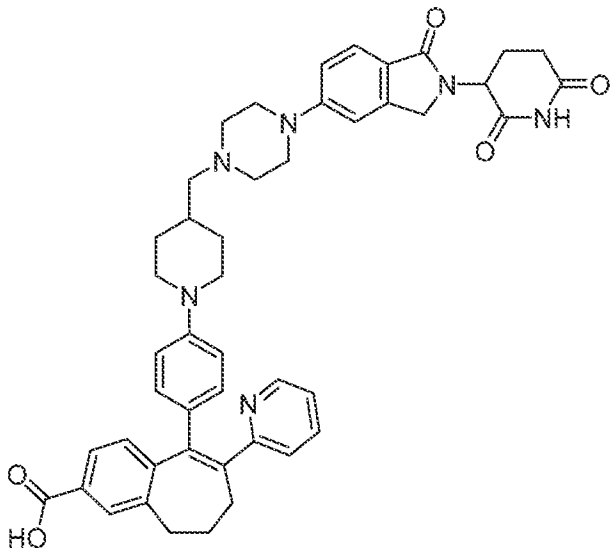
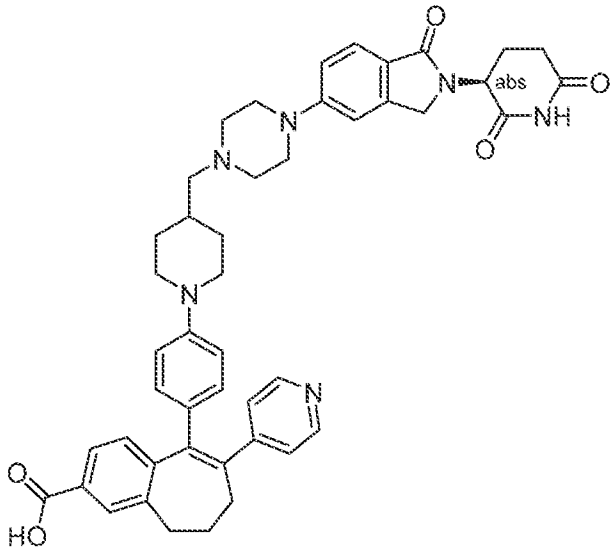
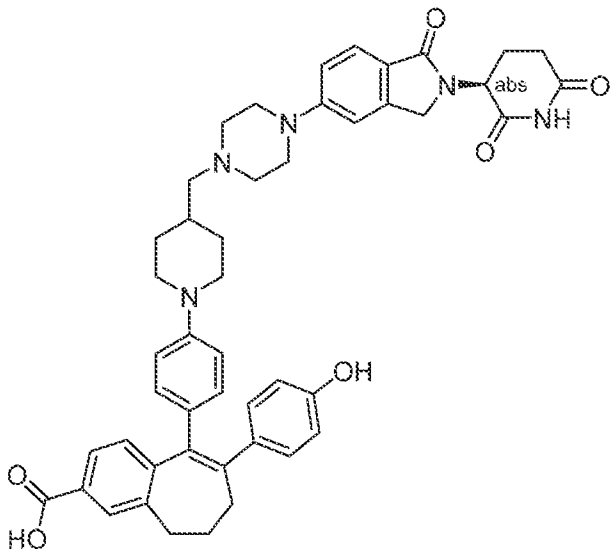
I-8	
I-9	
I-10	

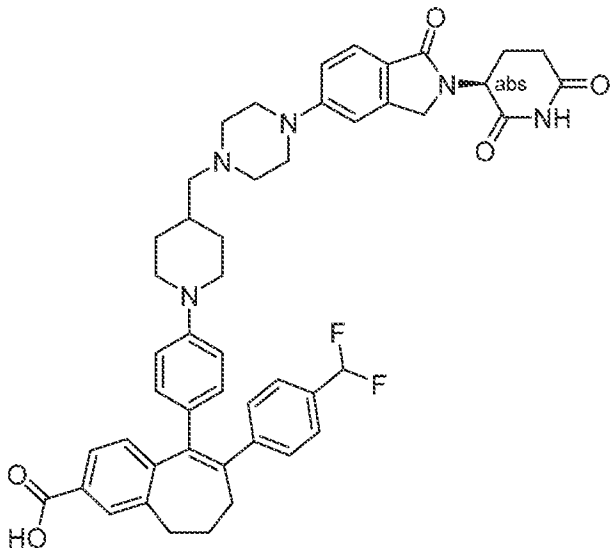
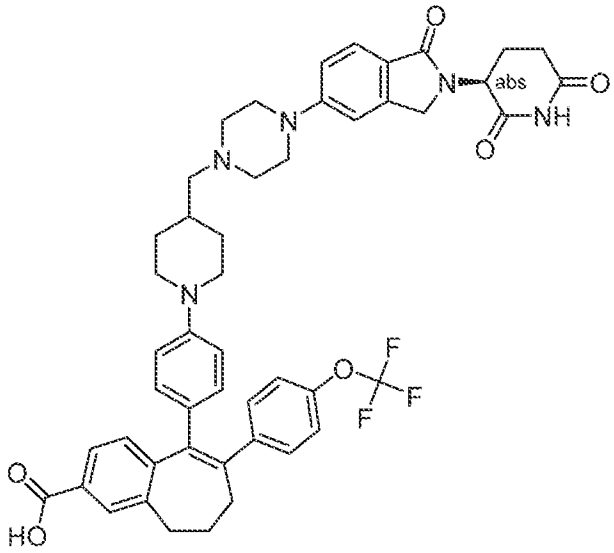
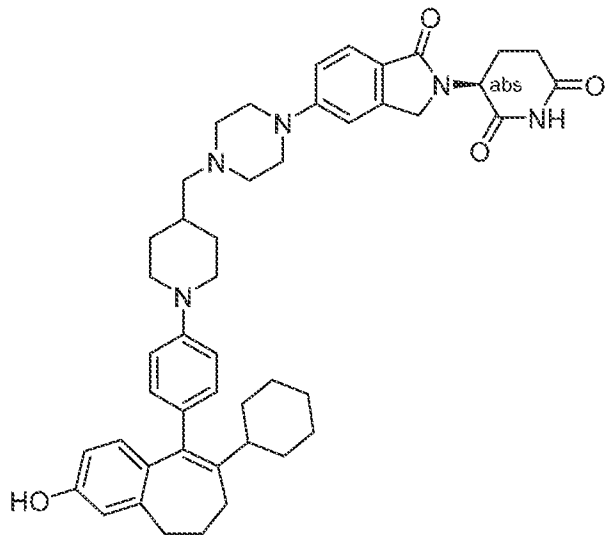
I-11	
I-12	
I-13	

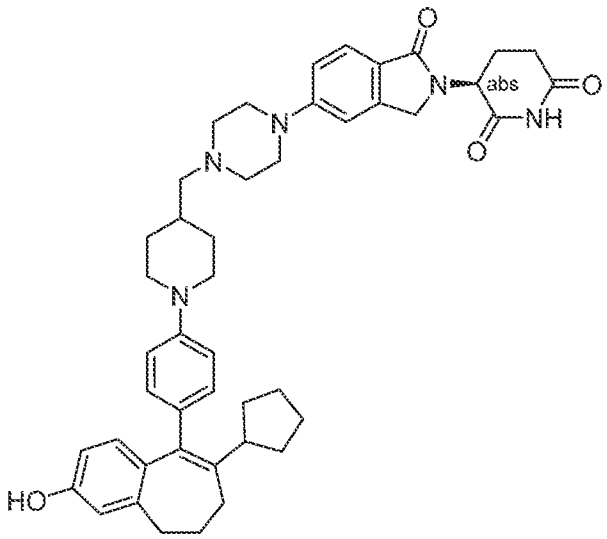
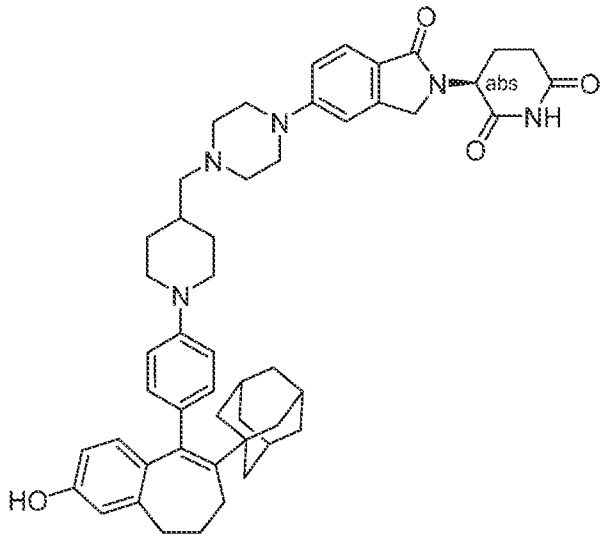
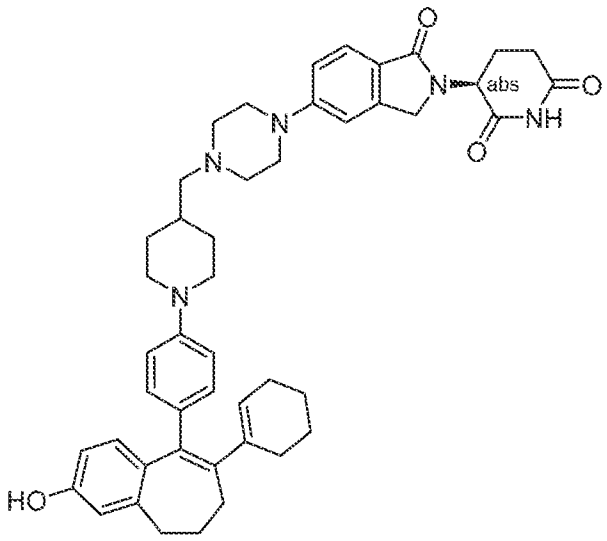
I-14	
I-15	
I-16	

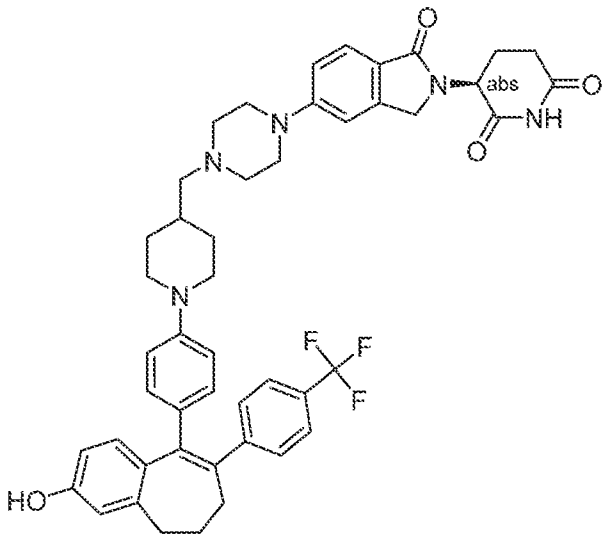
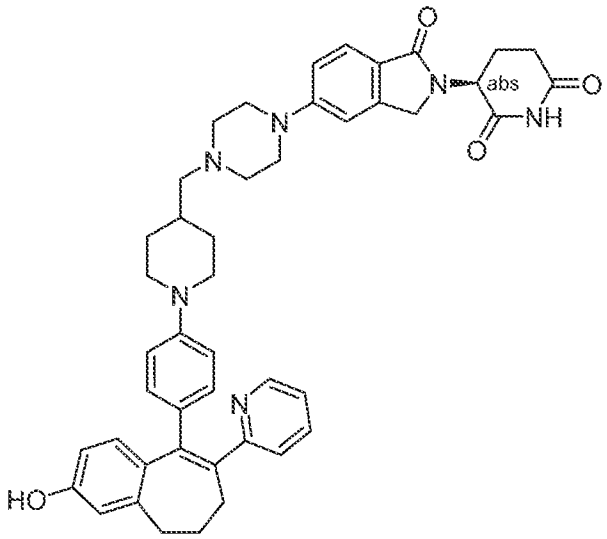
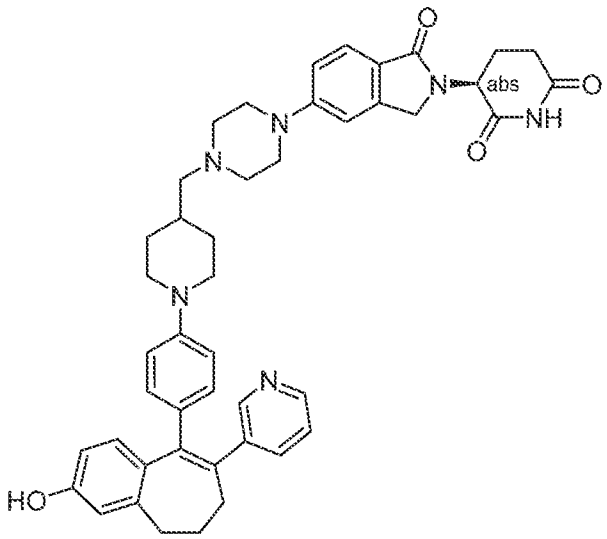
I-17 (*)	
I-18	
I-19 (*)	

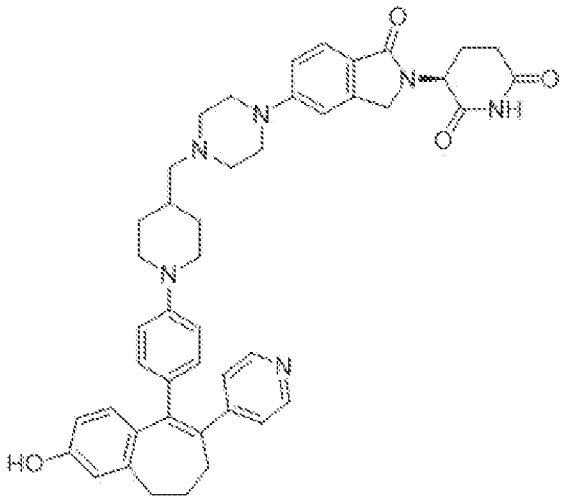
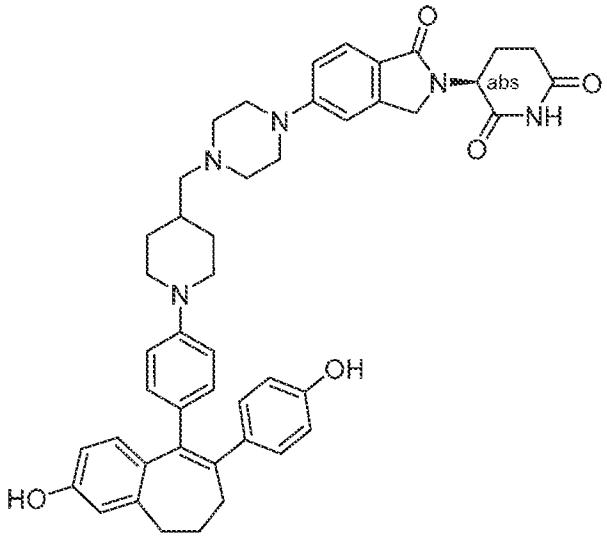
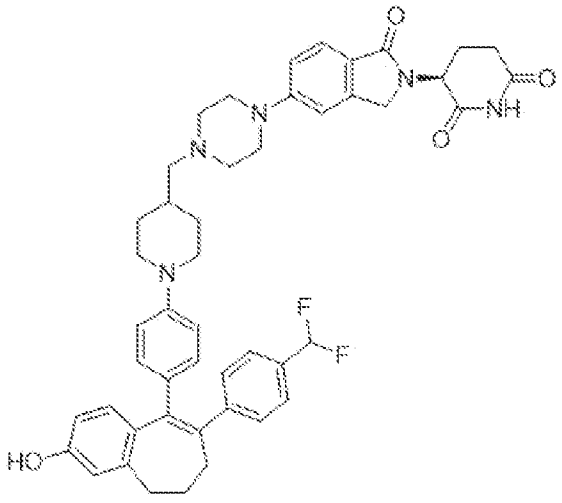
I-20	
I-21	
I-22	

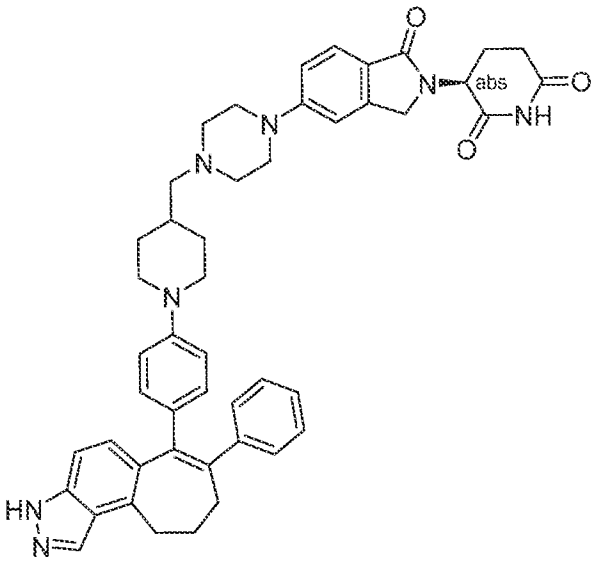
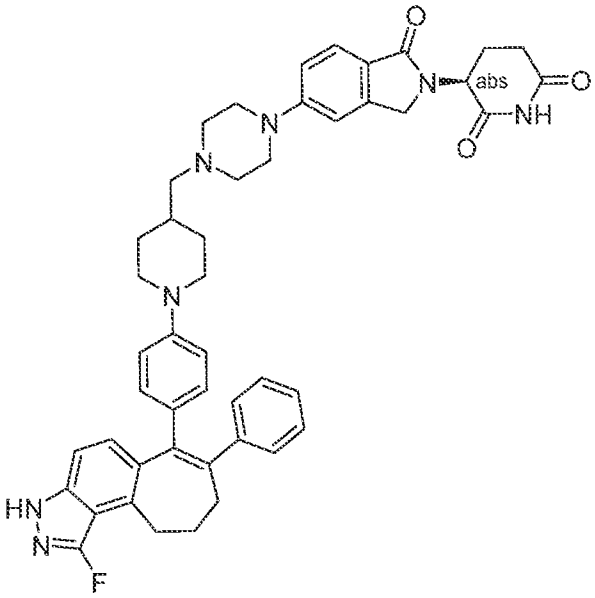
I-23	
I-24	
I-25	

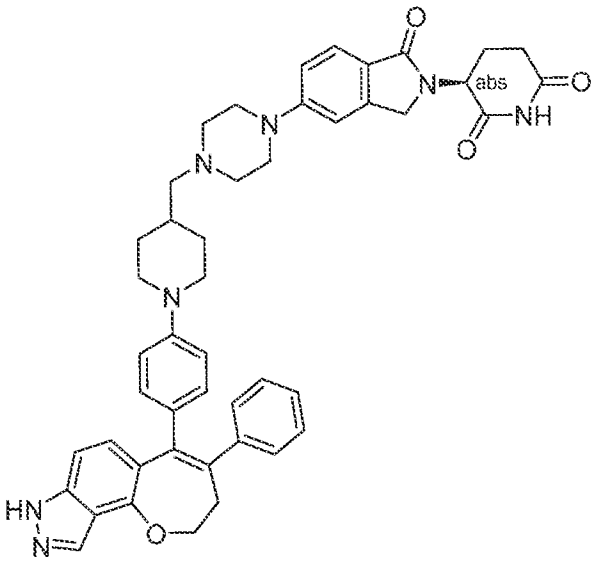
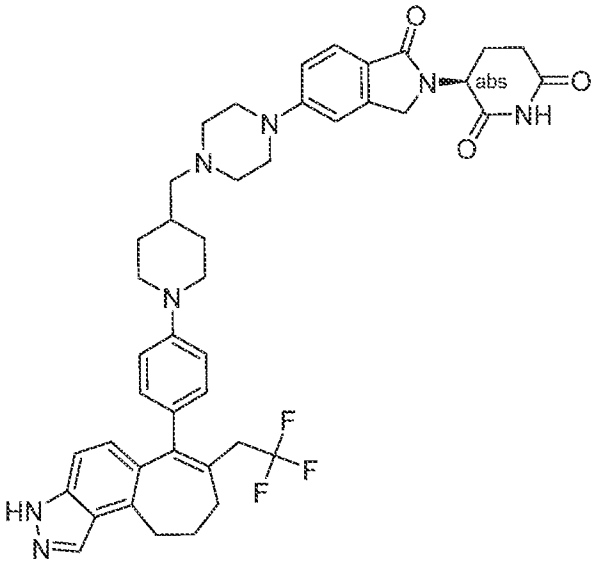
I-26	
I-27	
I-28	

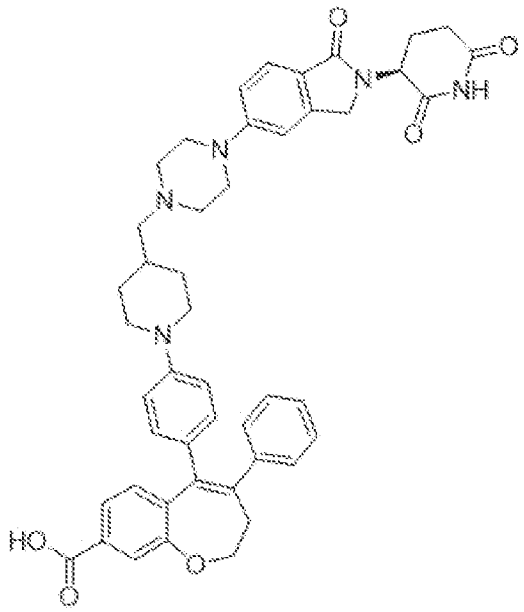
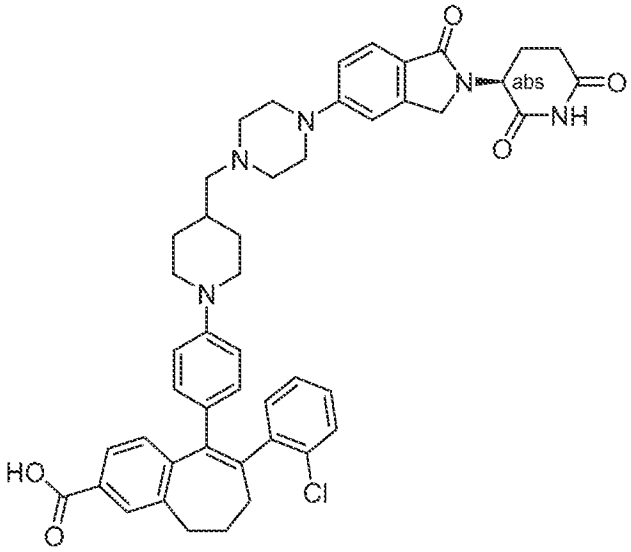
I-29	
I-30	
I-31	

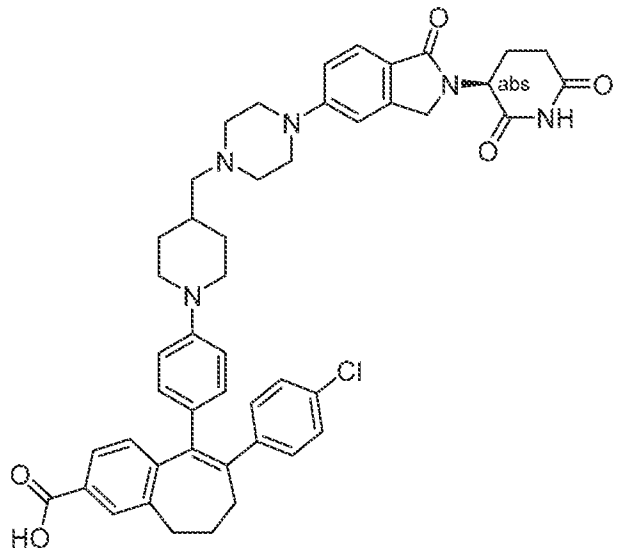
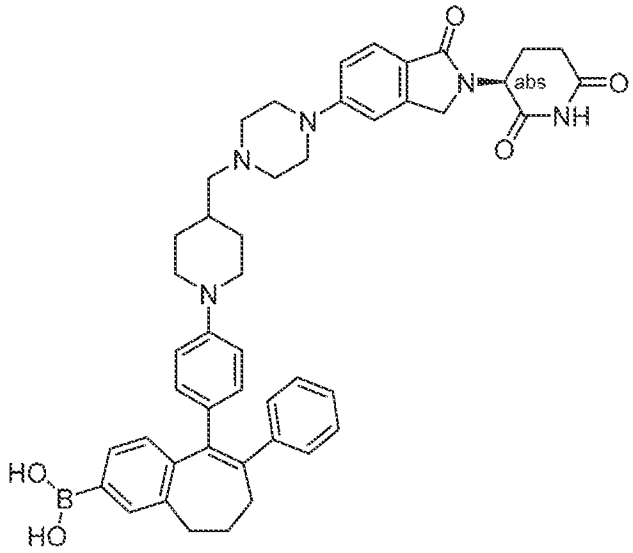
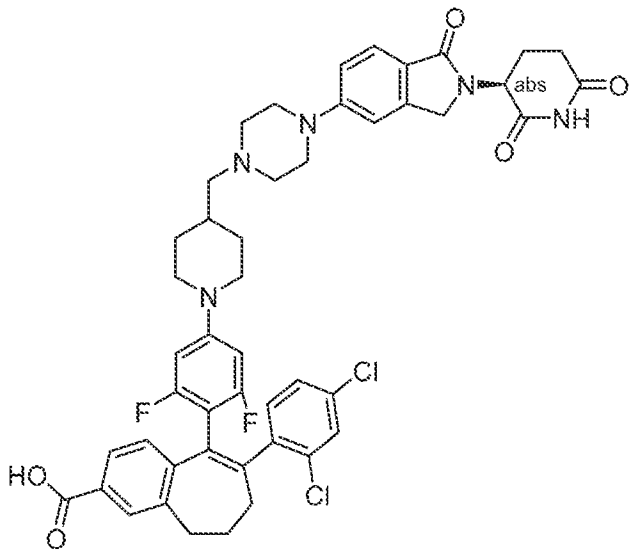
I-32	
I-33	
I-34	

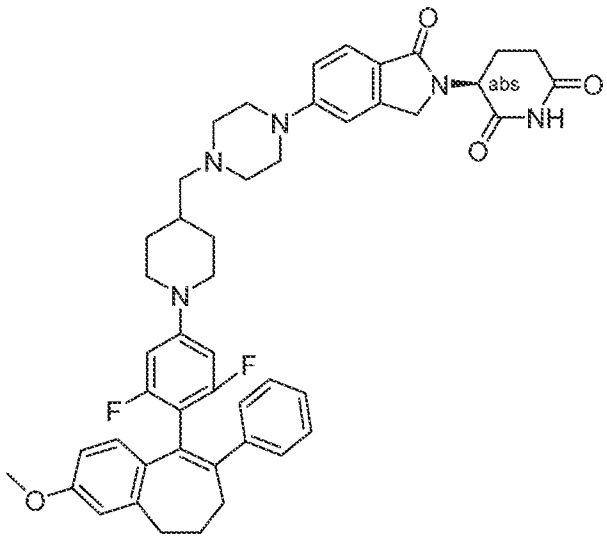
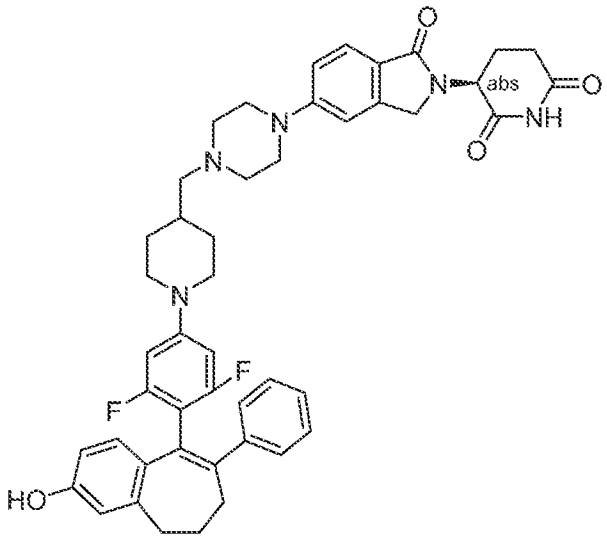
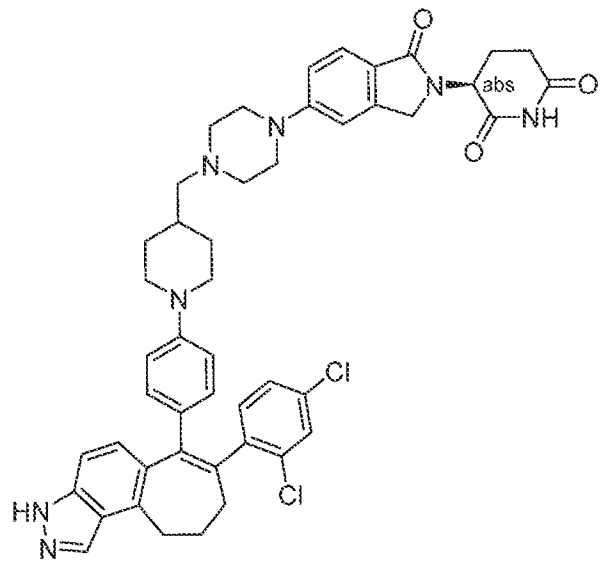
I-35	
I-36	
I-37	

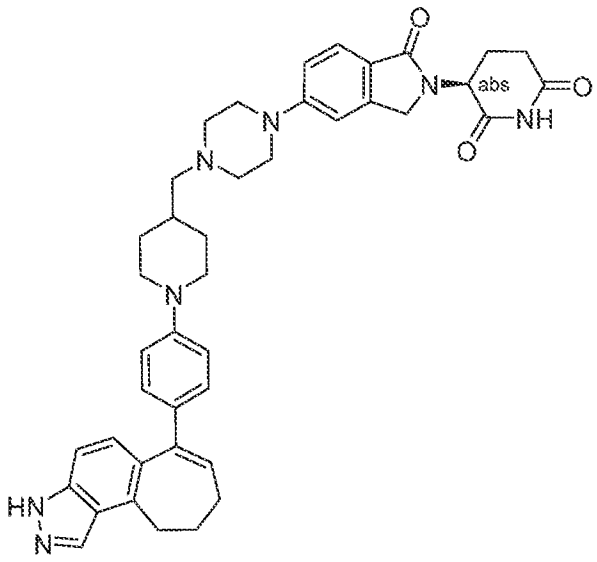
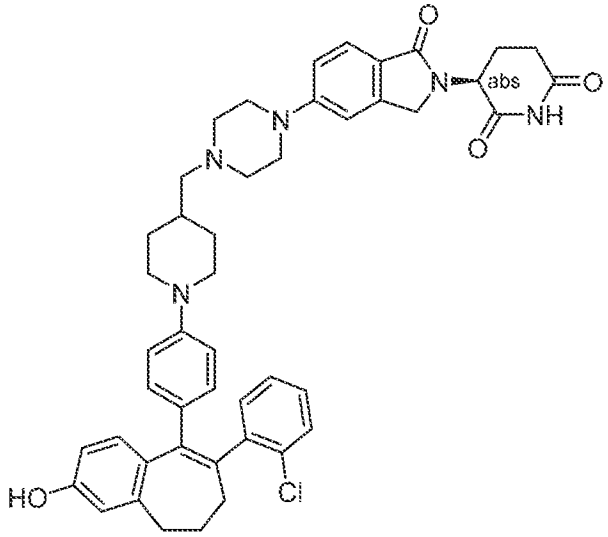
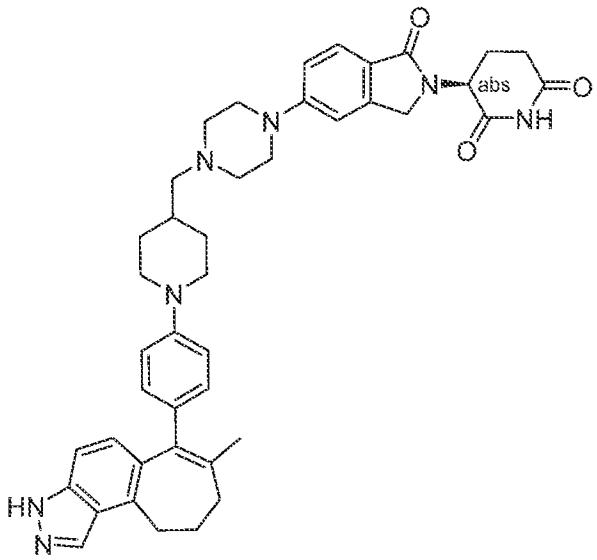
I-38	
I-39	

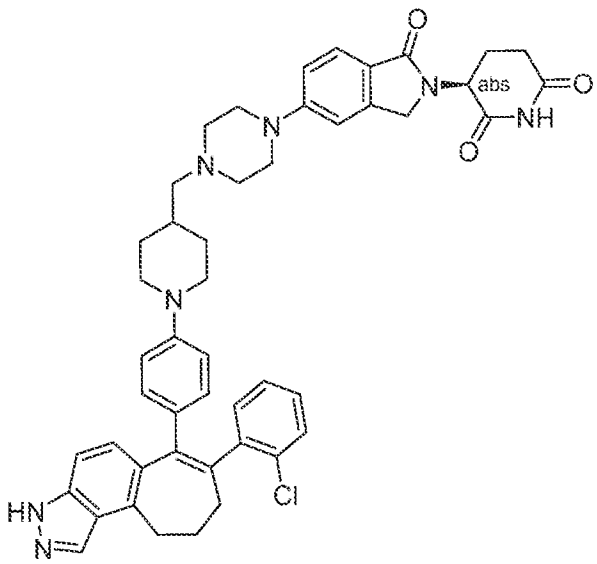
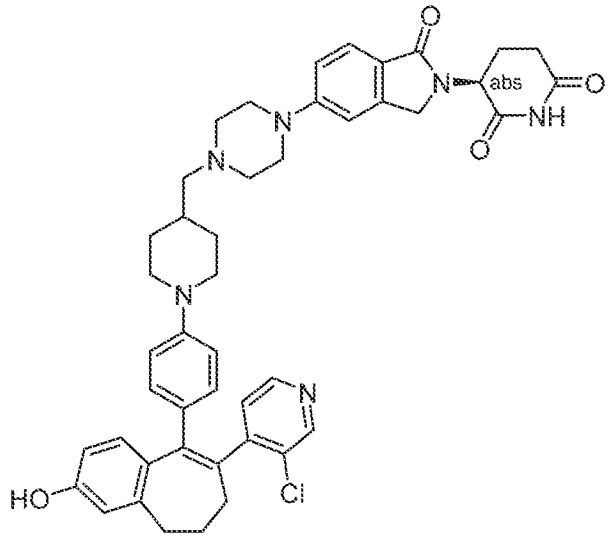
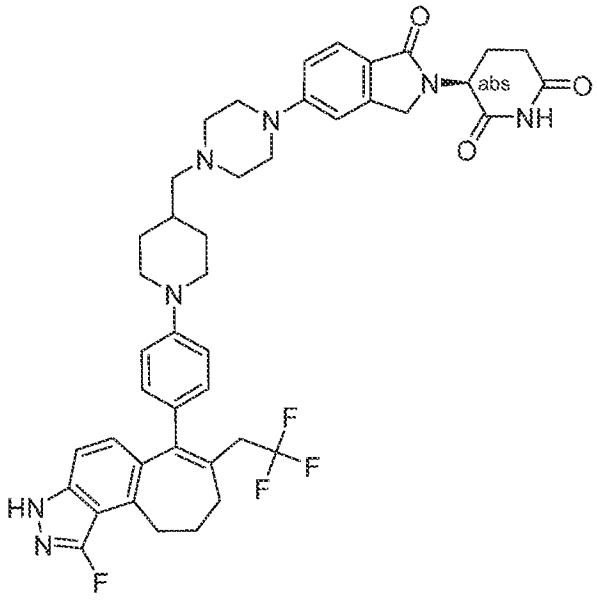
I-40	
I-41	

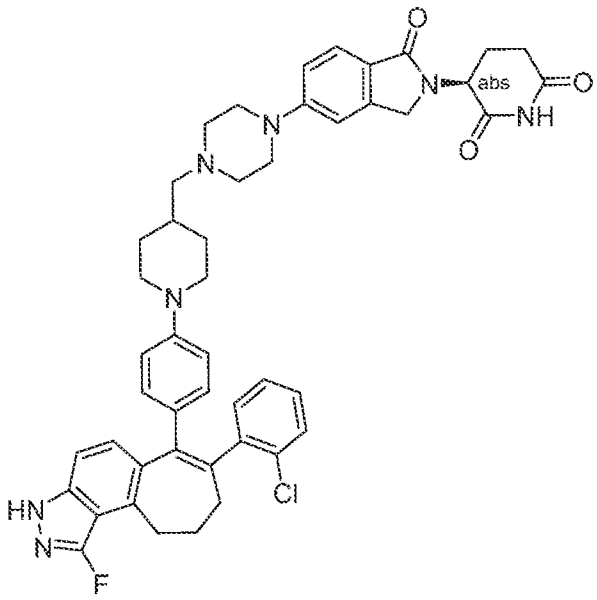
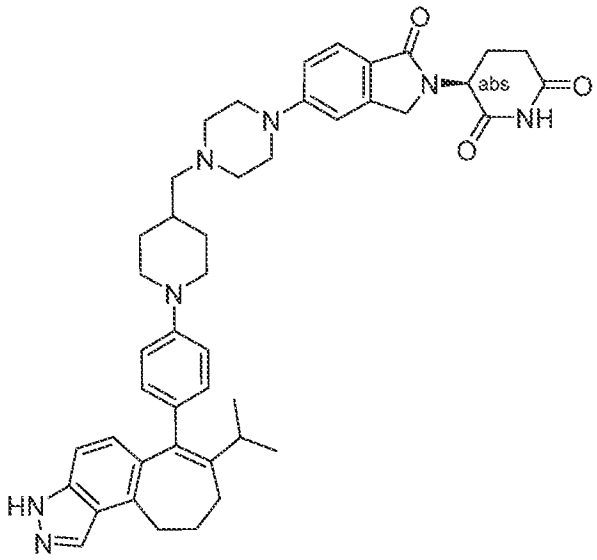
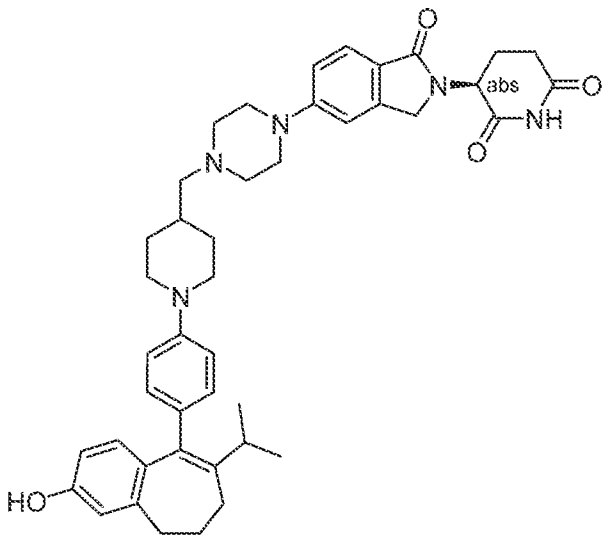
I-42 (*)	
I-43	

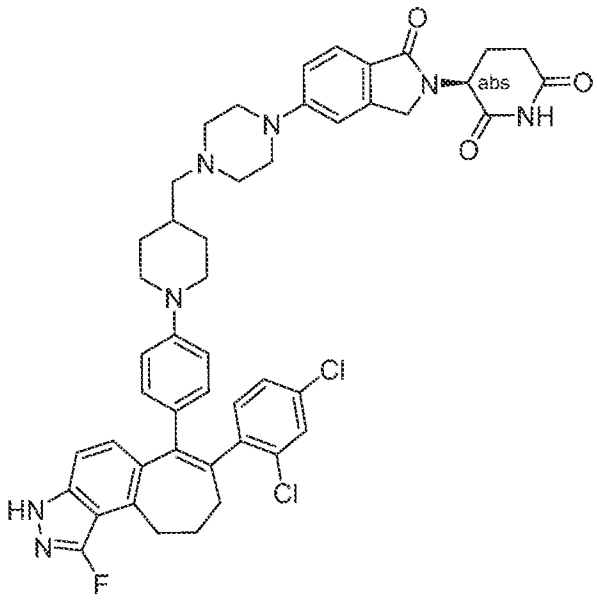
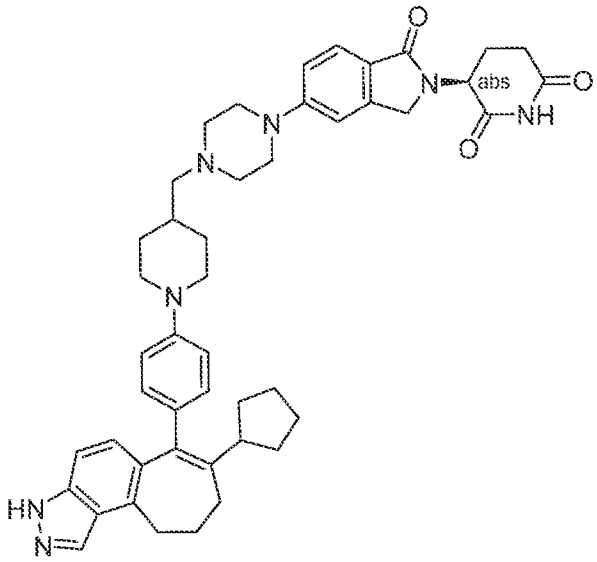
I-44	
I-45	
I-46	

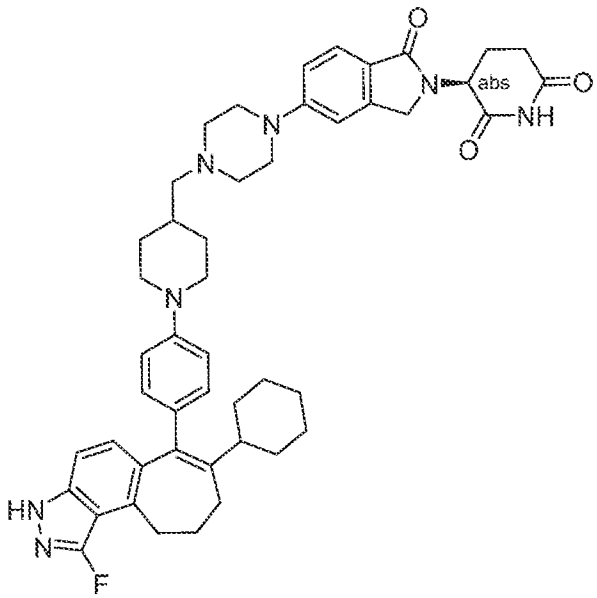
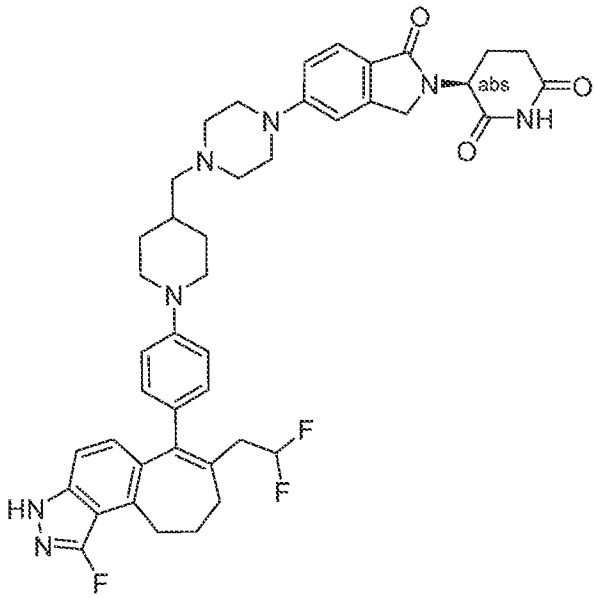
I-47	
I-48	
I-49	

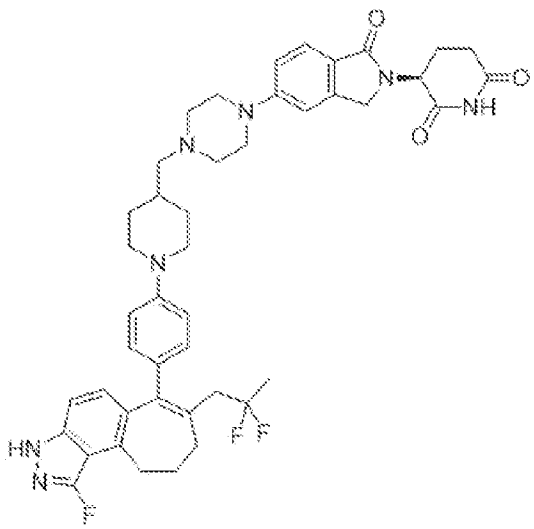
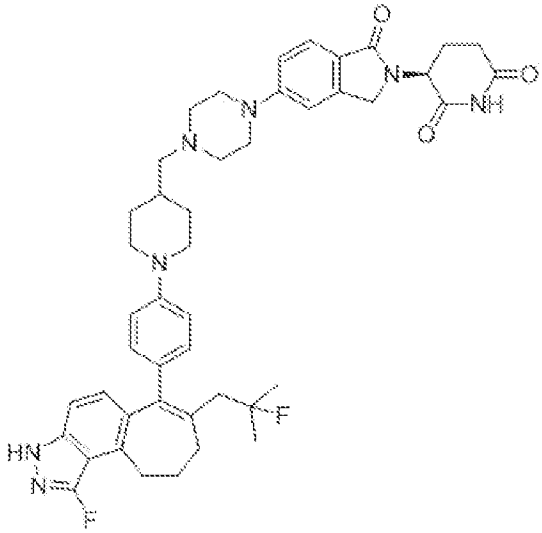
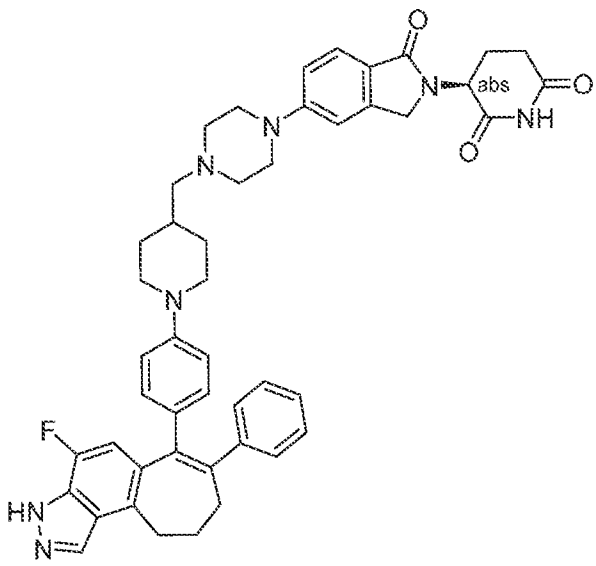
I-50	
I-51	
I-52	

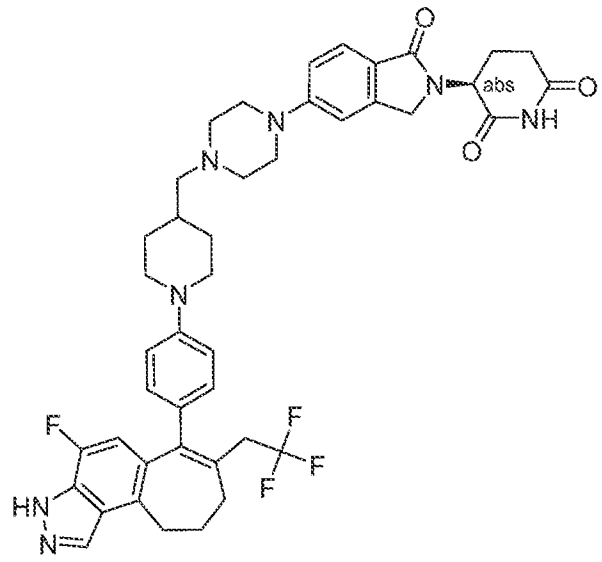
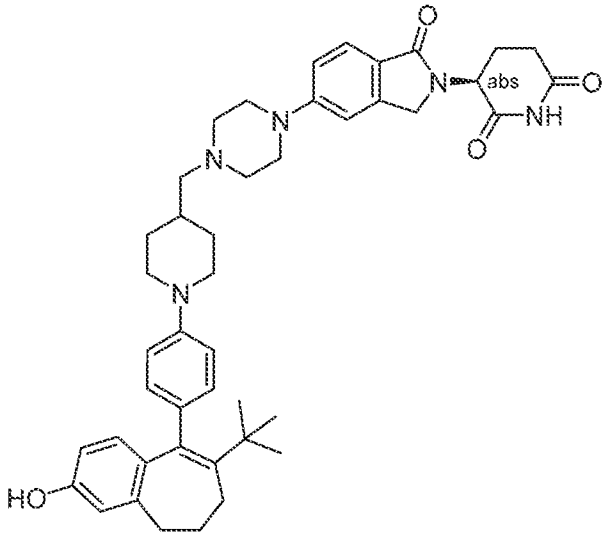
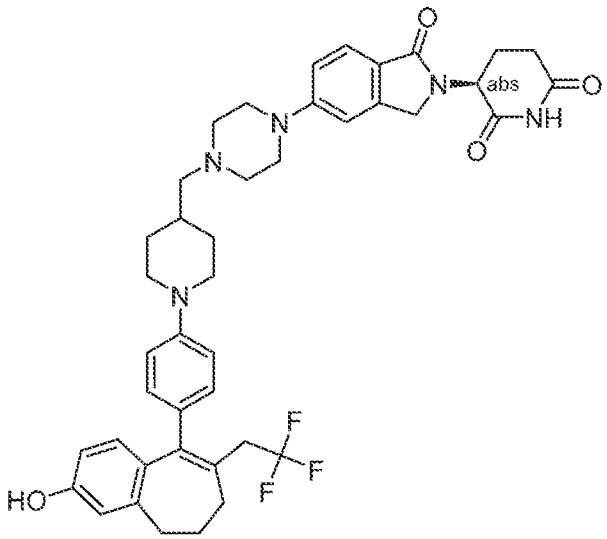
I-53	
I-54	
I-55	

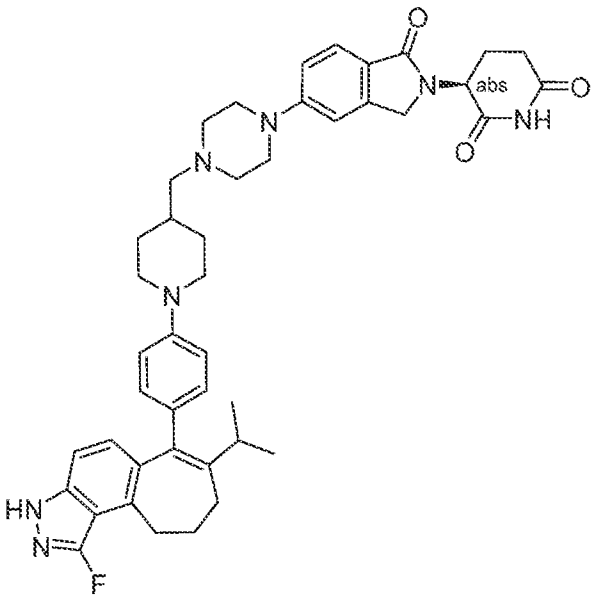
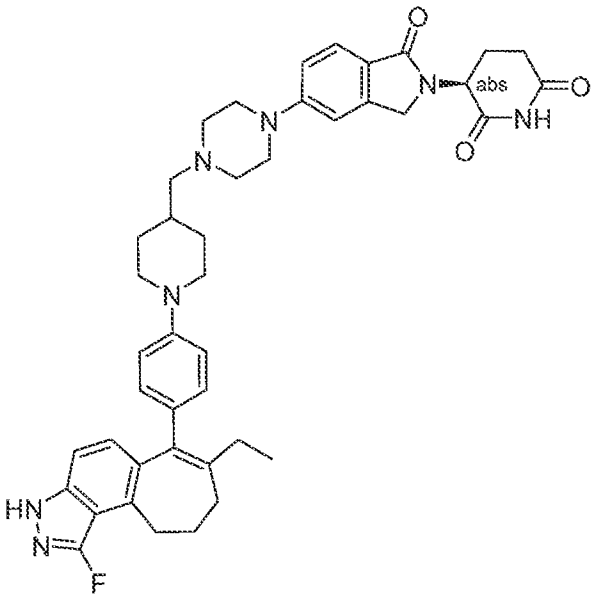
I-56	
I-57	
I-58	

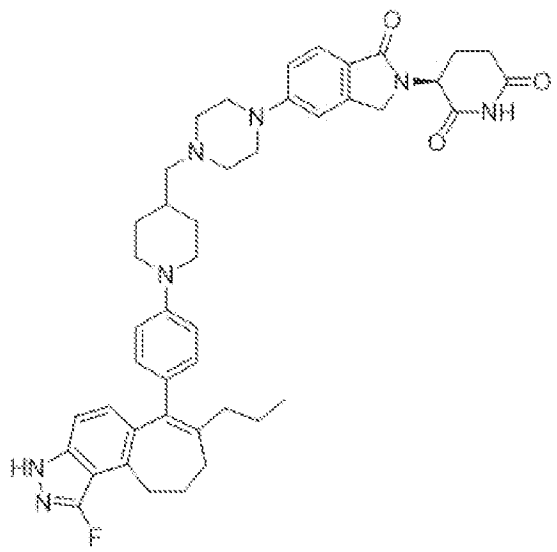
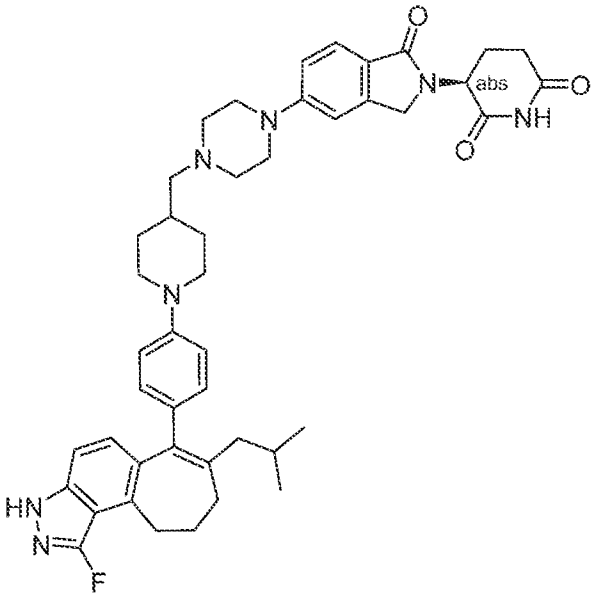
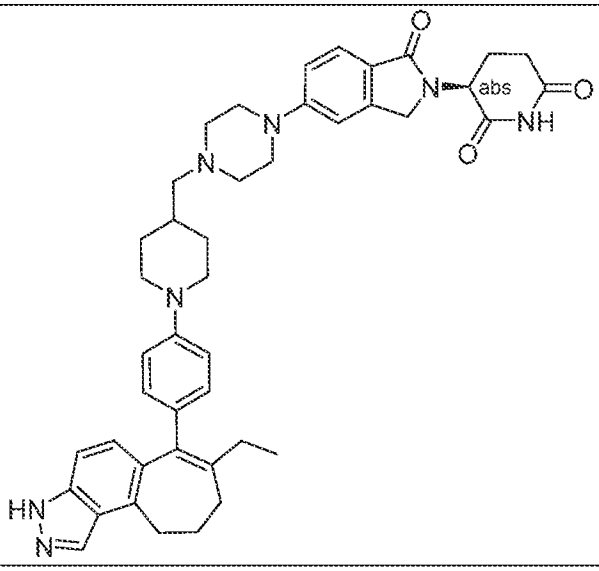
I-59	
I-60	

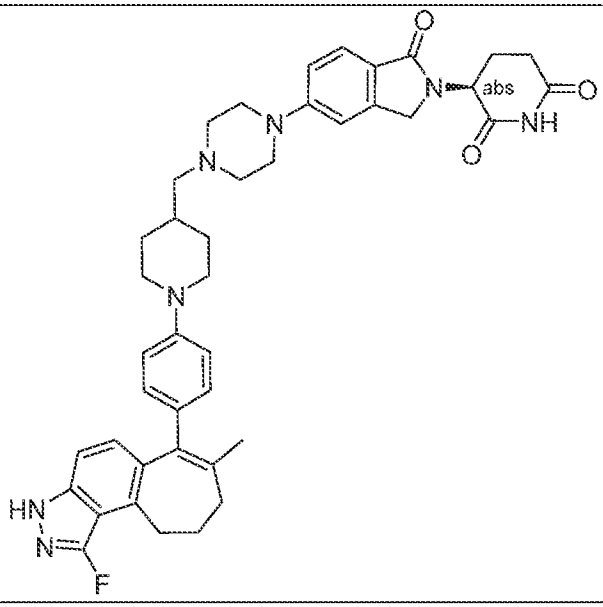
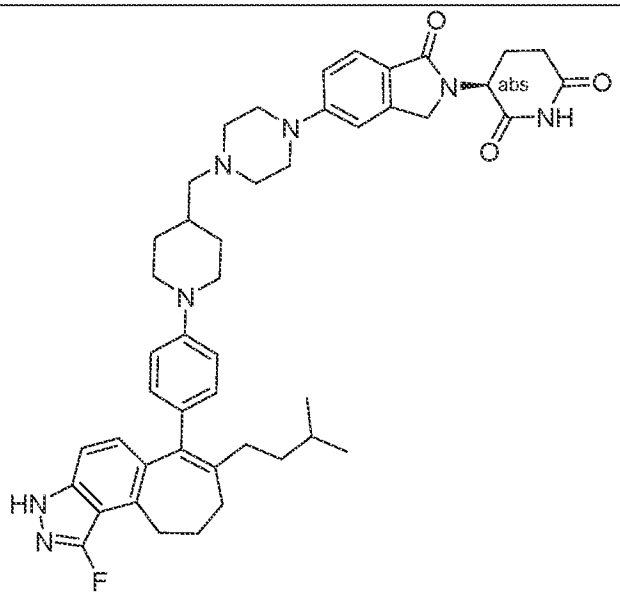
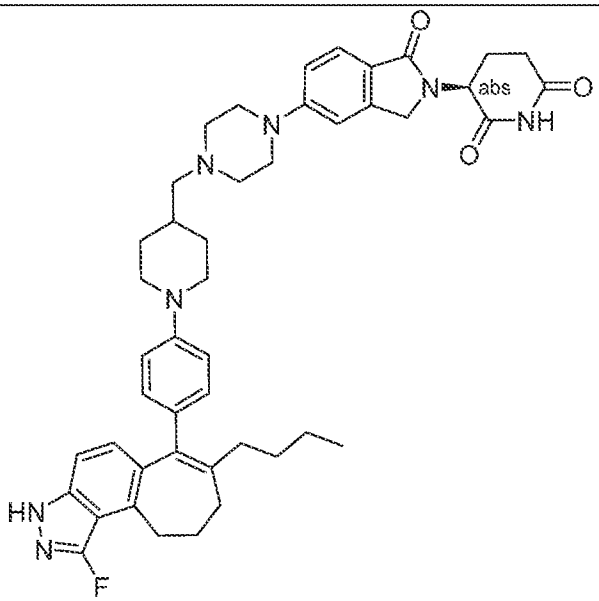
I-61	
I-62	

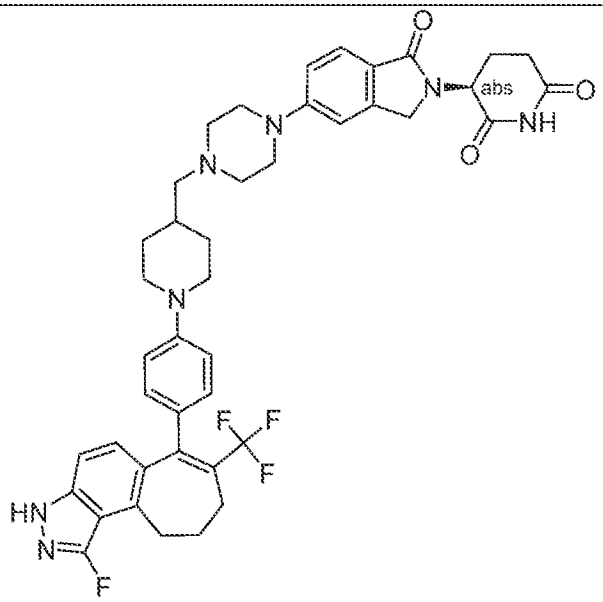
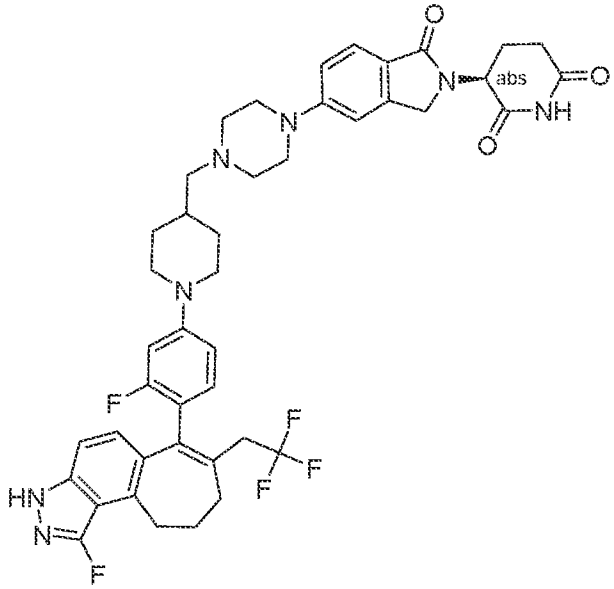
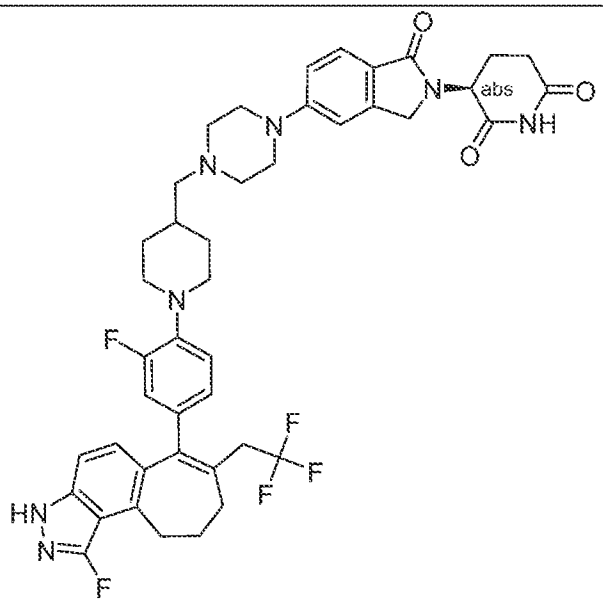
I-63 (*)	
I-64 (*)	
I-65	

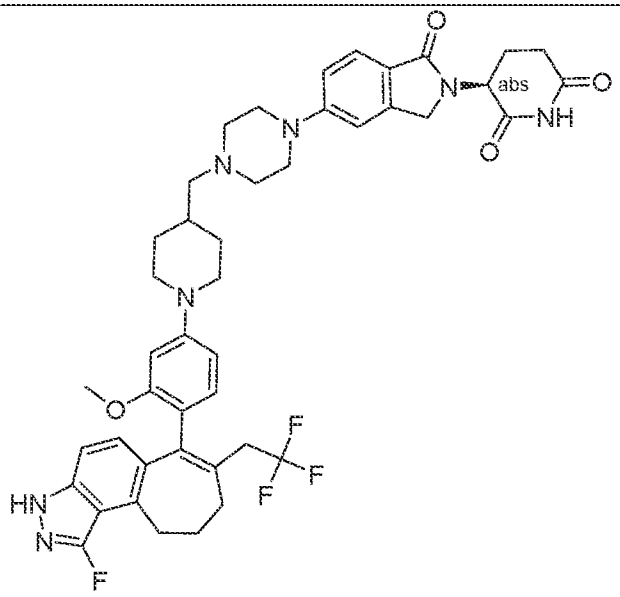
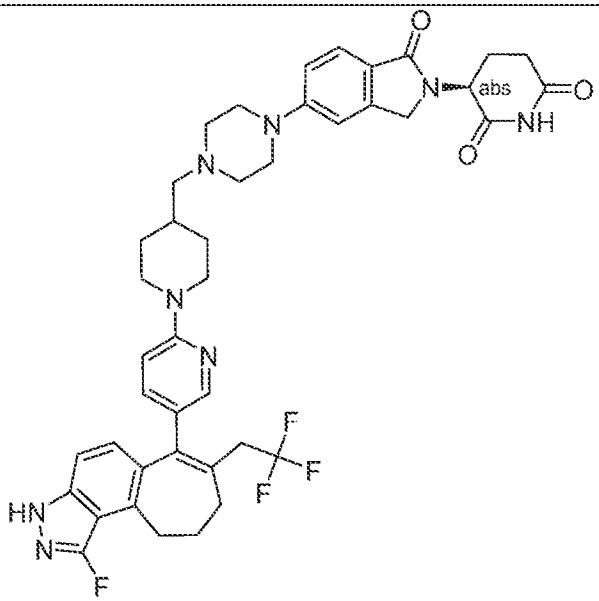
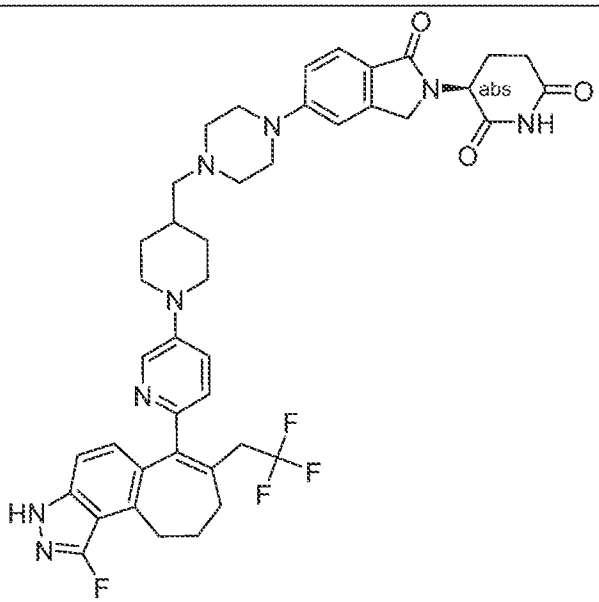
I-66	
I-67	
I-68	

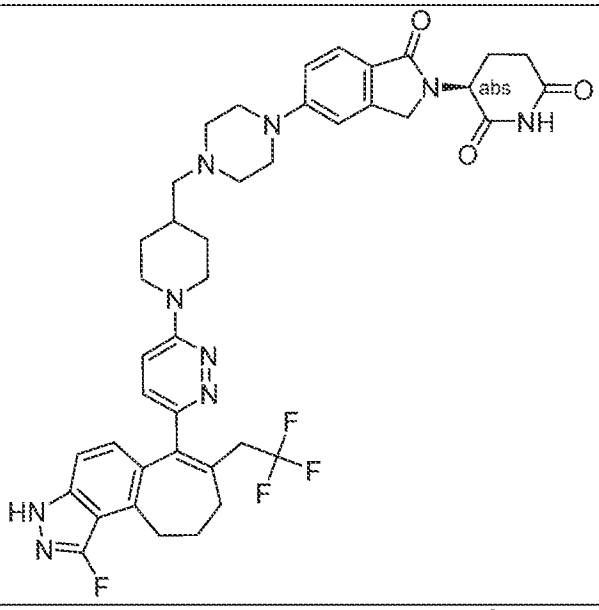
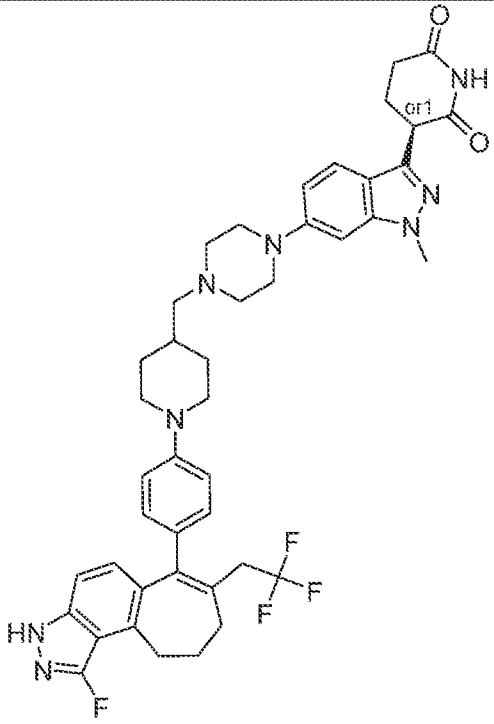
I-69	
I-70	

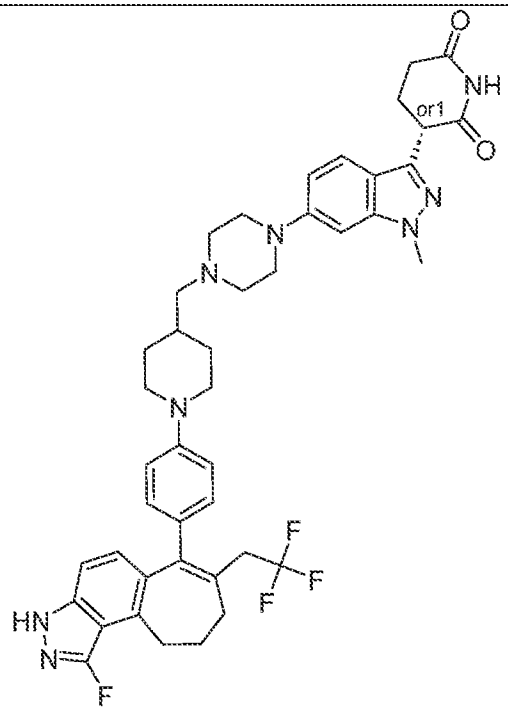
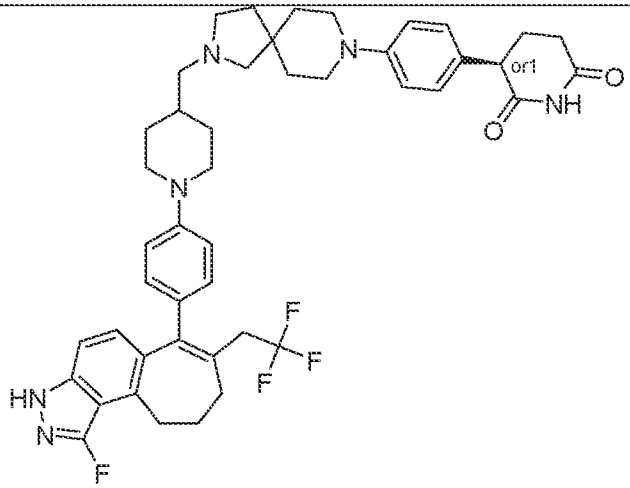
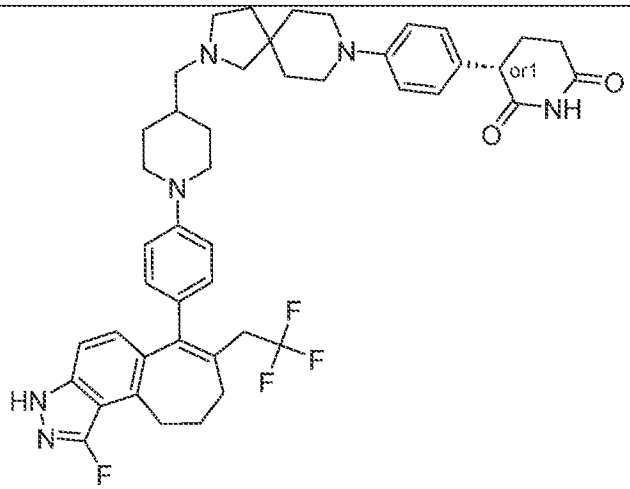
I-71 (*)	
I-72	
I-73	

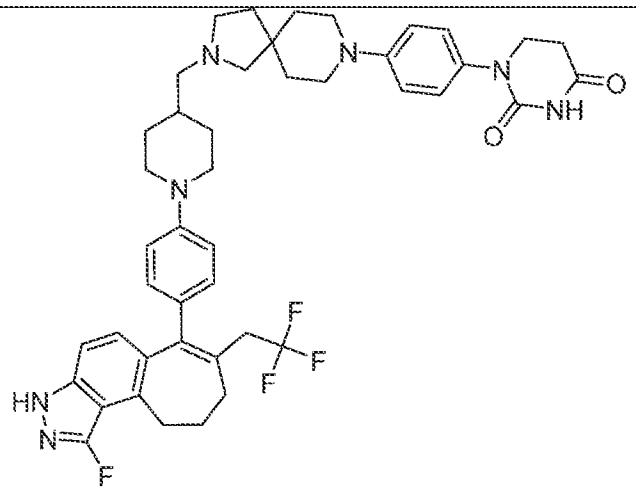
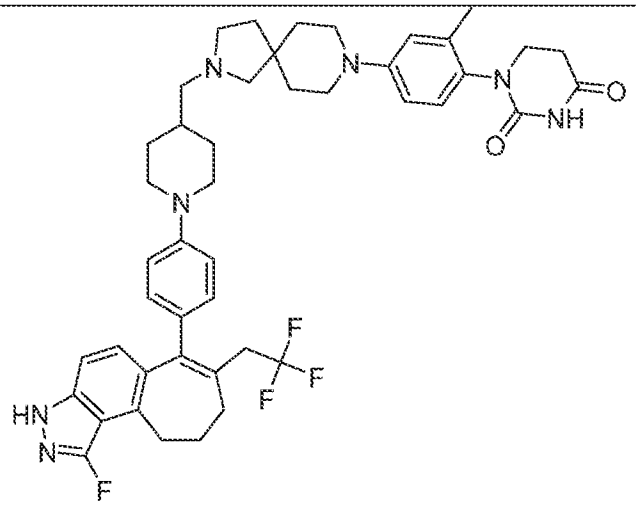
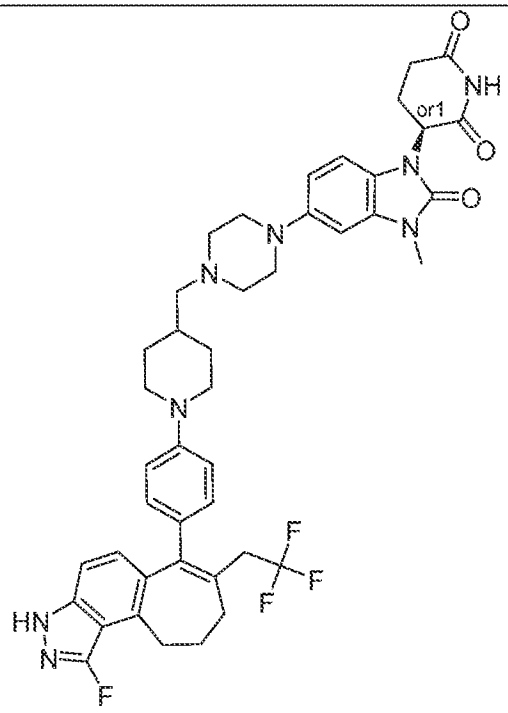
I-74	
I-75	
I-76	

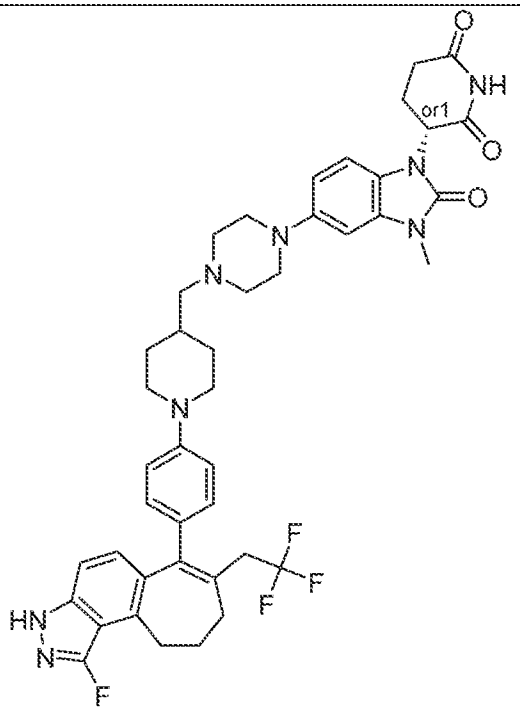
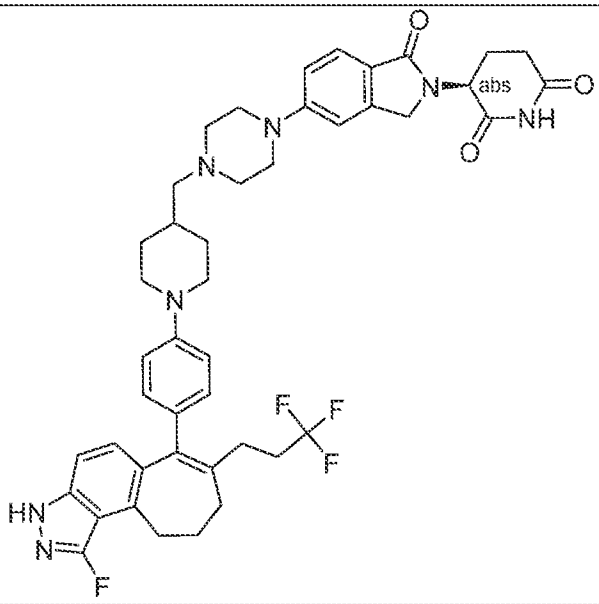
I-77	
I-78	
I-79	

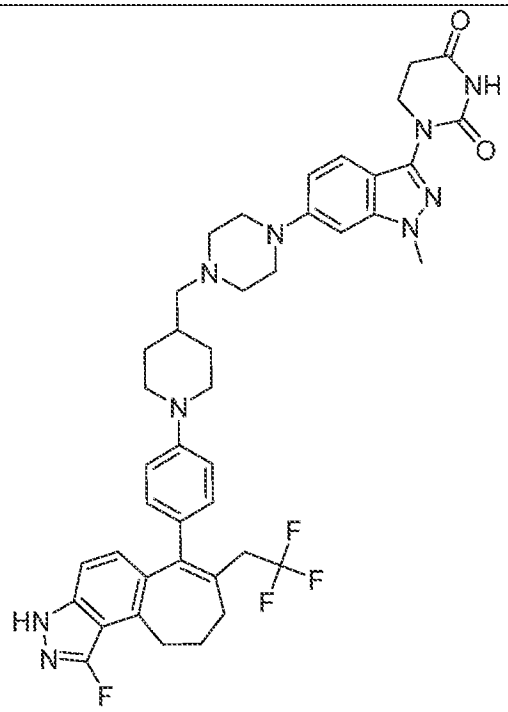
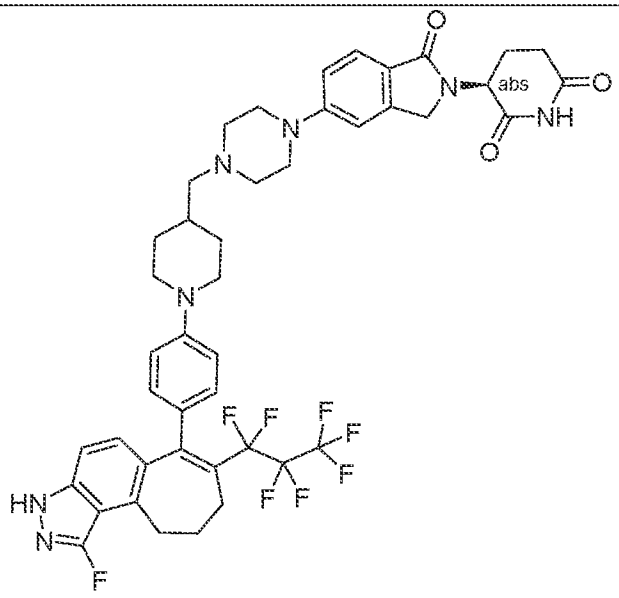
I-80	
I-81	
I-82	

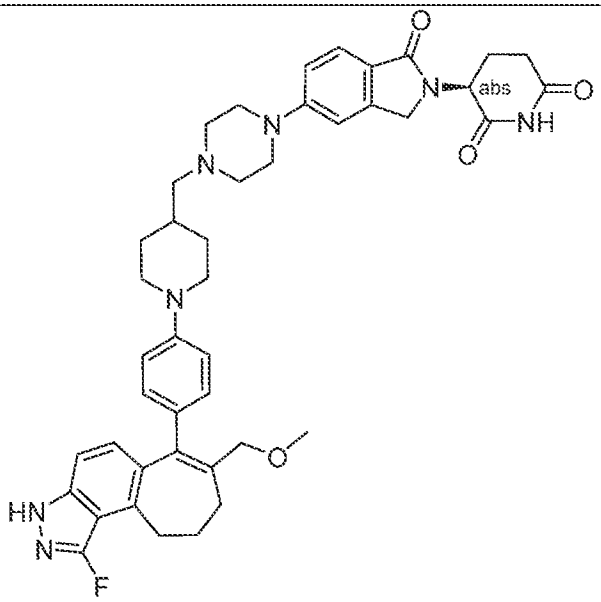
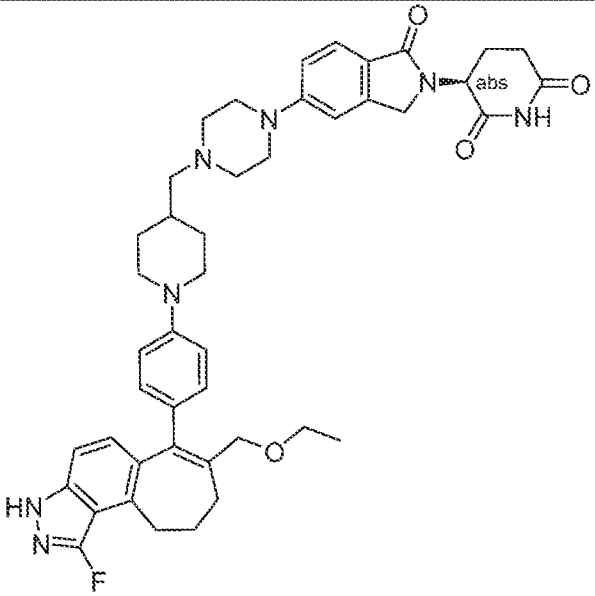
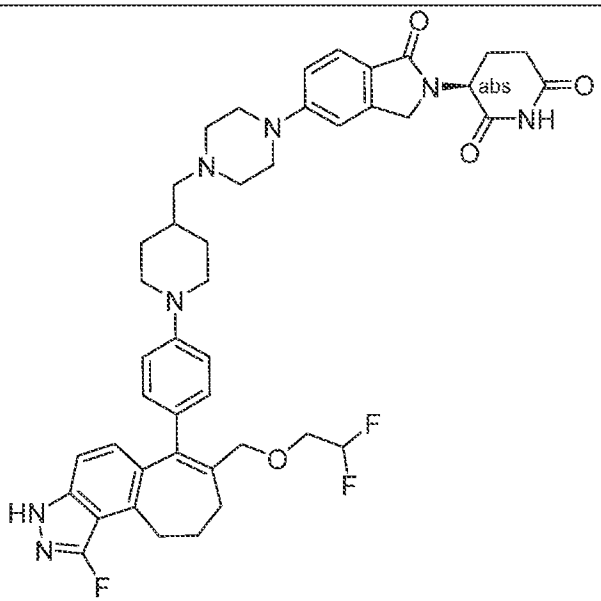
I-83	
I-84	

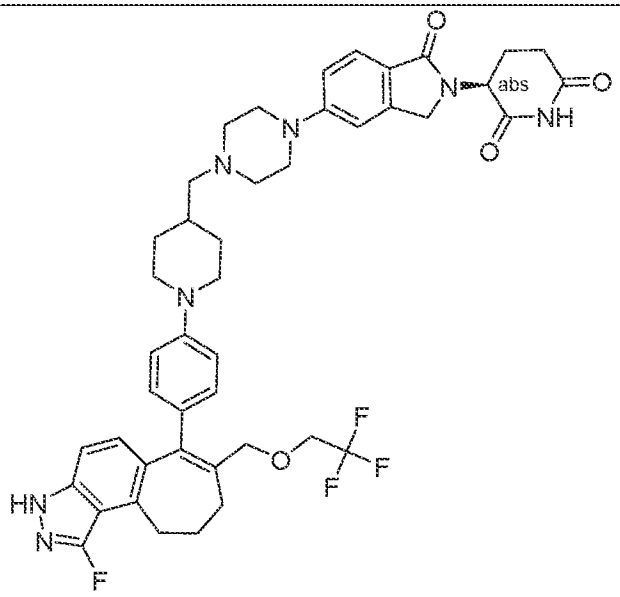
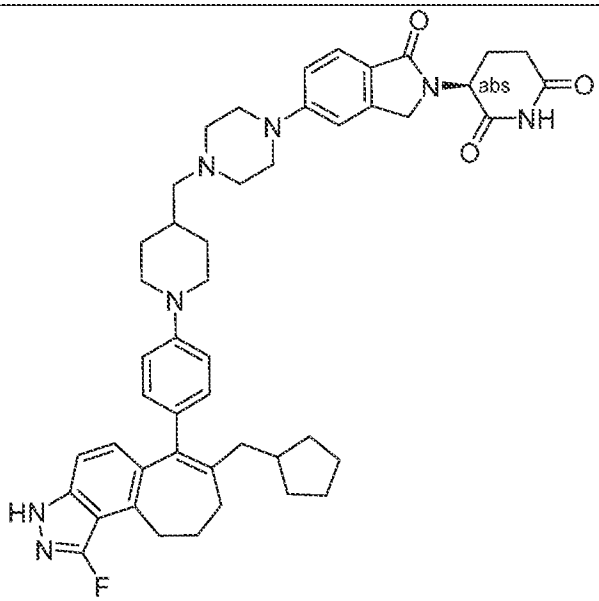
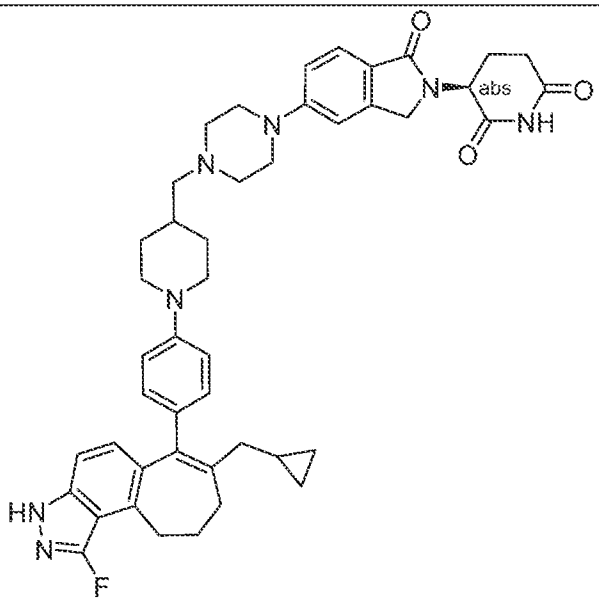
I-85	
I-86	
I-87	

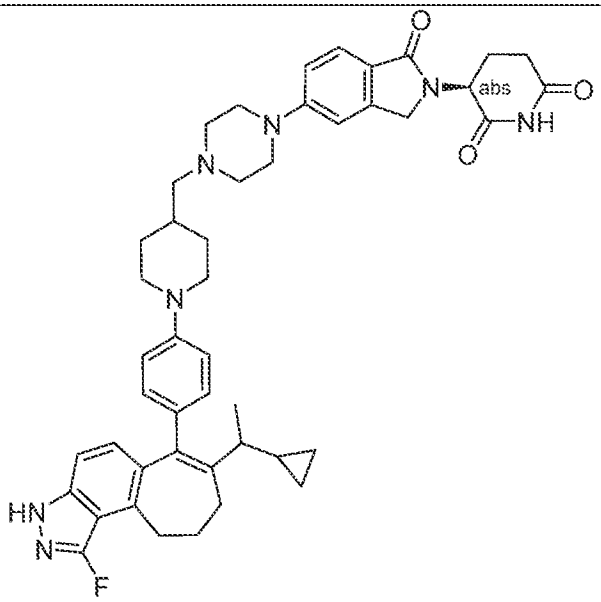
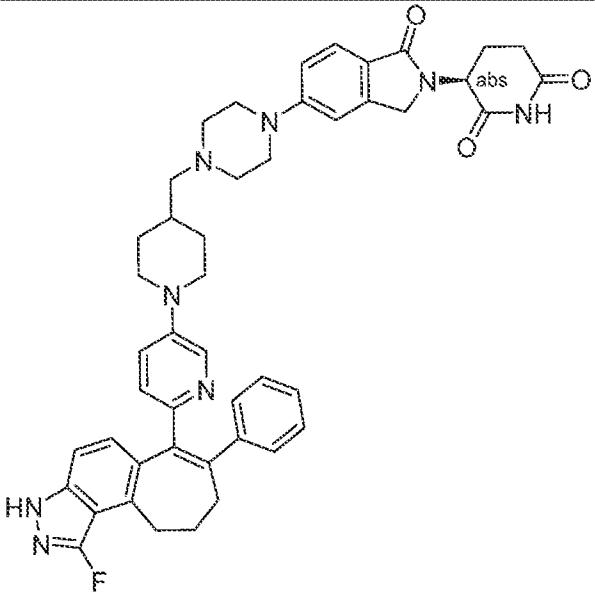
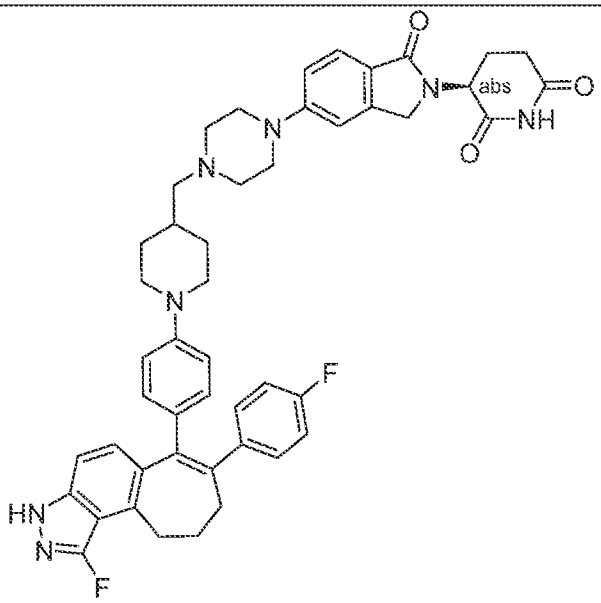
I-88	
I-89	
I-90	

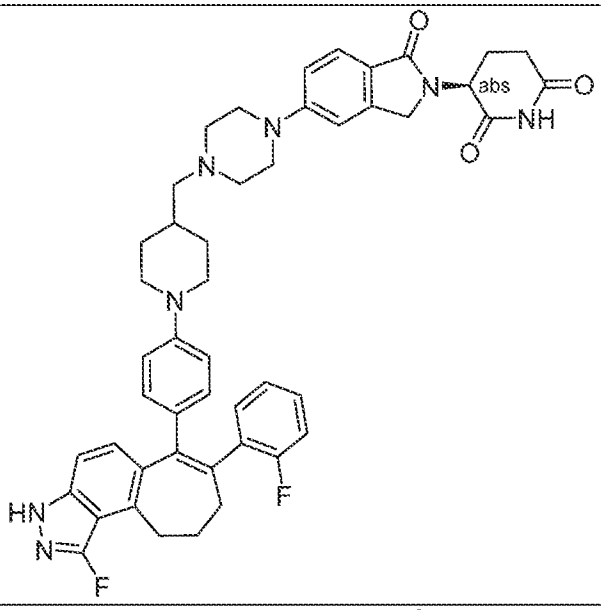
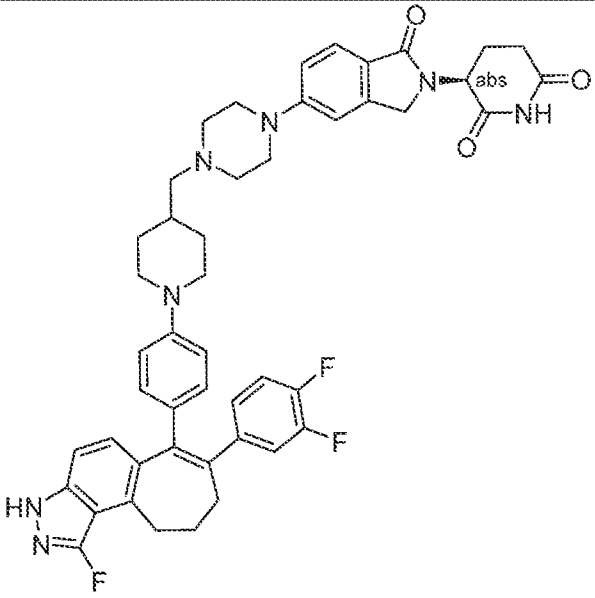
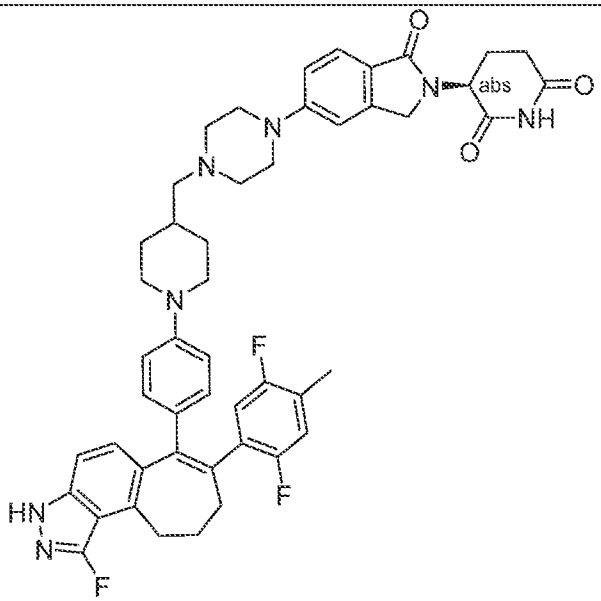
I-91	
I-92	

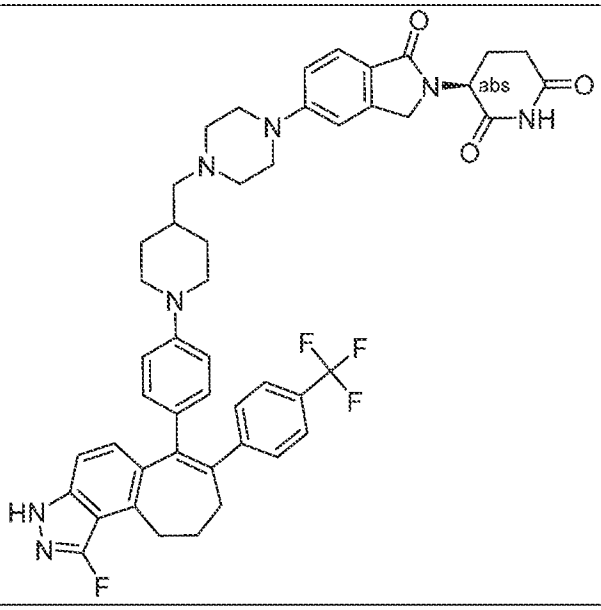
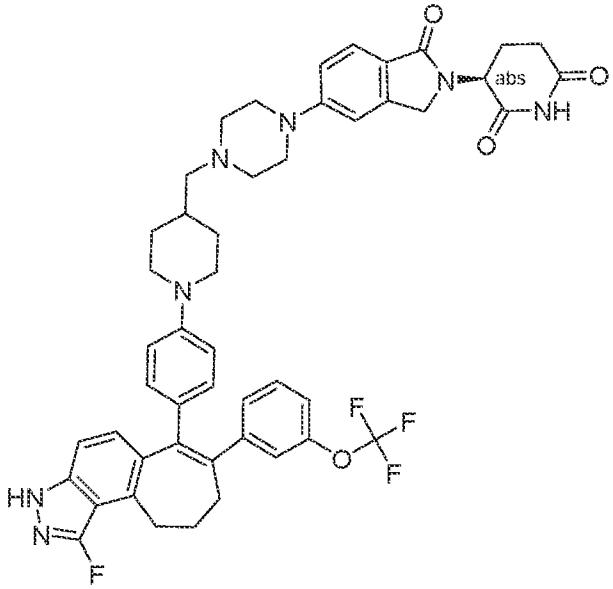
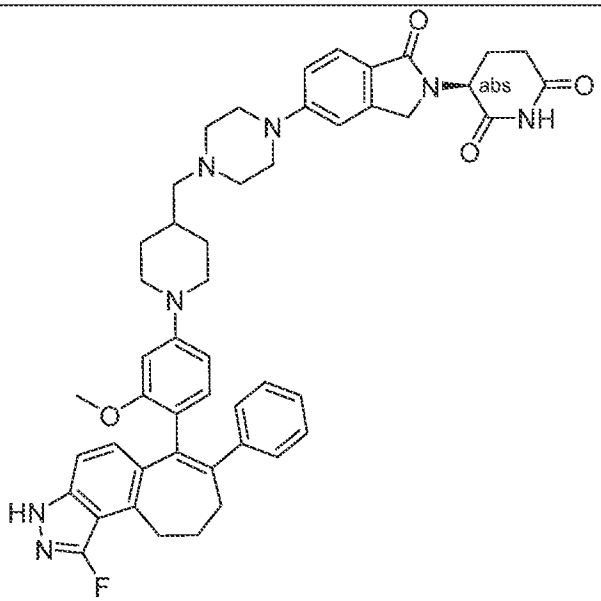
I-93	
I-94	

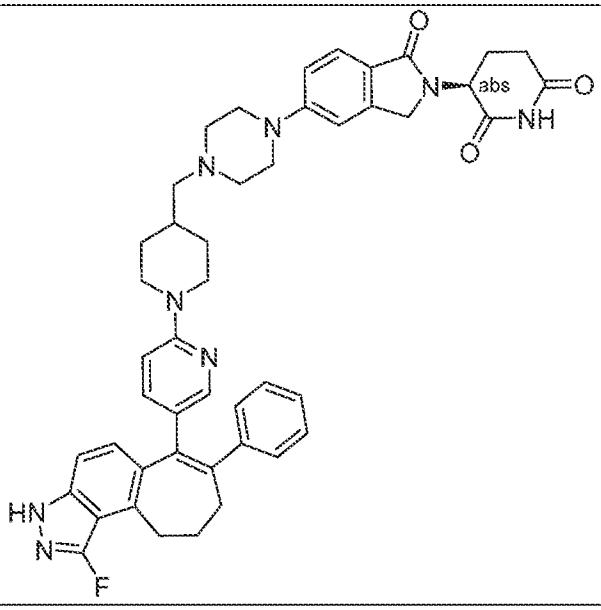
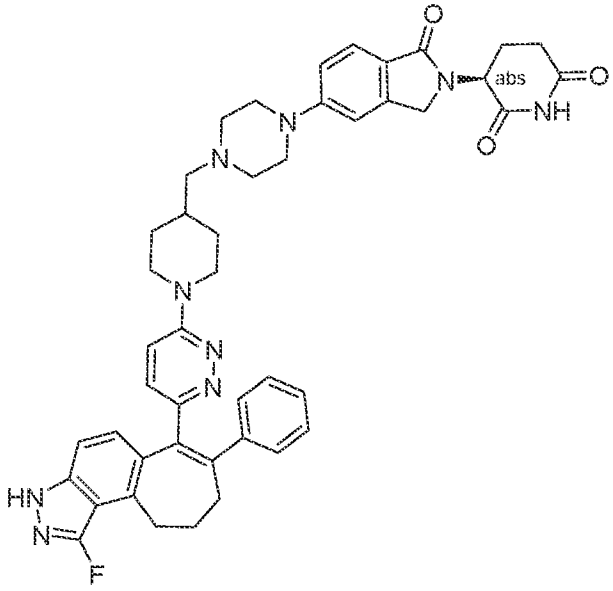
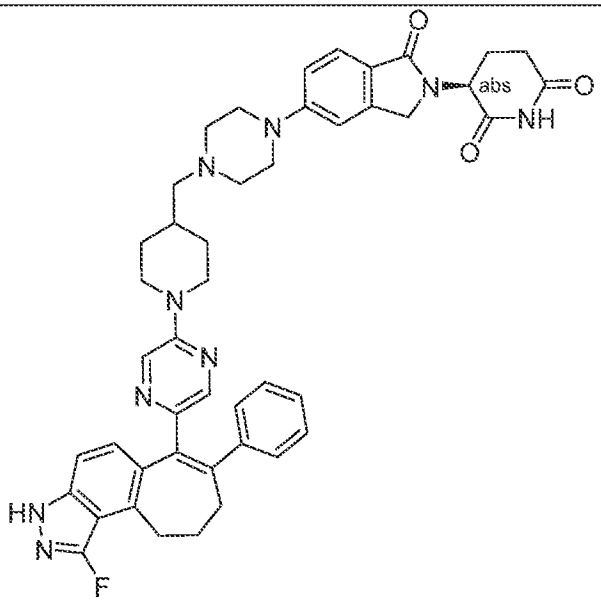
I-95	
I-96	
I-97	

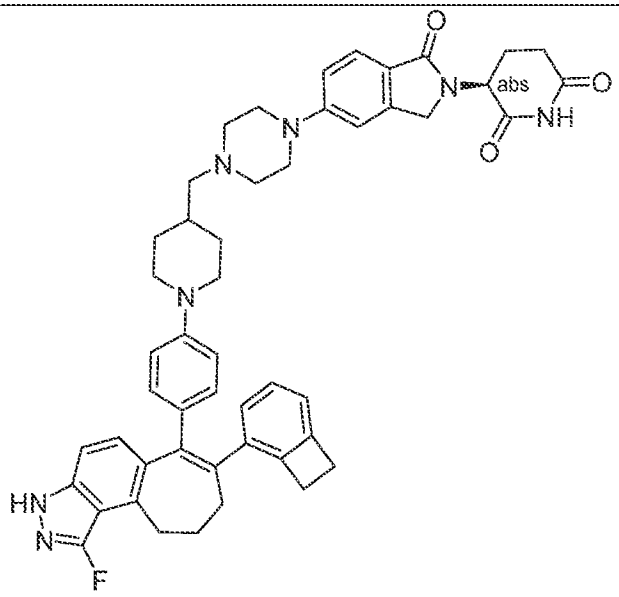
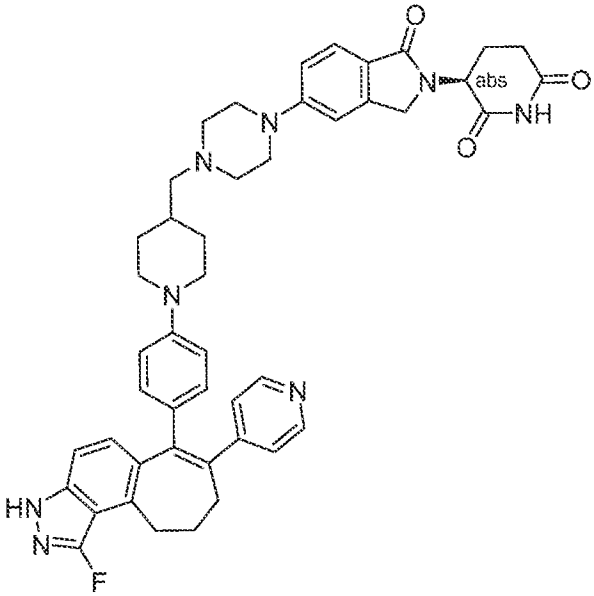
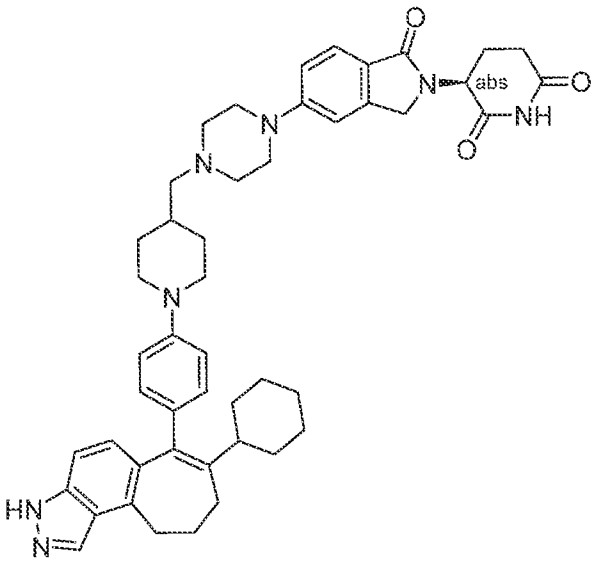
I-98	
I-99	
I-100	

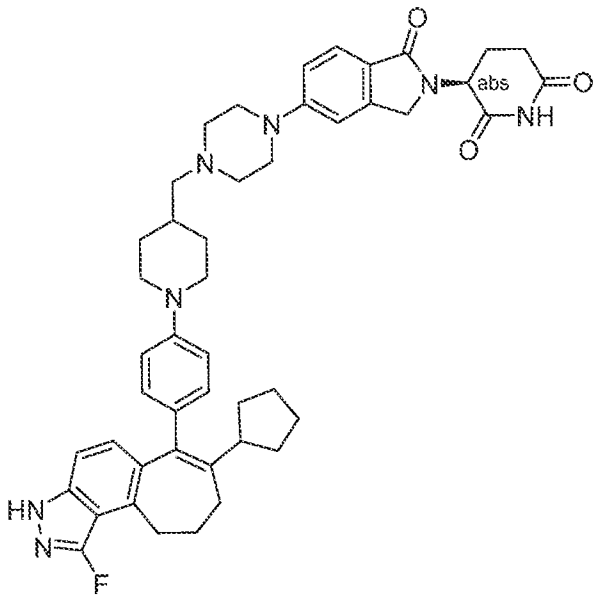
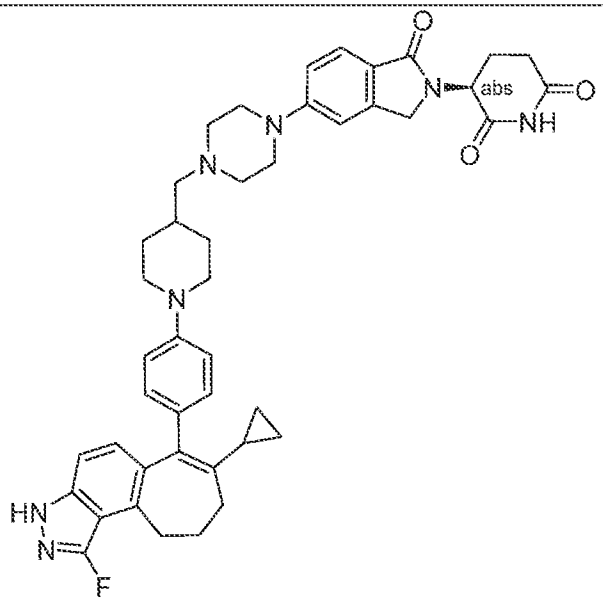
I-101	
I-102	
I-103	

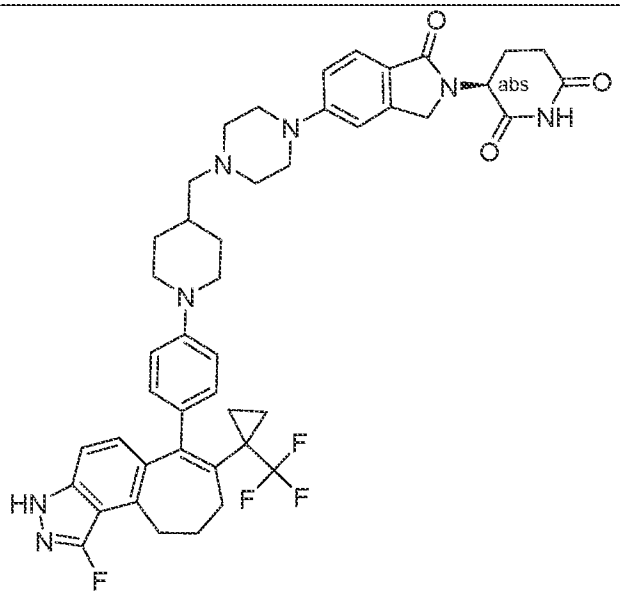
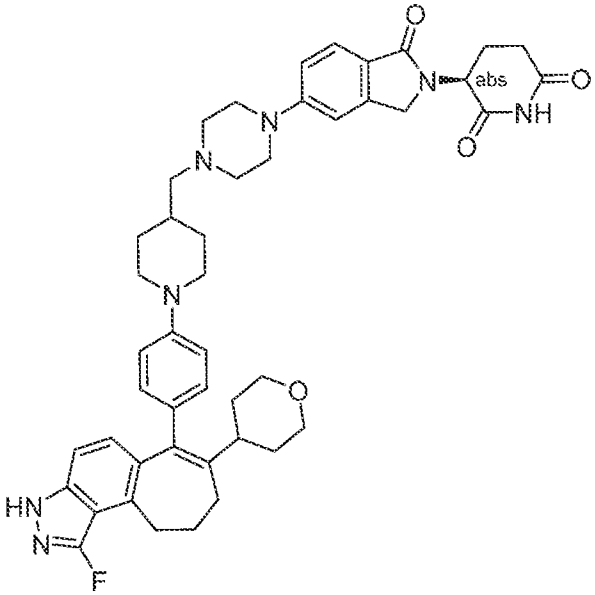
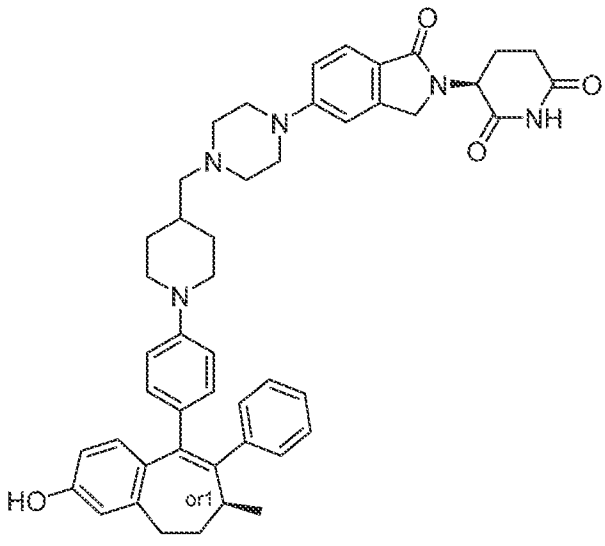
I-104	
I-105	
I-106	

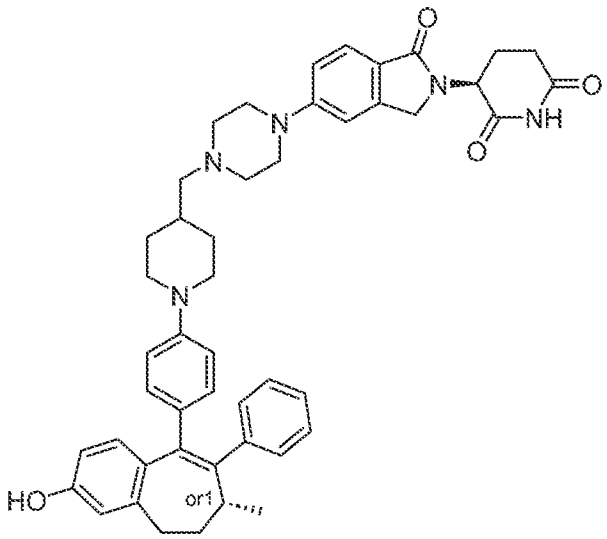
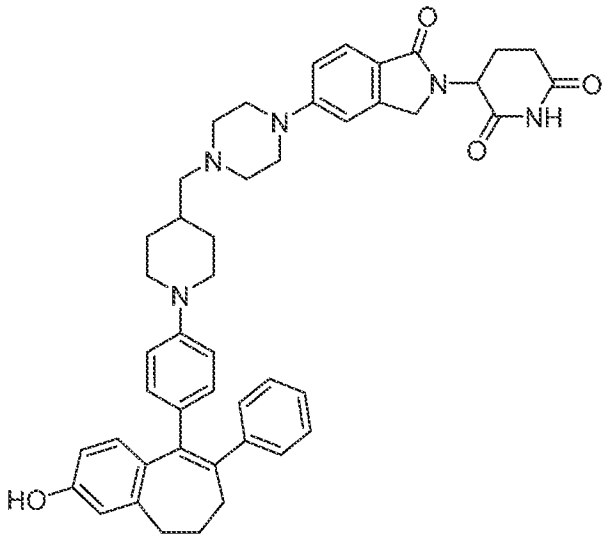
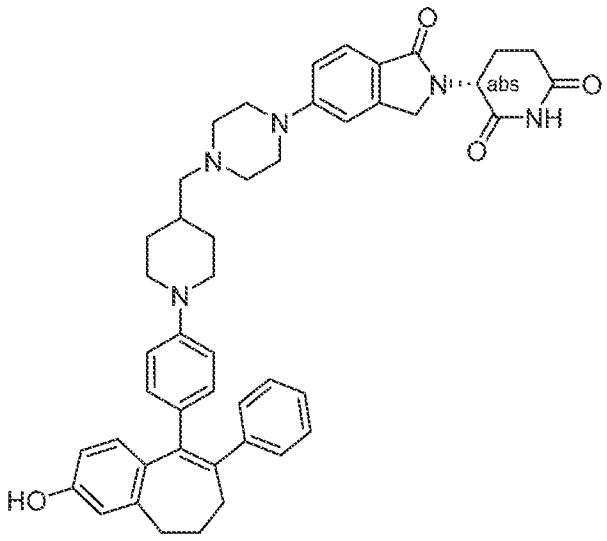
I-107	
I-108	
I-109	

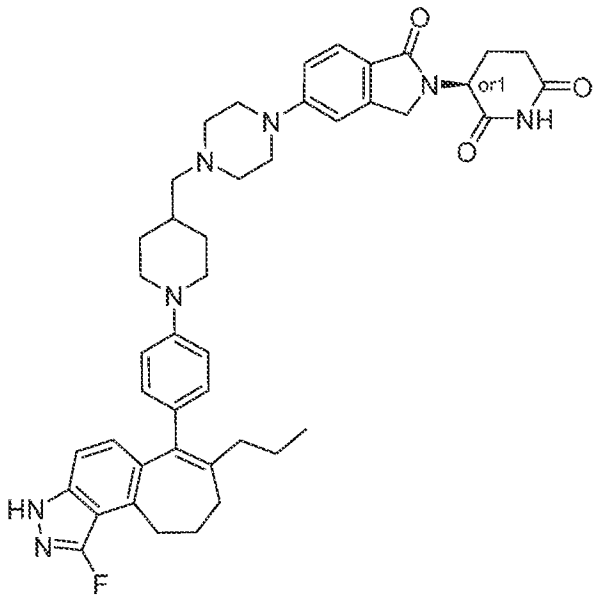
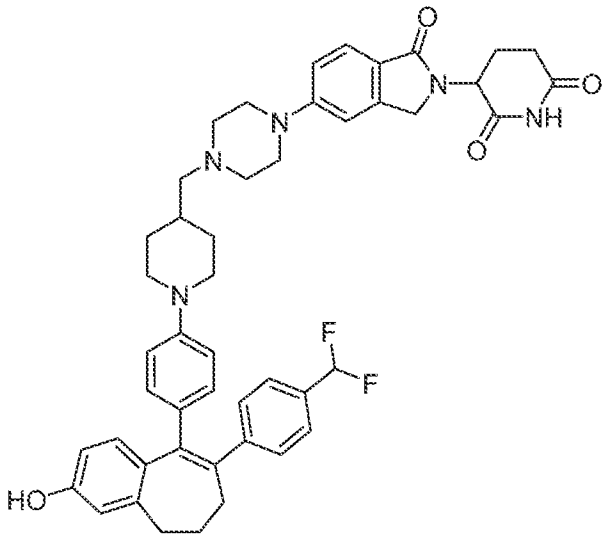
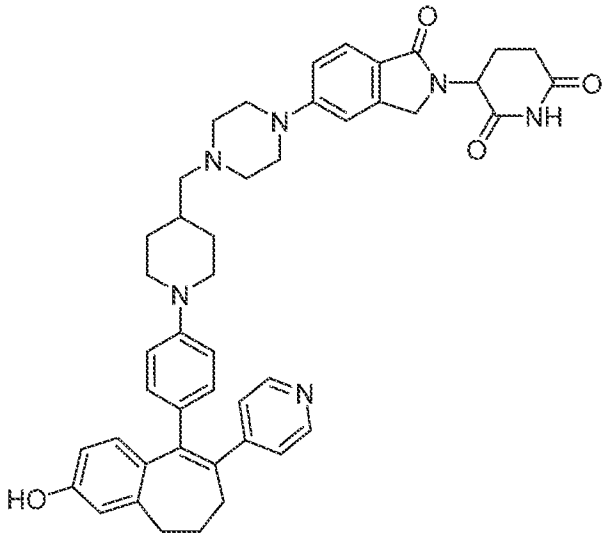
I-110	
I-111	
I-112	

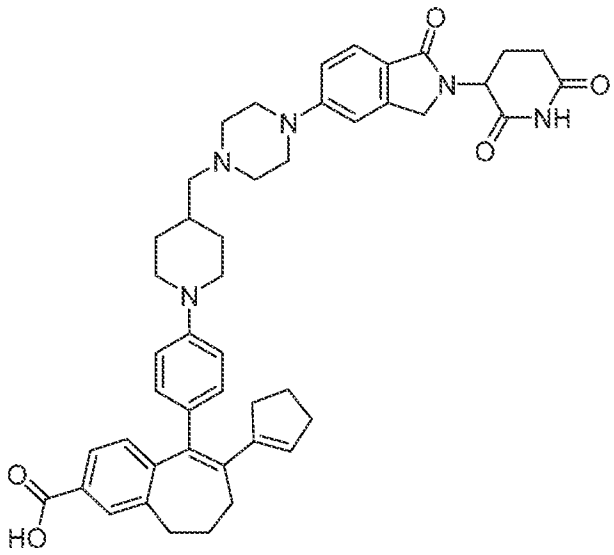
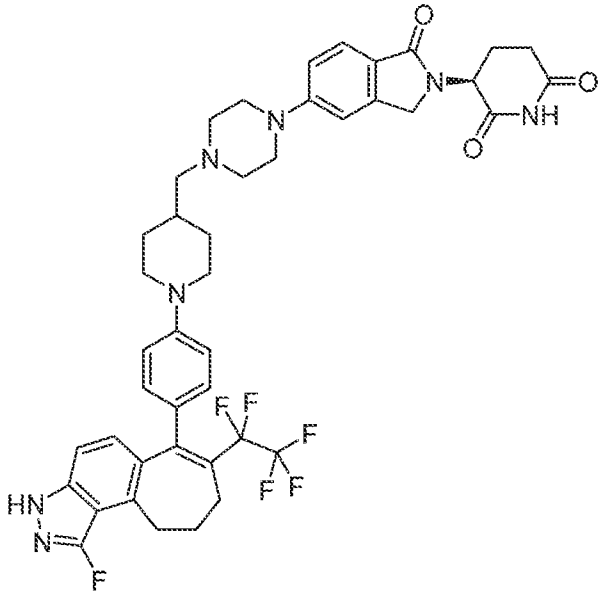
I-113	
I-114	
I-115	

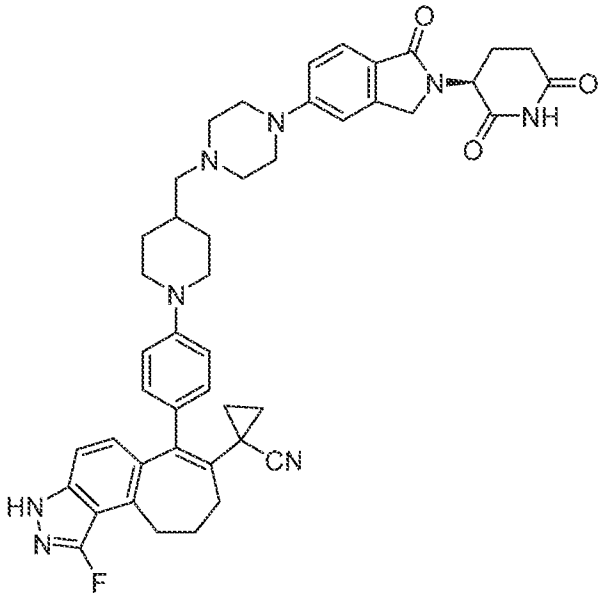
I-116	
I-117	

I-118	
I-119	
I-120	

I-121	
I-122	
I-123	

I-124	
I-125	
I-126	

I-127	
I-128	

I-129	

"‡" denotes compounds for which the initial stereochemistry was arbitrarily assigned, as indicated by the previous "or1" designation at the respective stereocenters. Current stereochemistry assignment has been confirmed by independent experiments, as indicated by the "abs" designation at the respective stereocenters.

[0523] In chemical structures in **Table 1**, above, and the Examples, below, stereogenic centers are described according to the Enhanced Stereo Representation format (MDL/Biovia, e.g. using labels "or1", "or2", "abs", "and1").

[0524] In some embodiments, the present disclosure comprises a compound of formula **I-a** selected from those depicted in **Table 1**, above, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof. In some embodiments, the present disclosure provides a compound of formula **I-a** selected from those depicted in **Table 1**, above, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound of formula **I-a** selected from those depicted in **Table 1**, above.

[0525] The compounds in **Table 1** were made in accordance with chemical procedures described in the Examples section, or similar procedures that would be readily understood by a person of skill in the art on the basis of the instant disclosure and knowledge present in the art. The compounds marked with (*) in **Table 1** are prophetic examples and can be made by methods similar to those included in the Examples section.

4. Uses, Formulation, and Administration

Pharmaceutically Acceptable Compositions

[0526] According to another embodiment, the disclosure provides a composition comprising a compound of this disclosure, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of this disclosure, and a pharmaceutically acceptable carrier. The amount of compound in compositions of this disclosure is such that is effective to measurably degrade ERα, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this disclosure is such that it is effective to measurably degrade ERα, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this disclosure is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this disclosure is formulated for oral administration to a patient.

[0527] The terms "subject" and "patient," as used herein, means an animal (i.e., a member of the animal kingdom), preferably a mammal, and most preferably a human. In some embodiments, the subject is a human, mouse, rat, cat, monkey, dog, horse, or pig. In some embodiments, the subject is a human. In some embodiments, the subject is a mouse, rat, cat, monkey, dog, horse, or pig.

[0528] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0529] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this disclosure that, upon administration to a recipient, is

capable of providing, either directly or indirectly, a compound of this disclosure or an inhibitorily active metabolite or residue thereof.

[0530] As used herein, the term "degratorily active metabolite or residue thereof" means that a metabolite or residue thereof is also a degrader of ERα, or a mutant thereof.

[0531] Compositions of the present disclosure may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[0532] Sterile injectable forms of the compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0533] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0534] Pharmaceutically acceptable compositions of this disclosure may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose

and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0535] Alternatively, pharmaceutically acceptable compositions of this disclosure may be administered in the form of suppositories for rectal or vaginal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal or vaginal temperature and therefore will melt in the rectum or vagina to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0536] Pharmaceutically acceptable compositions of this disclosure may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0537] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0538] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0539] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0540] Pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0541] Preferably, pharmaceutically acceptable compositions of this disclosure are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this disclosure are administered without food. In other embodiments, pharmaceutically acceptable compositions of this disclosure are administered with food.

[0542] The amount of compounds of the present disclosure that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the patient treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0543] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present disclosure in the composition will also depend upon the particular compound in the composition.

[0544] The precise dose to be employed in the compositions will also depend on the route of administration, and should be decided according to the judgment of the practitioner and each subject's circumstances. In specific embodiments of the disclosure, suitable dose ranges for oral administration of the compounds of the disclosure are generally about 1 mg/day to about 1000 mg/day. In some embodiments, the oral dose is about 1 mg/day to about 800 mg/day. In some embodiments, the oral dose is about 1 mg/day to about 500 mg/day. In some embodiments, the oral dose is about 1 mg/day to about 250 mg/day. In some embodiments, the oral dose is about 1 mg/day to about 100 mg/day. In some embodiments, the oral dose is about 5 mg/day to about 50 mg/day. In some embodiments, the oral dose is about 5 mg/day. In some embodiments, the oral dose is about 10 mg/day. In some embodiments, the oral dose is about 20 mg/day. In some embodiments, the oral dose is about 30 mg/day. In some embodiments, the oral dose is about 40

mg/day. In some embodiments, the oral dose is about 50 mg/day. In some embodiments, the oral dose is about 60 mg/day. In some embodiments, the oral dose is about 70 mg/day. In some embodiments, the oral dose is about 100 mg/day. It will be recognized that any of the dosages listed herein may constitute an upper or lower dosage range, and may be combined with any other dosage to constitute a dosage range comprising an upper and lower limit.

[0545] In some embodiments, pharmaceutically acceptable compositions contain a provided compound and/or a pharmaceutically acceptable salt thereof at a concentration ranging from about 0.01 to about 90 wt%, about 0.01 to about 80 wt%, about 0.01 to about 70 wt%, about 0.01 to about 60 wt%, about 0.01 to about 50 wt%, about 0.01 to about 40 wt%, about 0.01 to about 30 wt%, about 0.01 to about 20 wt%, about 0.01 to about 2.0 wt%, about 0.01 to about 1 wt%, about 0.05 to about 0.5 wt%, about 1 to about 30 wt%, or about 1 to about 20 wt%. The composition can be formulated as a solution, suspension, ointment, or a capsule, and the like. The pharmaceutical composition can be prepared as an aqueous solution and can contain additional components, such as preservatives, buffers, tonicity agents, antioxidants, stabilizers, viscosity-modifying ingredients and the like.

[0546] Pharmaceutically acceptable carriers are well-known to those skilled in the art, and include, *e.g.*, adjuvants, diluents, excipients, fillers, lubricants and vehicles. In some embodiments, the carrier is a diluent, adjuvant, excipient, or vehicle. In some embodiments, the carrier is a diluent, adjuvant, or excipient. In some embodiments, the carrier is a diluent or adjuvant. In some embodiments, the carrier is an excipient.

[0547] Examples of pharmaceutically acceptable carriers may include, *e.g.*, water or saline solution, polymers such as polyethylene glycol, carbohydrates and derivatives thereof, oils, fatty acids, or alcohols. Non-limiting examples of oils as pharmaceutical carriers include oils of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical carriers may also be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. Other examples of suitable pharmaceutical carriers are described in *e.g.*, Remington's: The Science and Practice of Pharmacy, 22nd Ed. (Allen, Loyd V., Jr ed., Pharmaceutical Press (2012)); Modern Pharmaceutics, 5th Ed. (Alexander T. Florence, Juergen Siepmann, CRC Press (2009)); Handbook of Pharmaceutical Excipients, 7th Ed. (Rowe, Raymond C.; Sheskey, Paul J.; Cook, Walter G.; Fenton, Marian E. eds., Pharmaceutical Press (2012)) (each of which hereby incorporated by reference in its entirety).

[0548] The pharmaceutically acceptable carriers employed herein may be selected from various organic or inorganic materials that are used as materials for pharmaceutical formulations and which are incorporated as analgesic agents, buffers, binders, disintegrants, diluents, emulsifiers, excipients, extenders, glidants, solubilizers, stabilizers, suspending agents, tonicity agents, vehicles and viscosity-increasing agents. Pharmaceutical additives, such as antioxidants, aromatics, colorants, flavor-improving agents, preservatives, and sweeteners, may also be added. Examples of acceptable pharmaceutical carriers include carboxymethyl cellulose, crystalline cellulose, glycerin, gum arabic, lactose, magnesium stearate, methyl cellulose, powders, saline, sodium alginate, sucrose, starch, talc and water, among others. In some embodiments, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0549] Surfactants such as, *e.g.*, detergents, are also suitable for use in the formulations. Specific examples of surfactants include polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and of vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol or polyoxyethylenated esters of sorbitan; lecithin or sodium carboxymethylcellulose; or acrylic derivatives, such as methacrylates and others, anionic surfactants, such as alkaline stearates, in particular sodium, potassium or ammonium stearate; calcium stearate or triethanolamine stearate; alkyl sulfates, in particular sodium lauryl sufate and sodium cetyl sulfate; sodium dodecylbenzenesulphonate or sodium dioctyl sulphosuccinate; or fatty acids, in particular those derived from coconut oil, cationic surfactants, such as water-soluble quaternary ammonium salts of formula $N^+R'R''R'''R''''Y^-$, in which the R radicals are identical or different optionally hydroxylated hydrocarbon radicals and Y^- is an anion of a strong acid, such as halide, sulfate and sulfonate anions; cetyltrimethylammonium bromide is one of the cationic surfactants which can be used, amine salts of formula $N^+R'R''R'''$, in which the R radicals are identical or different optionally hydroxylated hydrocarbon radicals; octadecylamine hydrochloride is one of the cationic surfactants which can be used, non-ionic surfactants, such as optionally polyoxyethylenated esters of sorbitan, in particular Polysorbate 80, or polyoxyethylenated alkyl ethers; polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids or copolymers of ethylene oxide and of propylene oxide, amphoteric surfactants, such as substituted lauryl compounds of betaine.

[0550] Suitable pharmaceutical carriers may also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, polyethylene glycol 300, water, ethanol, polysorbate 20, and the like. The present compositions, if desired, may also contain wetting or emulsifying agents, or pH buffering agents.

[0551] Tablets and capsule formulations may further contain one or more adjuvants, binders, diluents, disintegrants, excipients, fillers, or lubricants, each of which are known in the art. Examples of such include carbohydrates such as lactose or sucrose, dibasic calcium phosphate anhydrous, corn starch, mannitol, xylitol, cellulose or derivatives thereof, microcrystalline cellulose, gelatin, stearates, silicon dioxide, talc, sodium starch glycolate, acacia, flavoring agents, preservatives, buffering agents, disintegrants, and colorants. Orally administered compositions may contain one or more optional agents such as, *e.g.*, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preservative agents, to provide a pharmaceutically palatable preparation.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[0552] Compounds and compositions described herein are generally useful for the degradation of ERα. In some embodiments, the nuclear transcription factor degraded by the compounds and compositions described herein is ERα.

[0553] Compounds or compositions of the disclosure can be useful in applications that benefit from the degradation of ERα. For example, ERα degraders of the present disclosure are useful for the treatment of cellular proliferative diseases generally.

[0554] The activity of a compound utilized in this disclosure as an degrader of ERα, or a mutant thereof, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the signaling activity and/or the subsequent functional consequences, of an activated ERα, or a mutant thereof. Alternative *in vitro* assays quantitate the ability of the degrader to degrade ERα. Representative *in vitro* and *in vivo* assays useful in assaying an ERα degrader include those described and disclosed in the patent and scientific publications described herein. Detailed conditions for assaying a compound utilized in this disclosure as an degrader of ERα, or a mutant thereof, are set forth in the Examples below.

Treatment of Disorders

[0555] Provided compounds are degraders of ERα and are therefore useful for treating one or more disorders associated with activity of ERα or mutants thereof. Thus, in certain embodiments, the present disclosure provides a method of treating an ERα-mediated disorder in a subject, comprising administering a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition of either of the foregoing, to a subject in need thereof. In certain embodiments, the present disclosure provides a method of treating an ERα-mediated disorder in a subject comprising administering a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable composition thereof, to a subject in need thereof. In some embodiments, the subject has a mutant ERα. In some embodiments, the subject has ERα containing a D538G, Y537S, or L536R mutation.

[0556] As used herein, the term "ERα-mediated" disorders, diseases, and/or conditions means any disease or other deleterious condition in which ERα or a mutant thereof is known to play a role. Accordingly, another embodiment of the present disclosure relates to treating or lessening the severity of one or more diseases in which ERα, or a mutant thereof, is known to play a role. Such ERα-mediated disorders include, but are not limited to, cellular proliferative disorders (e.g. cancer). In some embodiments, the ERα-mediated disorder is a disorder mediated by a mutant ERα. In some embodiments, the ERα-mediated disorder is a disorder mediated by an ERα containing a D538G, Y537S, or L536R mutation.

[0557] In some embodiments, the present disclosure provides a method for treating a cellular proliferative disease, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition of either of the foregoing. In some embodiments, the present disclosure provides a method for treating a cellular proliferative disease, said method comprising administering to a patient in need thereof, a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable composition thereof.

[0558] In some embodiments, the method of treatment comprises the steps of: i) identifying a subject in need of such treatment; (ii) providing a disclosed compound, or a pharmaceutically acceptable salt thereof; and (iii) administering said provided compound in a therapeutically

effective amount to treat, suppress and/or prevent the disease state or condition in a subject in need of such treatment. In some embodiments, the subject has a mutant ERα. In some embodiments, the subject has ERα containing a D538G, Y537S, or L536R mutation.

[0559] In some embodiments, the method of treatment comprises the steps of: i) identifying a subject in need of such treatment; (ii) providing a composition comprising a disclosed compound, or a pharmaceutically acceptable salt thereof; and (iii) administering said composition in a therapeutically effective amount to treat, suppress and/or prevent the disease state or condition in a subject in need of such treatment. In some embodiments, the subject has a mutant ERα. In some embodiments, the subject has ERα containing a D538G, Y537S, or L536R mutation.

[0560] Another aspect of the disclosure provides a compound according to the definitions herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of either of the foregoing, for use in the treatment of a disorder described herein. Another aspect of the disclosure provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of either of the foregoing, for the treatment of a disorder described herein. Similarly, the disclosure provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disorder described herein.

Cellular Proliferative Diseases

[0561] In some embodiments, the disorder is a cellular proliferative disease. In some embodiments, the cellular proliferative disease is cancer. In some embodiments, the cancer is a tumor. In some embodiments, the cancer is a hematopoietic cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cellular proliferative disease is a tumor and/or cancerous cell growth. In some embodiments, the cellular proliferative disease is a tumor. In some embodiments, the cellular proliferative disease is a solid tumor. In some embodiments, the cellular proliferative disease is a cancerous cell growth.

[0562] In some embodiments, the cancer is selected from sarcoma; lung; bronchus; prostate; breast (including sporadic breast cancers and sufferers of Cowden disease); pancreas; gastrointestinal; colon; rectum; carcinoma; colon carcinoma; adenoma; colorectal adenoma; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; glioma; glioblastoma; endometrial; melanoma; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary (including clear cell ovarian cancer); multiple myeloma; esophagus; a leukemia;

acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; a carcinoma of the brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; villous colon adenoma; a neoplasia; a neoplasia of epithelial character; lymphoma; a mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; neck; head; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Waldenstrom macroglobulinemia.

[0563] In some embodiments, the cancer is selected from lung; bronchus; prostate; breast (including sporadic breast cancers and Cowden disease); pancreas; gastrointestinal; colon; rectum; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; endometrial; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary (including clear cell ovarian cancer); esophagus; a leukemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; neck; and head. In some embodiments, the cancer is selected from sarcoma; carcinoma; colon carcinoma; adenoma; colorectal adenoma; glioma; glioblastoma; melanoma; multiple myeloma; a carcinoma of the brain; non-Hodgkin lymphoma; villous colon adenoma; a neoplasia; a neoplasia of epithelial character; lymphoma; a mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Waldenstrom macroglobulinemia.

[0564] In some embodiments, the cancer is selected from lung; bronchus; prostate; breast (including sporadic breast cancers and Cowden disease); pancreas; gastrointestinal; colon; rectum; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; endometrial; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary (including clear cell ovarian cancer); esophagus; brain; oral cavity and pharynx; larynx; small intestine; neck; and head. In some embodiments, the cancer is a leukemia. In some embodiments, the cancer is acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; or myeloid leukemia.

[0565] In some embodiments, the cancer is breast cancer (including sporadic breast cancers and Cowden disease). In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is ER+ breast cancer. In some embodiments, the cancer is ER+/HER2- breast cancer. In some embodiments, the cancer is ER+/HER2- breast cancer, and the subject is intolerant to, or ineligible for, treatment with alpelisib. In some embodiments, the cancer is sporadic breast cancer. In some embodiments, the cancer is Cowden disease. In some embodiments, the cancer is ER+

advanced/metastatic breast cancer. In some embodiments, the cancer is ER+/HER2- advanced/metastatic breast cancer. In some embodiments, the breast cancer has mutant ERα. In some embodiments, the breast cancer has ERα containing a D538G, Y537S, or L536R mutation.

[0566] In some embodiments, the cancer is uterine cancer. In some embodiments, the uterine cancer has mutant ERα. In some embodiments, the uterine cancer has ERα containing a D538G, Y537S, or L536R mutation.

[0567] In some embodiments, the ERα-mediated disorder is endometriosis. In some embodiments, the endometriosis has mutant ERα. In some embodiments, the endometriosis has ERα containing a D538G, Y537S, or L536R mutation.

[0568] In some embodiments, the cellular proliferative disease displays overexpression or amplification of ERα, or somatic mutation of ERα.

Routes of Administration and Dosage Forms

[0569] The compounds and compositions, according to the methods of the present disclosure, may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder (e.g. a proliferative disorder). The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the disclosure are preferably formulated in unit dosage form for ease of administration and uniformity of dosage. The expression "unit dosage form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0570] Pharmaceutically acceptable compositions of this disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like. In certain embodiments, the compounds of the disclosure may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0571] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0572] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0573] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0574] In order to prolong the effect of a compound of the present disclosure, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption

of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0575] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0576] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0577] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding

compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[0578] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0579] Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this disclosure. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Dosage Amounts and Regimens

[0580] In accordance with the methods of the present disclosure, the compounds of the disclosure are administered to the subject in a therapeutically effective amount, *e.g.*, to reduce or ameliorate symptoms of the disorder in the subject. This amount is readily determined by the skilled artisan,

based upon known procedures, including analysis of titration curves established *in vivo* and methods and assays disclosed herein.

[0581] In some embodiments, the methods comprise administration of a therapeutically effective dosage of the compounds of the disclosure. In some embodiments, the therapeutically effective dosage is at least about 0.0001 mg/kg body weight, at least about 0.001 mg/kg body weight, at least about 0.01 mg/kg body weight, at least about 0.05 mg/kg body weight, at least about 0.1 mg/kg body weight, at least about 0.25 mg/kg body weight, at least about 0.3 mg/kg body weight, at least about 0.5 mg/kg body weight, at least about 0.75 mg/kg body weight, at least about 1 mg/kg body weight, at least about 2 mg/kg body weight, at least about 3 mg/kg body weight, at least about 4 mg/kg body weight, at least about 5 mg/kg body weight, at least about 6 mg/kg body weight, at least about 7 mg/kg body weight, at least about 8 mg/kg body weight, at least about 9 mg/kg body weight, at least about 10 mg/kg body weight, at least about 15 mg/kg body weight, at least about 20 mg/kg body weight, at least about 25 mg/kg body weight, at least about 30 mg/kg body weight, at least about 40 mg/kg body weight, at least about 50 mg/kg body weight, at least about 75 mg/kg body weight, at least about 100 mg/kg body weight, at least about 200 mg/kg body weight, at least about 250 mg/kg body weight, at least about 300 mg/kg body weight, at least about 350 mg/kg body weight, at least about 400 mg/kg body weight, at least about 450 mg/kg body weight, at least about 500 mg/kg body weight, at least about 550 mg/kg body weight, at least about 600 mg/kg body weight, at least about 650 mg/kg body weight, at least about 700 mg/kg body weight, at least about 750 mg/kg body weight, at least about 800 mg/kg body weight, at least about 900 mg/kg body weight, or at least about 1000 mg/kg body weight. It will be recognized that any of the dosages listed herein may constitute an upper or lower dosage range, and may be combined with any other dosage to constitute a dosage range comprising an upper and lower limit.

[0582] In some embodiments, the therapeutically effective dosage is in the range of about 0.1 mg to about 10 mg/kg body weight, about 0.1 mg to about 6 mg/kg body weight, about 0.1 mg to about 4 mg /kg body weight, or about 0.1 mg to about 2 mg/kg body weight.

[0583] In some embodiments the therapeutically effective dosage is in the range of about 1 to 500 mg, about 2 to 150 mg, about 2 to 120 mg, about 2 to 80 mg, about 2 to 40 mg, about 5 to 150 mg, about 5 to 120 mg, about 5 to 80 mg, about 10 to 150 mg, about 10 to 120 mg, about 10 to 80 mg, about 10 to 40 mg, about 20 to 150 mg, about 20 to 120 mg, about 20 to 80 mg, about 20 to 40 mg, about 40 to 150 mg, about 40 to 120 mg or about 40 to 80 mg.

[0584] In some embodiments, the methods comprise a single dosage or administration (*e.g.*, as a single injection or deposition). Alternatively, in some embodiments, the methods comprise administration once daily, twice daily, three times daily or four times daily to a subject in need thereof for a period of from about 2 to about 28 days, or from about 7 to about 10 days, or from about 7 to about 15 days, or longer. In some embodiments, the methods comprise chronic administration. In yet other embodiments, the methods comprise administration over the course of several weeks, months, years or decades. In still other embodiments, the methods comprise administration over the course of several weeks. In still other embodiments, the methods comprise administration over the course of several months. In still other embodiments, the methods comprise administration over the course of several years. In still other embodiments, the methods comprise administration over the course of several decades.

[0585] The dosage administered can vary depending upon known factors such as the pharmacodynamic characteristics of the active ingredient and its mode and route of administration; time of administration of active ingredient; age, sex, health and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment and the effect desired; and rate of excretion. These are all readily determined and may be used by the skilled artisan to adjust or titrate dosages and/or dosing regimens.

Degradation of ERα

[0586] According to one embodiment, the disclosure relates to a method of degrading ERα in a biological sample comprising the step of contacting said biological sample with a compound of this disclosure, or a composition comprising said compound. According to another embodiment, the disclosure relates to a method of degrading ERα, or a mutant thereof, in a biological sample comprising the step of contacting said biological sample with a compound of this disclosure, or a composition comprising said compound. According to another embodiment, the disclosure relates to a method of degrading ERα, or a mutant thereof, in a biological sample comprising the step of contacting said biological sample with a compound of this disclosure, or a composition comprising said compound. In some embodiments, the ERα is a mutant ERα. In some embodiments, ERα contains a D538G, Y537S, or L536R mutation.

[0587] Without wishing to be bound by any particular theory, it is contemplated that compounds of the present invention catalyze the destruction of ERα. The compounds of the present invention are proteolysis targeting chimeras (PROTACs). A PROTAC is a bifunctional molecule, with one

portion capable of engaging an E3 ubiquitin ligase, and the other portion having the ability to bind to a target protein meant for degradation by the cellular protein quality control machinery. Recruitment of the target protein to the specific E3 ligase results in its tagging for destruction (i.e., ubiquitination) and subsequent degradation by the proteasome. Any E3 ligase can be used. The portion of the PROTAC that engages the E3 ligase is connected to the portion of the PROTAC that engages the target protein via a linker which consists of a variable chain of atoms. Recruitment of ERα to the E3 ligase will thus result in the destruction of the ERα protein. The variable chain of atoms can include, for example, rings, heteroatoms, and/or repeating polymeric units. It can be rigid or flexible. It can be attached to the two portions described above using standard techniques in the art of organic synthesis.

[0588] In some embodiments, the disclosure provides a method of selectively inhibiting a mutant ERα over a wild-type ERα.

[0589] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0590] Inhibition of activity of a ERα (for example, ERα, or a mutant thereof) in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0591] Another embodiment of the present disclosure relates to a method of inhibiting ERα-mediated transcription regulation in a patient comprising the step of administering to said patient a compound of the present disclosure, or a composition comprising said compound.

[0592] According to another embodiment, the disclosure relates to a method of inhibiting activity of a ERα, or a mutant thereof, in a patient comprising the step of administering to said patient a compound of the present disclosure, or a composition comprising said compound. In some embodiments, the disclosure relates to a method of inhibiting activity of ERα, or a mutant thereof, in a patient comprising the step of administering to said patient a compound of the present disclosure, or a composition comprising said compound. In some embodiments, the ERα is a mutant ERα. In some embodiments, the ERα contains a D538G, Y537S, or L536R mutation.

[0593] According to another embodiment, the present disclosure provides a method for treating a disorder mediated by a ERα, or a mutant thereof, in a patient in need thereof, comprising the step

of administering to said patient a compound according to the present disclosure or pharmaceutically acceptable composition thereof. In some embodiments, the present disclosure provides a method for treating a disorder mediated by ERα, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present disclosure or pharmaceutically acceptable composition thereof. In some embodiments, the ERα is a mutant ERα. In some embodiments, the ERα contains a D538G, Y537S, or L536R mutation.

[0594] According to another embodiment, the present disclosure provides a method of inhibiting ERα-mediated transcription regulation, or a mutant thereof, in a subject, comprising administering a therapeutically effective amount of a compound according to the present disclosure, or a pharmaceutically acceptable composition thereof, to a subject in need thereof. In some embodiments, the present disclosure provides a method of inhibiting ERα-mediated transcription regulation in a subject, comprising administering a therapeutically effective amount of a compound according to the present disclosure, or a pharmaceutically acceptable composition thereof, to a subject in need thereof. In some embodiments, the ERα is a mutant ERα. In some embodiments, the ERα contains a D538G, Y537S, or L536R mutation. In some embodiments, the subject has a D538G, Y537S, or L536R mutant ERα. In some embodiments, the subject has ERα containing D538G, Y537S, or L536R mutation.

Combination Therapies

[0595] Depending upon the particular disorder, condition, or disease, to be treated, additional therapeutic agents, that are normally administered to treat that condition, may be administered in combination with compounds and compositions of this disclosure. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[0596] Accordingly, in certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with one or more additional therapeutic agents. In certain other embodiments, the methods of treatment comprise administering the compound or composition of the disclosure as the only therapeutic agent.

[0597] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[0598] A compound of the current disclosure may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[0599] A compound of the current disclosure can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the disclosure and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current disclosure can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[0600] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this disclosure in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0601] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this disclosure. For example, a compound of the present disclosure may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present disclosure provides a single unit dosage form comprising a compound of the current disclosure, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0602] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this disclosure

should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

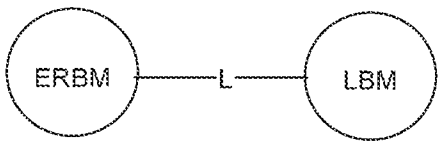
[0603] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this disclosure may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[0604] The amount of additional therapeutic agent present in the compositions of this disclosure will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0605] Any of the compounds and/or compositions of the disclosure may be provided in a kit comprising the compounds and/or compositions. Thus, in some embodiments, the compound and/or composition of the disclosure is provided in a kit.

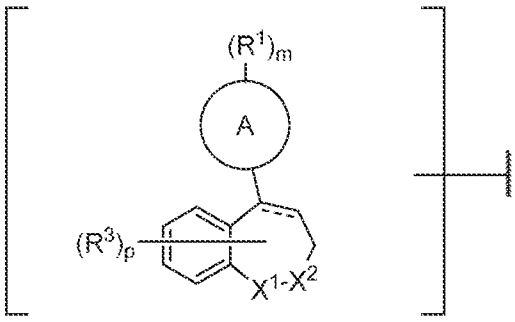
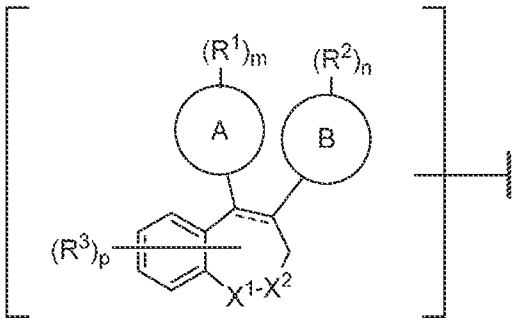
Selected Embodiments

Embodiment 1. A compound of formula **I-c**:



I-c

or a pharmaceutically acceptable salt thereof, wherein:

ERBM is selected from  and  , wherein ⊣ indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and ≈ indicates a single or double bond;

each of X^1 and X^2 is independently $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, –S(O)–, $–S(O)_2–$, or $–N(R^{A2})–$;

each instance of R^1, R^2, R^4, R^5, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C;

each instance of R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A is independently oxo, deuterium, halogen, –CN, $–NO_2$, –OR, $–SF_5$, –SR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –S(O)(NCN)R, –S(NCN)R, –C(O)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, –P(O)(R)OR, or $–B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or

partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

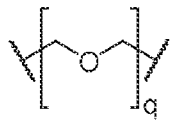
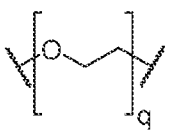
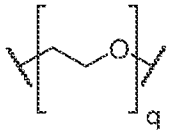
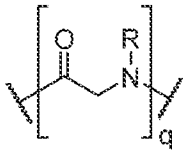
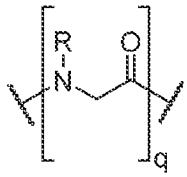
each instance of R^C is independently oxo, deuterium, halogen, –CN, $–NO_2$, –OR, $–SF_5$, –SR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, $–S(O)_2F$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)C(NR)NR_2$, $–N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–P(O)R_2$, –P(O)(R)OR, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

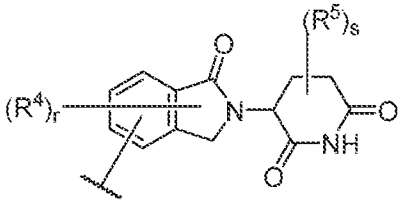
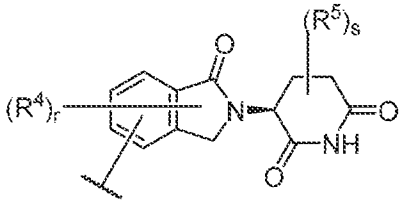
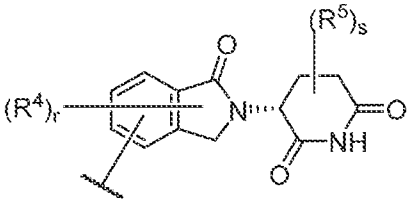
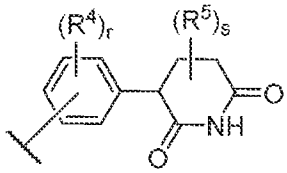
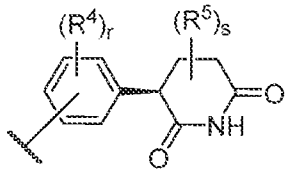
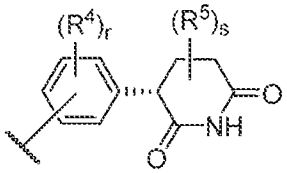
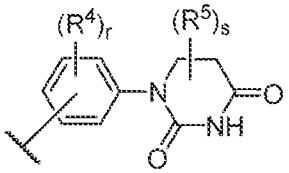
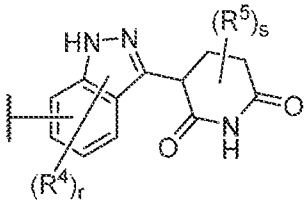
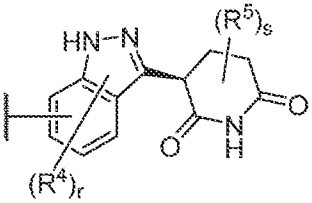
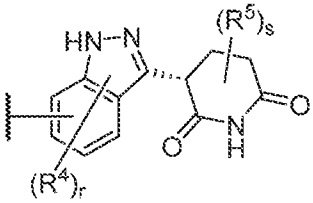
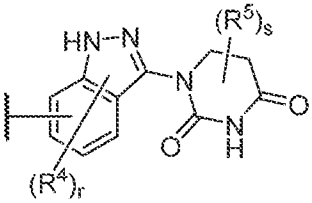
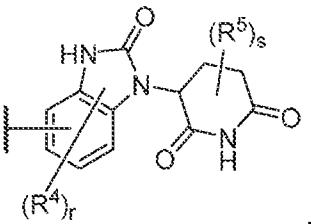
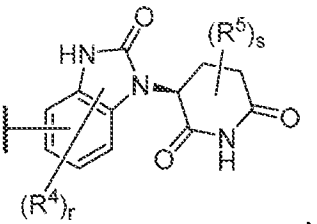
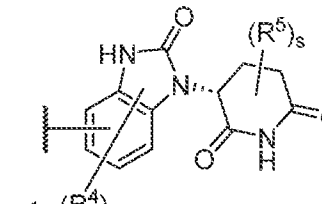
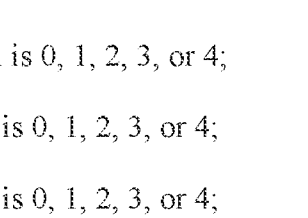
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic

heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, –$C(R)_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –$S(O)_2$–, –$NRS(O)_2$–, –$S(O)_2NR$–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,  ,  ,  , or  , wherein:

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

LBM is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , and ;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

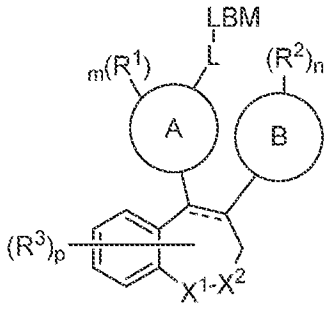
each of q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 0, 1, 2, 3, or 4; and

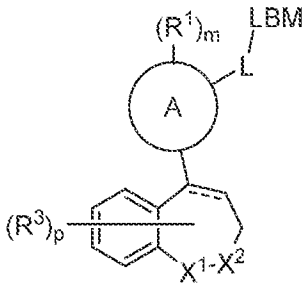
s is 0, 1, 2, 3, or 4;

provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

Embodiment 2. The compound of embodiment 1, wherein the compound is a compound of formula **I-d** or **I-e**



I-d

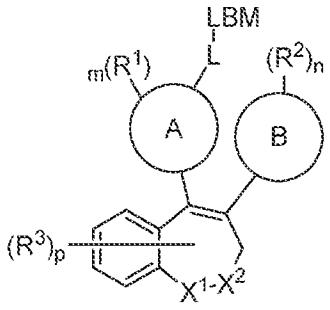


I-e or a pharmaceutically acceptable salt thereof.

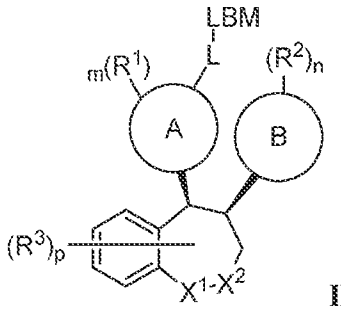
Embodiment 3. The compound of embodiment 1, wherein the compound is a compound of formula **I-d** or a pharmaceutically acceptable salt thereof.

Embodiment 4. The compound of embodiment 1, wherein the compound is a compound of formula **I-e** or a pharmaceutically acceptable salt thereof.

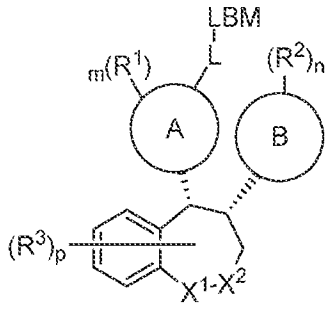
Embodiment 5. The compound of embodiment 1, wherein the compound is a compound of formula **I-f**, **I-g**, **I-h**, **I-i**, **I-j** or **I-k**:



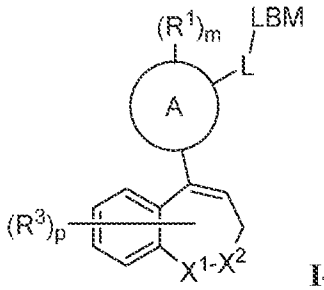
I-f



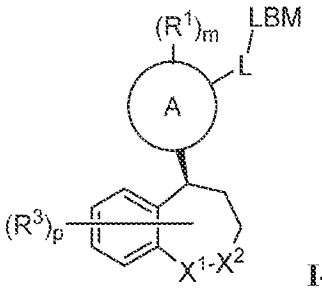
I-g



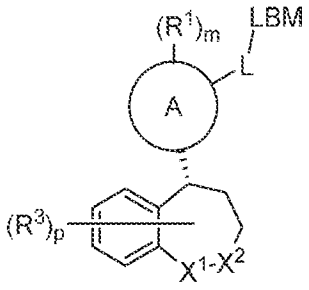
I-h



I-i



I-j



I-k or a pharmaceutically acceptable salt thereof.

Embodiment 6. The compound of embodiment 5, wherein the compound is a compound of formula **I-f**, **I-g**, **I-i** or **I-j**, or a pharmaceutically acceptable salt thereof.

Embodiment 7. The compound of embodiment 5, wherein the compound is a compound of formula **I-f**, **I-g** or **I-i**, or a pharmaceutically acceptable salt thereof.

Embodiment 8. The compound of embodiment 1, wherein the compound is a compound of formula **I-f**, or a pharmaceutically acceptable salt thereof.

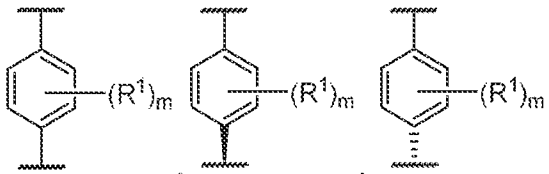
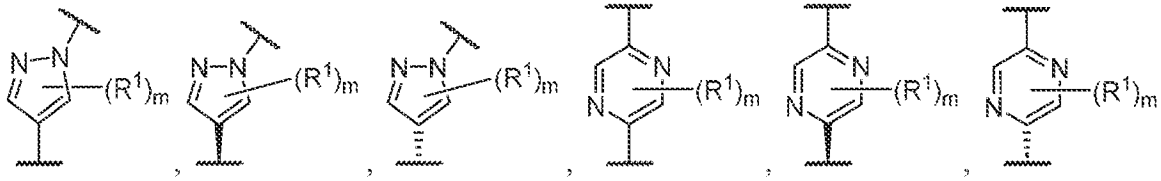
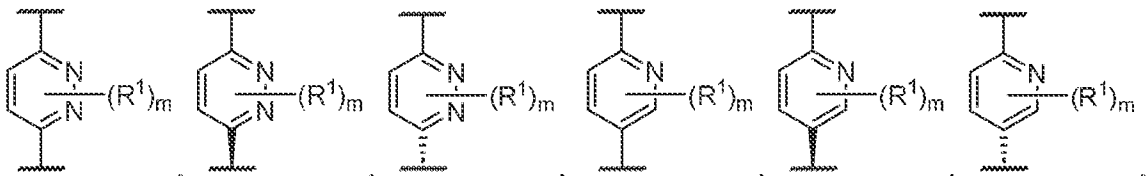
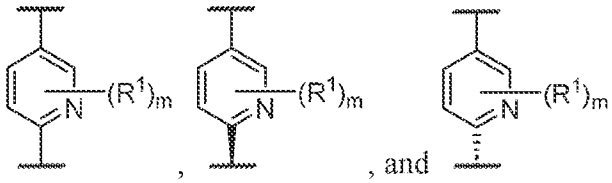
Embodiment 9. The compound of embodiment 1, wherein the compound is a compound of formula **I-g**, or a pharmaceutically acceptable salt thereof.

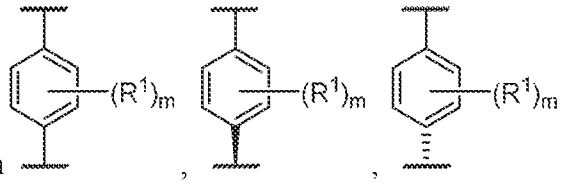
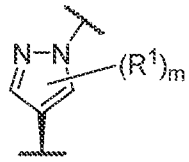
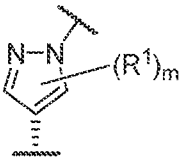
Embodiment 10. The compound of embodiment 1, wherein the compound is a compound of formula **I-h**, or a pharmaceutically acceptable salt thereof.

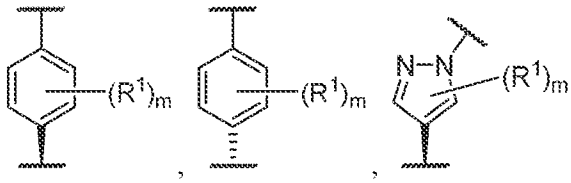
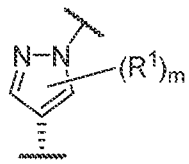
Embodiment 11. The compound of embodiment 1, wherein the compound is a compound of formula **I-i**, or a pharmaceutically acceptable salt thereof.

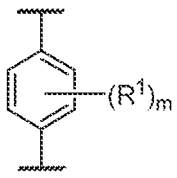
Embodiment 12. The compound of embodiment 1, wherein the compound is a compound of formula **I-j**, or a pharmaceutically acceptable salt thereof.

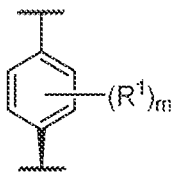
Embodiment 13. The compound of embodiment 1, wherein the compound is a compound of formula **I-k**, or a pharmaceutically acceptable salt thereof.

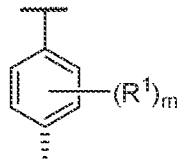
Embodiment 14. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is selected from  ,  ,  , and  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

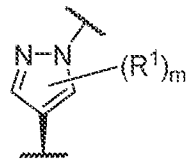
Embodiment 15. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is selected from  ,  , and  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

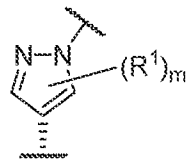
Embodiment 16. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is selected from  , and  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

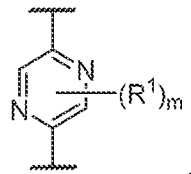
Embodiment 17. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

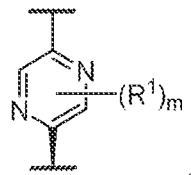
Embodiment 18. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

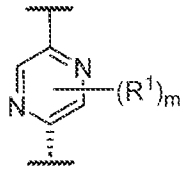
Embodiment 19. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

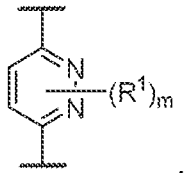
Embodiment 20. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

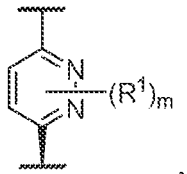
Embodiment 21. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

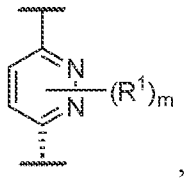
Embodiment 22. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

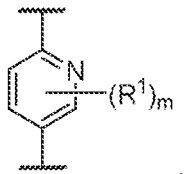
Embodiment 23. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

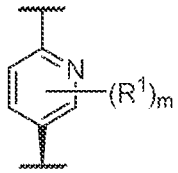
Embodiment 24. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

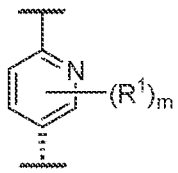
Embodiment 25. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

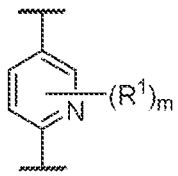
Embodiment 26. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

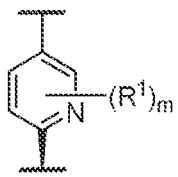
Embodiment 27. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

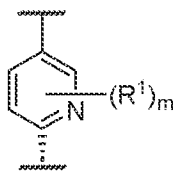
Embodiment 28. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

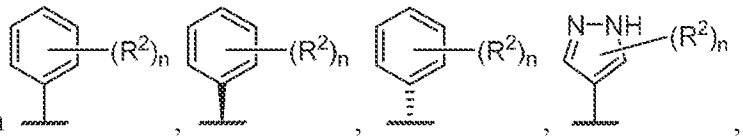
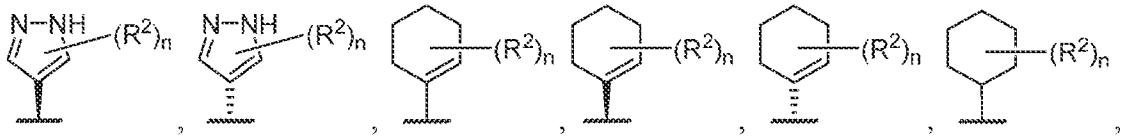
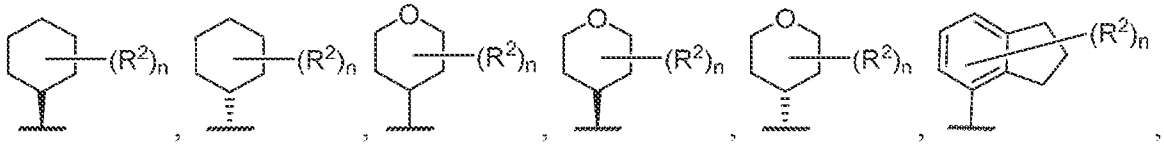
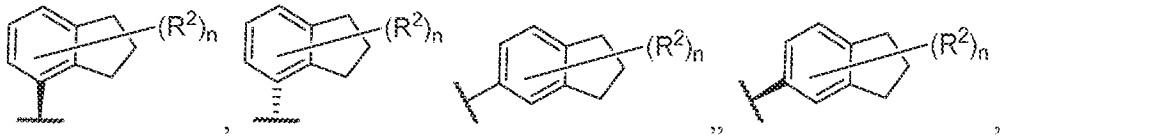
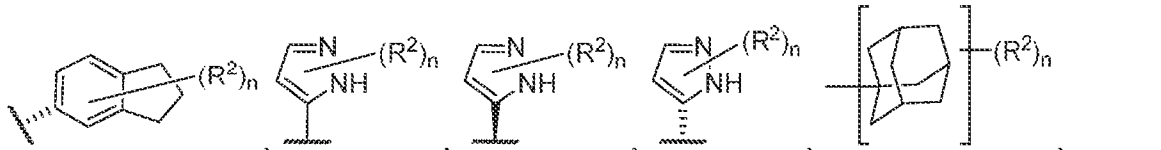
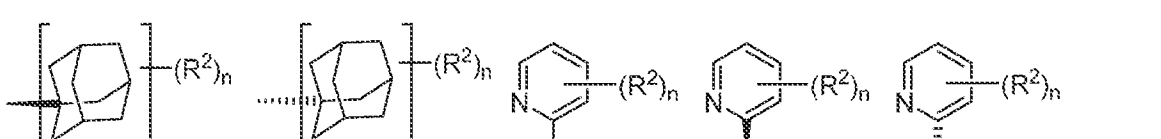
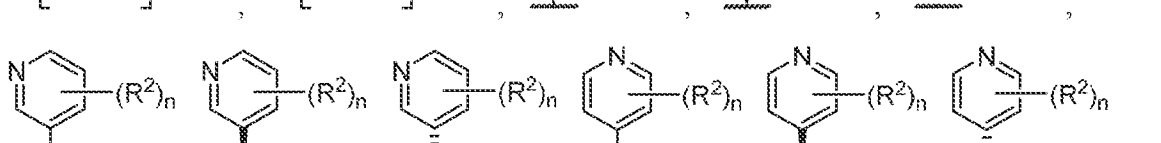
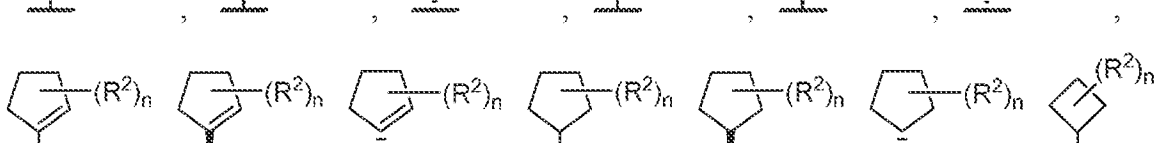
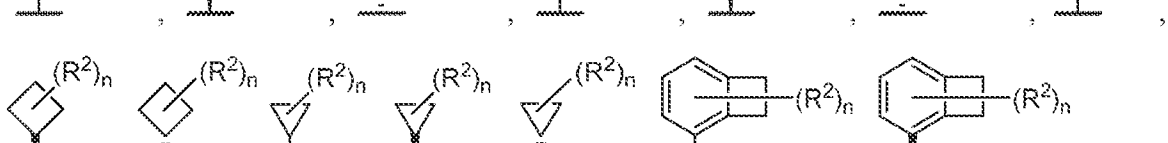
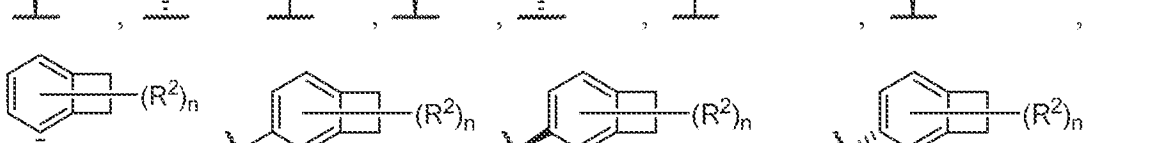
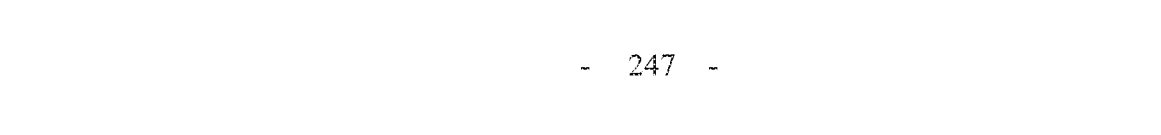
Embodiment 29. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

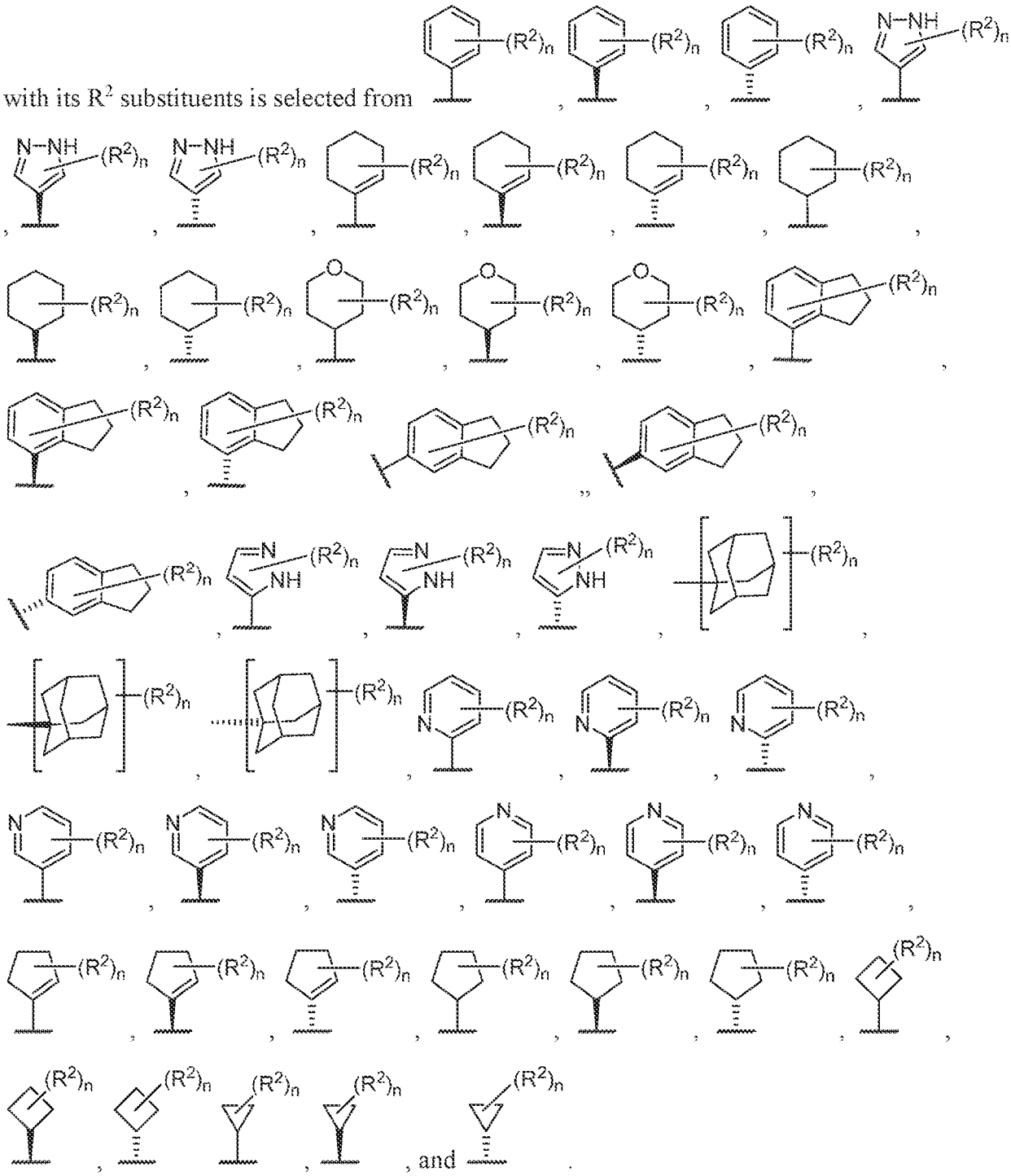
Embodiment 30. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

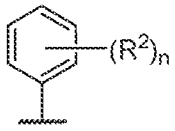
Embodiment 31. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

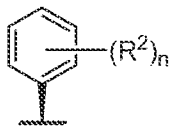
Embodiment 32. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

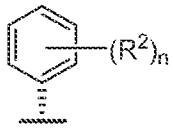
Embodiment 33. The compound of any one of embodiments 1-13, wherein Ring A together with its R^1 substituents is  , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

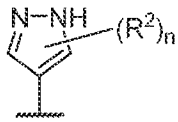
Embodiment 34. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  , and .

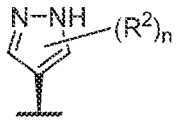
Embodiment 35. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is selected from  , and .

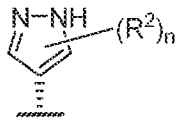
Embodiment 36. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

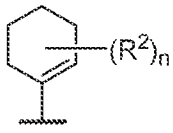
Embodiment 37. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

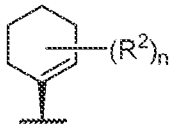
Embodiment 38. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

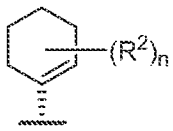
Embodiment 39. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

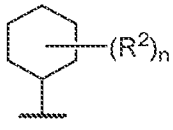
Embodiment 40. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

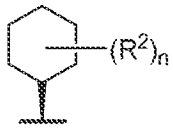
Embodiment 41. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

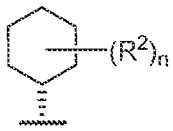
Embodiment 42. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

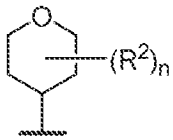
Embodiment 43. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

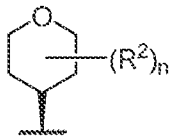
Embodiment 44. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

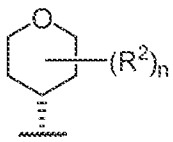
Embodiment 45. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

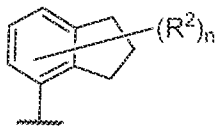
Embodiment 46. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

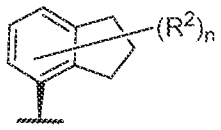
Embodiment 47. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

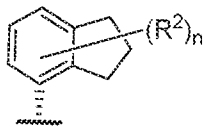
Embodiment 48. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

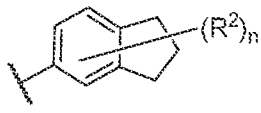
Embodiment 49. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

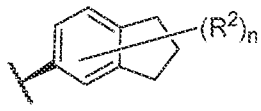
Embodiment 50. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

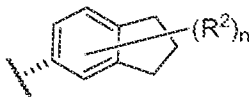
Embodiment 51. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

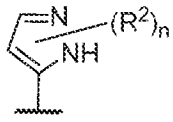
Embodiment 52. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

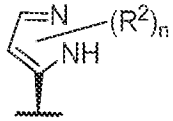
Embodiment 53. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

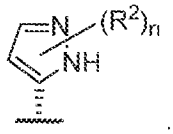
Embodiment 54. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

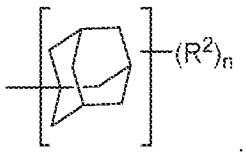
Embodiment 55. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

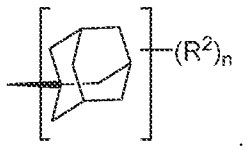
Embodiment 56. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

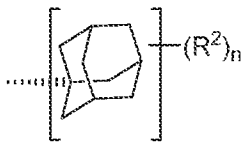
Embodiment 57. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

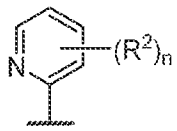
Embodiment 58. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

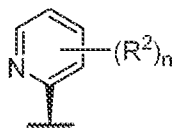
Embodiment 59. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

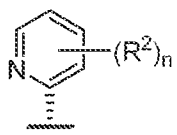
Embodiment 60. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

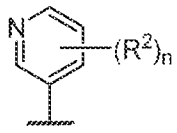
Embodiment 61. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

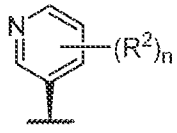
Embodiment 62. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

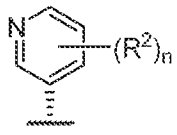
Embodiment 63. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

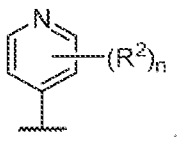
Embodiment 64. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

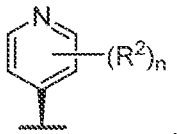
Embodiment 65. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

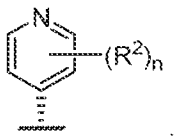
Embodiment 66. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

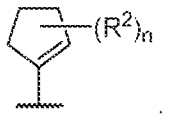
Embodiment 67. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

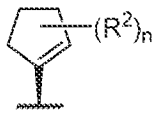
Embodiment 68. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

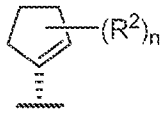
Embodiment 69. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

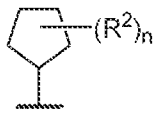
Embodiment 70. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

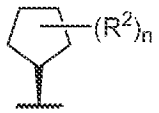
Embodiment 71. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

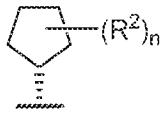
Embodiment 72. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

Embodiment 73. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

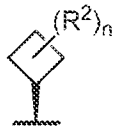
Embodiment 74. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

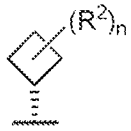
Embodiment 75. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

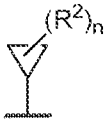
Embodiment 76. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

Embodiment 77. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

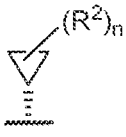
Embodiment 78. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is .

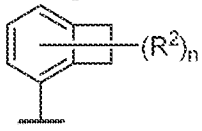
Embodiment 79. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

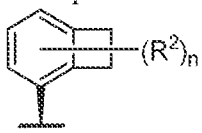
Embodiment 80. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

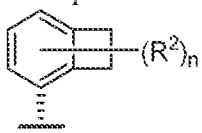
Embodiment 81. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

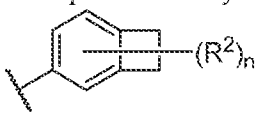
Embodiment 82. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is .

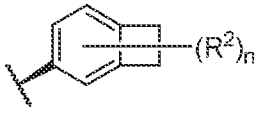
Embodiment 83. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

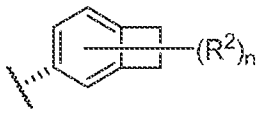
Embodiment 84. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

Embodiment 85. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

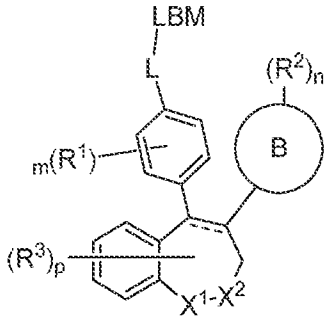
Embodiment 86. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

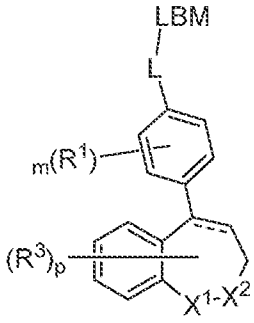
Embodiment 87. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

Embodiment 88. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

Embodiment 89. The compound of any one of embodiments 1-33, wherein Ring B together with its R^2 substituents is  .

Embodiment 90. The compound of embodiment 1, wherein the compound is a compound of formula **I-l** or **I-m**

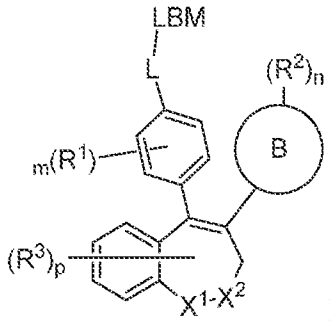

I-l


I-m, or a pharmaceutically acceptable salt thereof.

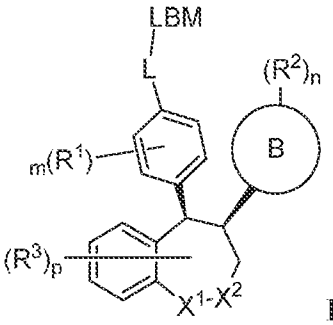
Embodiment 91. The compound of embodiment 90, wherein the compound is a compound of formula **I-l**, or a pharmaceutically acceptable salt thereof.

Embodiment 92. The compound of embodiment 90, wherein the compound is a compound of formula **I-m**, or a pharmaceutically acceptable salt thereof.

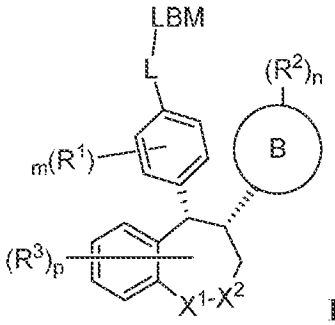
Embodiment 93. The compound of embodiment 1, wherein the compound is a compound of formula **I-n**, **I-o**, **I-p**, **I-q**, **I-r** or **I-s**:



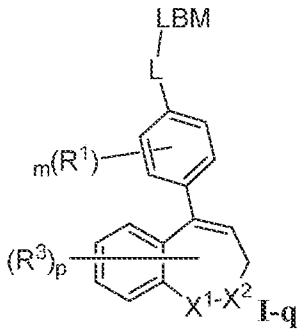
I-n



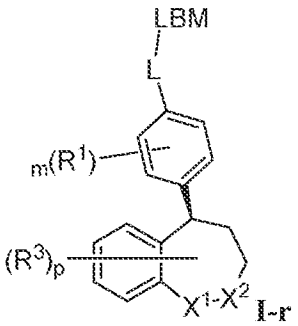
I-o



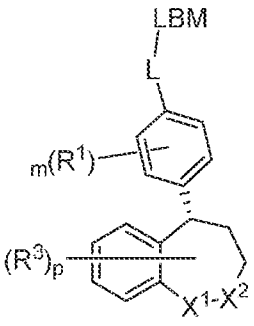
I-p



I-q



I-r



I-s, or a pharmaceutically acceptable salt thereof.

Embodiment 94. The compound of embodiment 93, wherein the compound is a compound of formula **I-n**, **I-o**, **I-q** or **I-r**, or a pharmaceutically acceptable salt thereof.

Embodiment 95. The compound of embodiment 93, wherein the compound is a compound of formula **I-n**, **I-o** or **I-q**, or a pharmaceutically acceptable salt thereof.

Embodiment 96. The compound of embodiment 93, wherein the compound is a compound of formula **I-n**, or a pharmaceutically acceptable salt thereof.

Embodiment 97. The compound of embodiment 93, wherein the compound is a compound of formula **I-o**, or a pharmaceutically acceptable salt thereof.

Embodiment 98. The compound of embodiment 93, wherein the compound is a compound of formula **I-p**, or a pharmaceutically acceptable salt thereof.

Embodiment 99. The compound of embodiment 93, wherein the compound is a compound of formula **I-q**, or a pharmaceutically acceptable salt thereof.

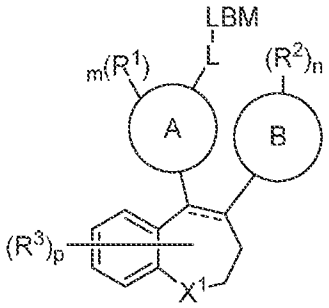
Embodiment 100. The compound of embodiment 93, wherein the compound is a compound of formula **I-r**, or a pharmaceutically acceptable salt thereof.

Embodiment 101. The compound of embodiment 93, wherein the compound is a compound of formula **I-s**, or a pharmaceutically acceptable salt thereof.

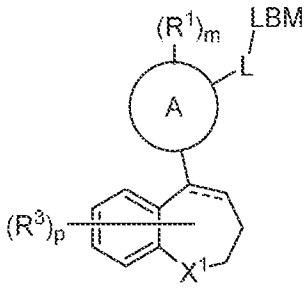
Embodiment 102. The compound of any one of embodiments 1-101, wherein X^2 is selected from –CH_2– and –O–.

Embodiment 103. The compound of any one of embodiments 1-101, wherein X^2 is –CH_2–.

Embodiment 104. The compound of embodiment 103, wherein the compound is a compound of formula **II-1** or **II-2**

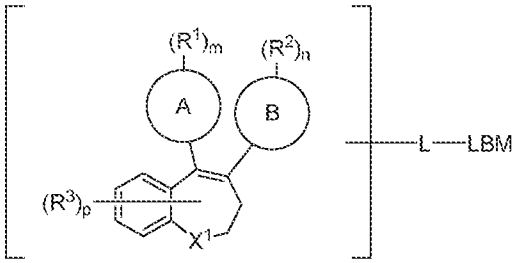


II-1

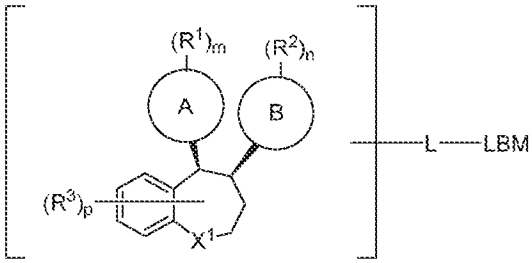


II-2, or a pharmaceutically acceptable salt thereof.

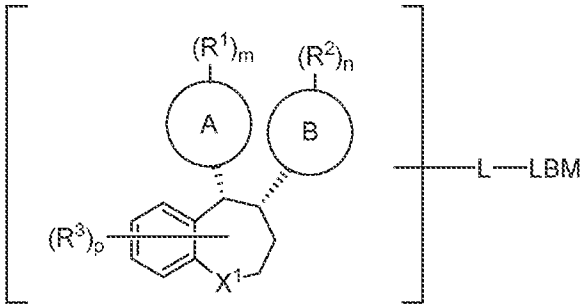
Embodiment 105. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, or **II-f**:



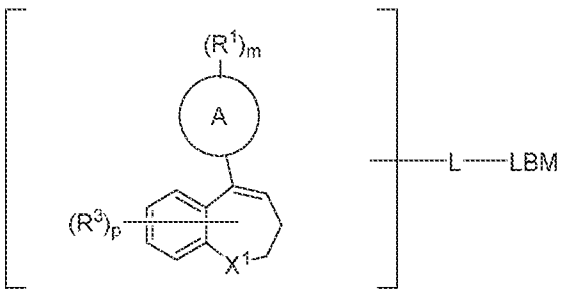
II-a



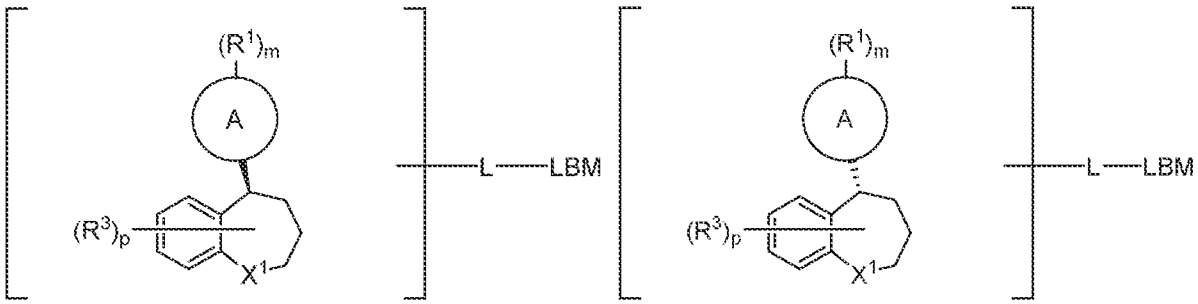
II-b



II-c



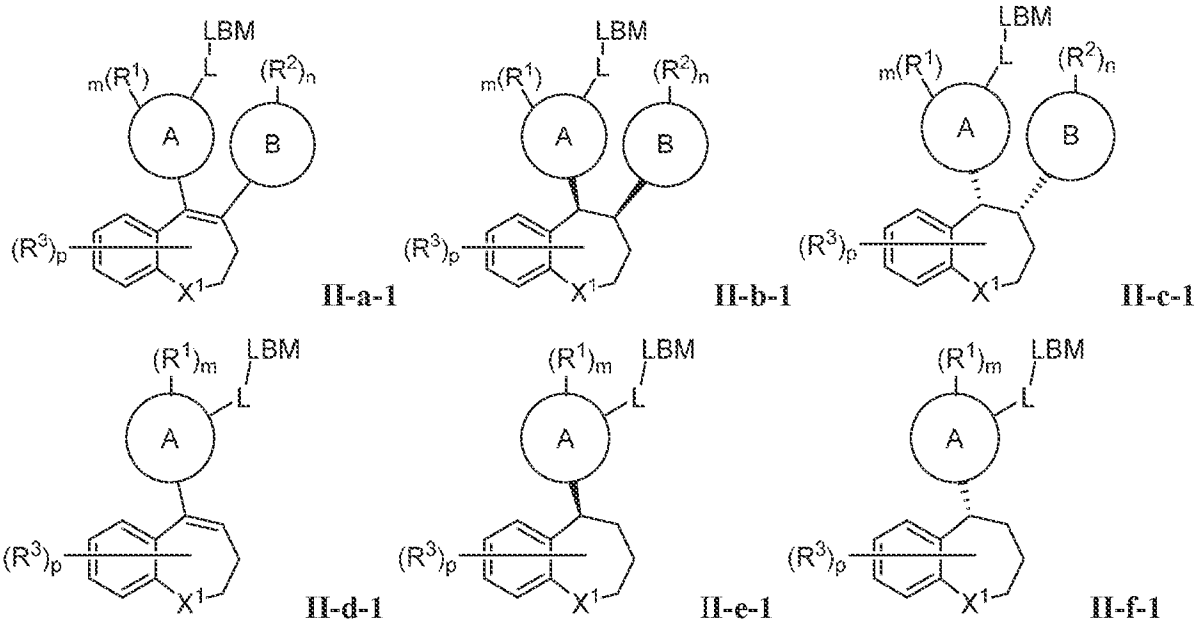
II-d



II-e **II-f**

or a pharmaceutically acceptable salt thereof.

Embodiment 106. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-a-1**, **II-b-1**, **II-c-1**, **II-d-1**, **II-e-1**, or **II-f-1**:



II-a-1 **II-b-1** **II-c-1**

II-d-1 **II-e-1** **II-f-1**

or a pharmaceutically acceptable salt thereof.

Embodiment 107. The compound of embodiment 106, wherein the compound is a compound of formula **II-a-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 108. The compound of embodiment 106, wherein the compound is a compound of formula **II-b-1**, or a pharmaceutically acceptable salt thereof.

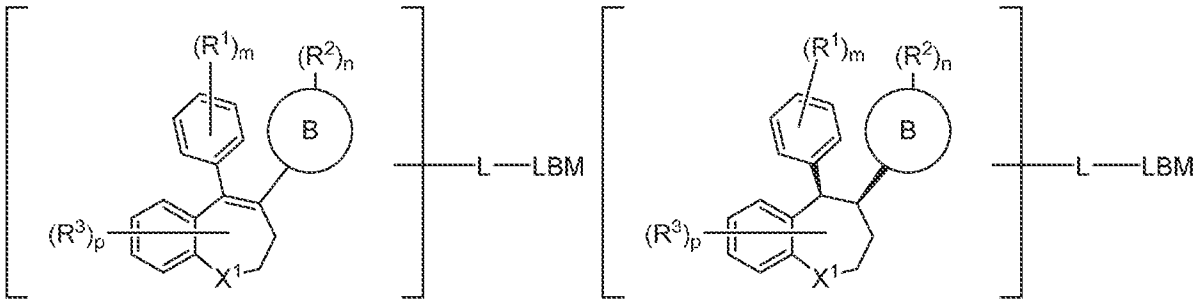
Embodiment 109. The compound of embodiment 106, wherein the compound is a compound of formula **II-c-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 110. The compound of embodiment 106, wherein the compound is a compound of formula **II-d-1**, or a pharmaceutically acceptable salt thereof.

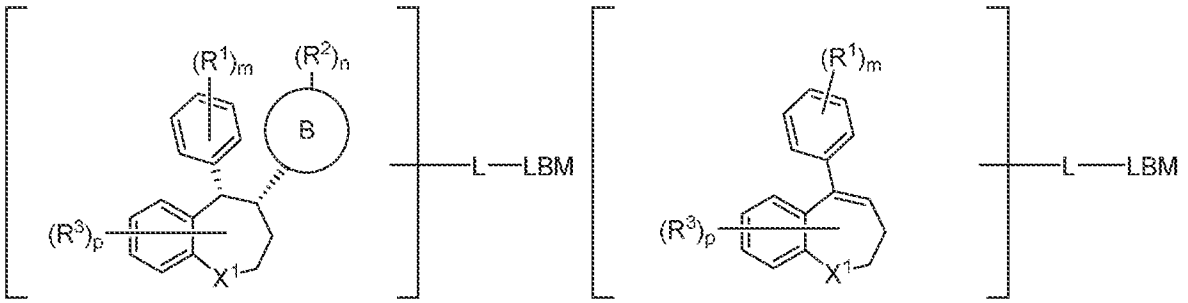
Embodiment 111. The compound of embodiment 106, wherein the compound is a compound of formula **II-e-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 112. The compound of embodiment 106, wherein the compound is a compound of formula **II-f-1**, or a pharmaceutically acceptable salt thereof.

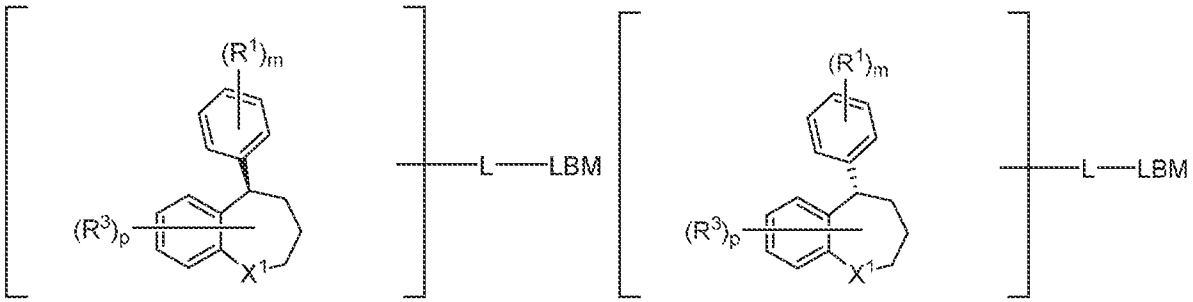
Embodiment 113. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-g**, **II-h**, **II-i**, **II-j**, **II-k**, or **II-l**:



II-g **II-h**



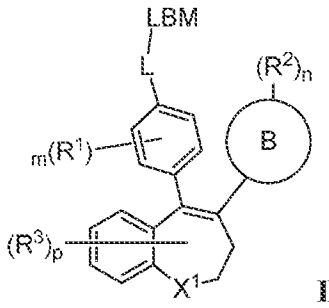
II-i **II-j**



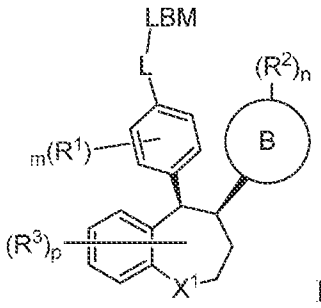
II-k **II-l**

, or a pharmaceutically acceptable salt thereof.

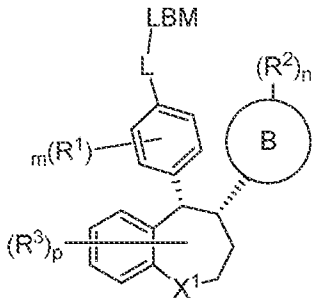
Embodiment 114. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-g-1**, **II-h-1**, **II-i-1**, **II-j-1**, **II-k-1**, or **II-l-1**:



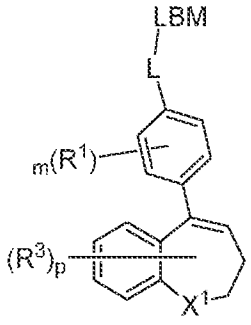
II-g-1



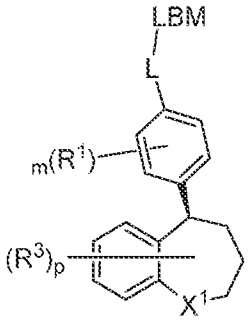
II-h-1



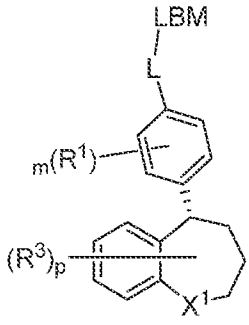
II-i-1



II-j-1



II-k-1



II-l-1, or a pharmaceutically acceptable salt thereof.

Embodiment 115. The compound of embodiment 114, wherein the compound is a compound of formula **II-g-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 116. The compound of embodiment 114, wherein the compound is a compound of formula **II-h-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 117. The compound of embodiment 114, wherein the compound is a compound of formula **II-i-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 118. The compound of embodiment 114, wherein the compound is a compound of formula **II-j-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 119. The compound of embodiment 114, wherein the compound is a compound of formula **II-k-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 120. The compound of embodiment 114, wherein the compound is a compound of formula **II-l-1**, or a pharmaceutically acceptable salt thereof.

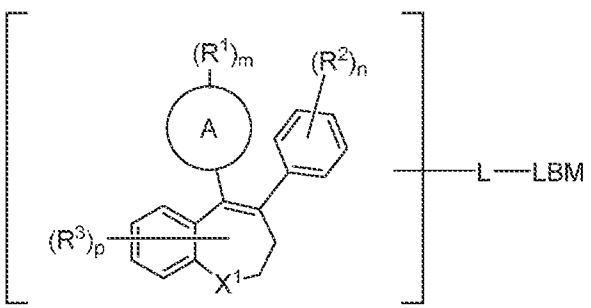
Embodiment 121. The compound of any one of embodiments 1-120, wherein X^1 is selected from $-CH_2-$, $-CH(R^{A1})-$, $-C(R^{A1})_2-$, $-O-$, $-S-$, $-S(O)_2-$, and $-N(R^{A2})-$, provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

Embodiment 122. The compound of any one of embodiments 1-120, wherein X^1 is selected from $-CH_2-$ and $-O-$ provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

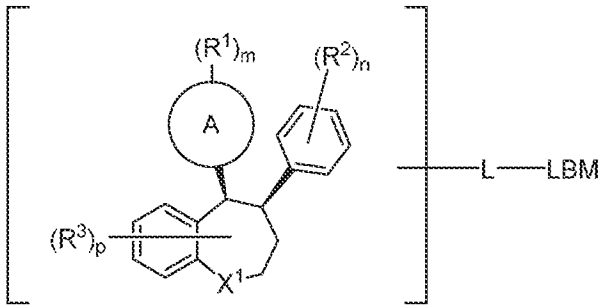
Embodiment 123. The compound of any one of embodiments 1-120, wherein X^1 is $-CH_2-$.

Embodiment 124. The compound of any one of embodiments 1-120, wherein X^1 is $-O-$ provided that X^2 is not a heteroatom.

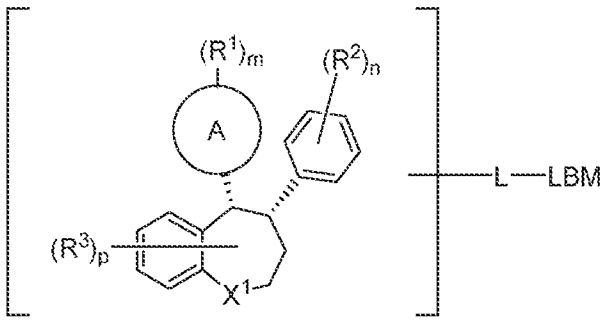
Embodiment 125. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-m**, **II-n**, **II-o**, **II-p**, **II-q**, **II-r**, **II-s**, **II-t**, **II-u**, **II-v**, **II-w**, **II-x**, **II-y**, **II-z**, or **II-aa**:



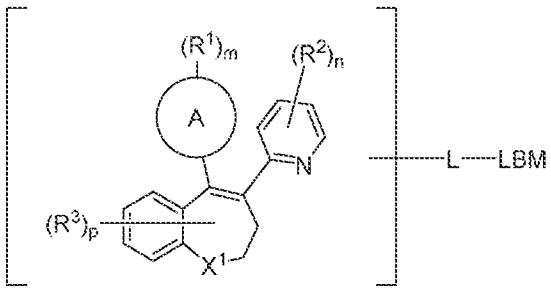
II-m



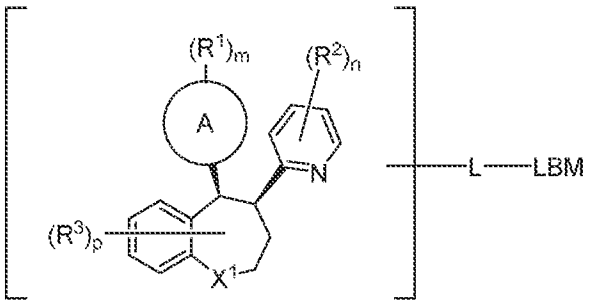
II-n



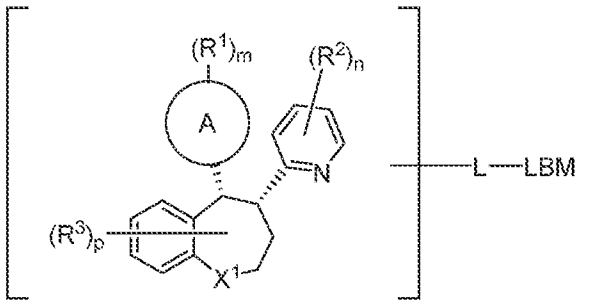
II-o



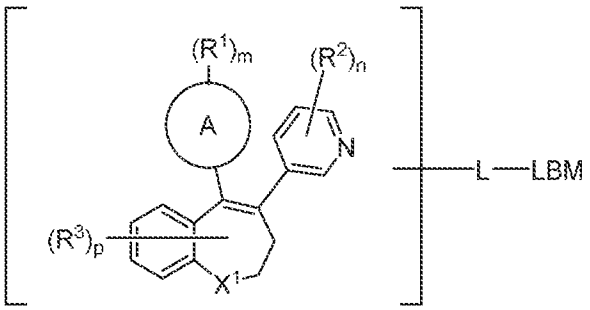
II-p



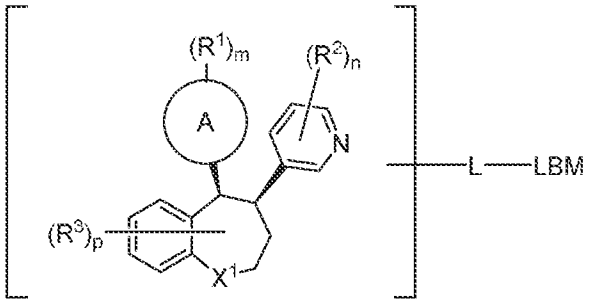
II-q



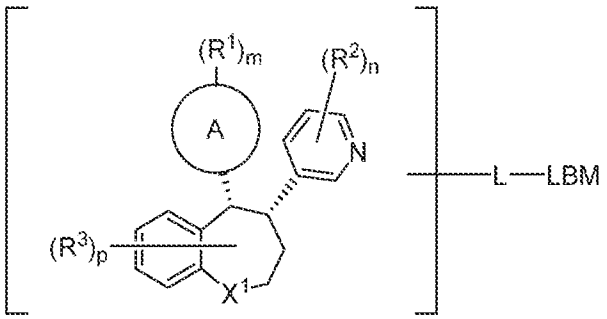
II-r



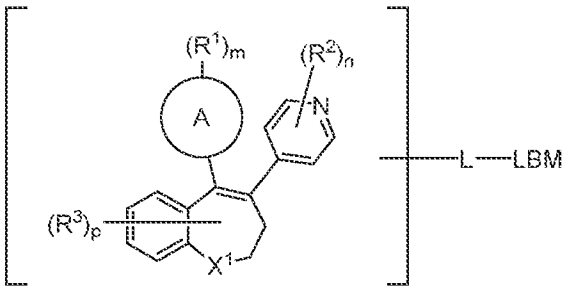
II-s



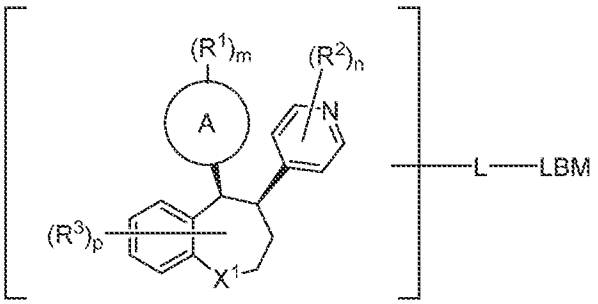
II-t



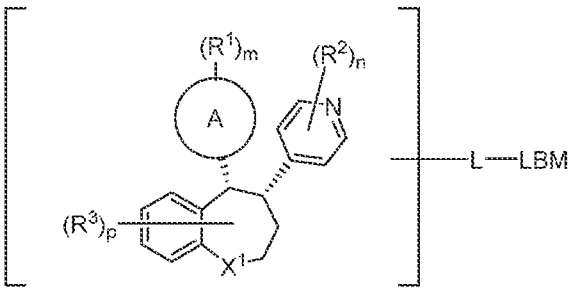
II-u



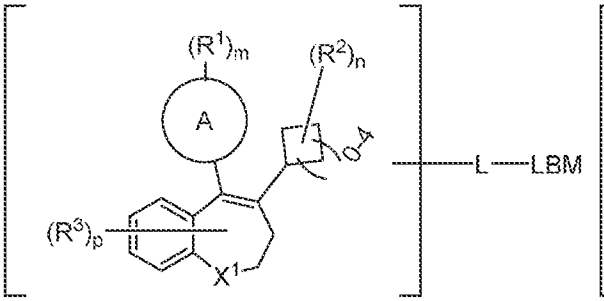
II-v

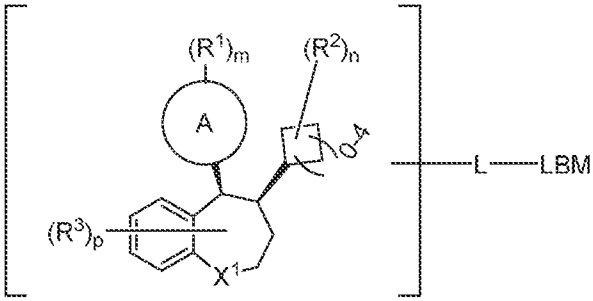


II-w

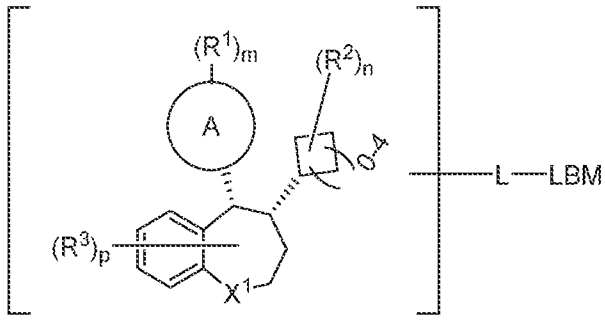


II-x





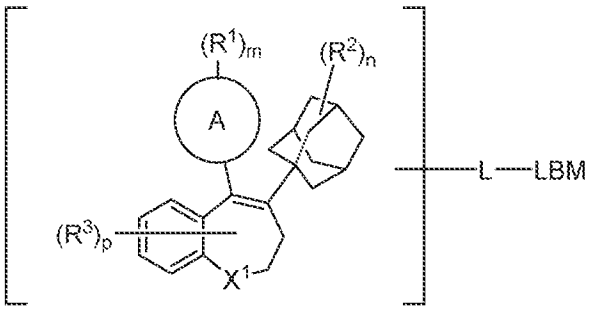
II-y **II-z**



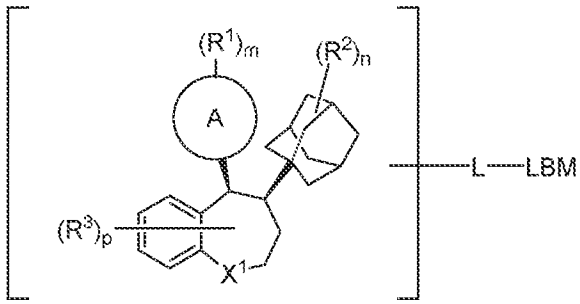
II-aa

or a pharmaceutically acceptable salt thereof.

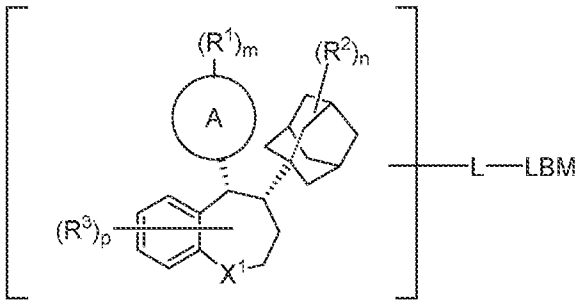
Embodiment 126. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-bb**, **II-cc**, **II-dd**, **II-ee**, **II-ff**, or **II-gg**:



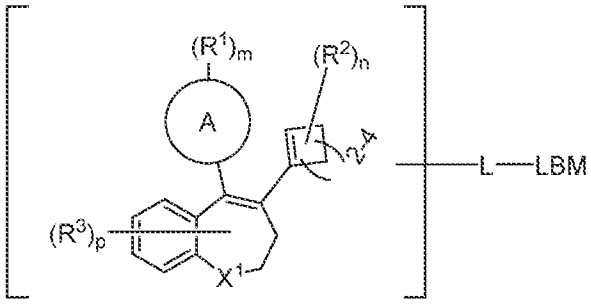
II-bb

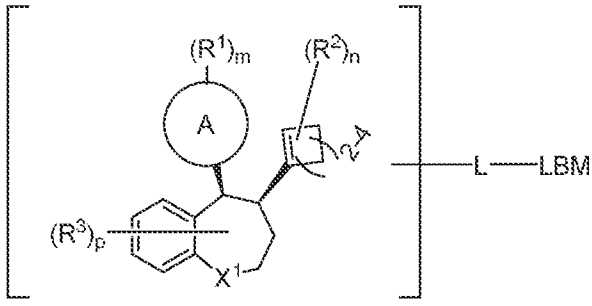


II-cc

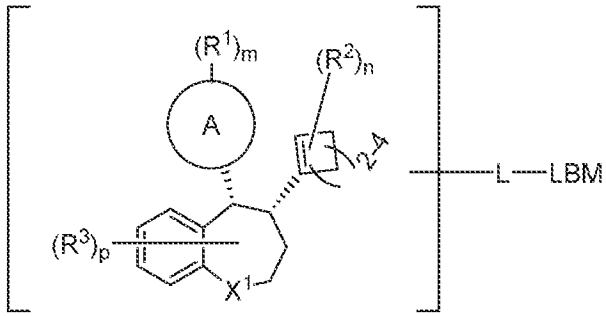


II-dd





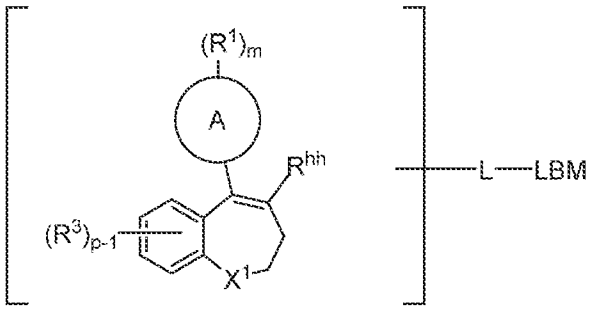
II-ee II-ff



II-gg

or a pharmaceutically acceptable salt thereof.

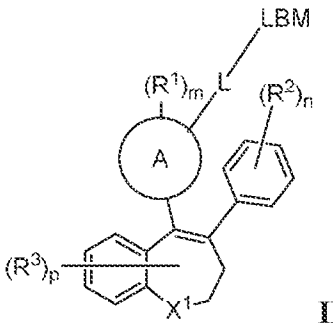
Embodiment 127. The compound of embodiment 1, wherein the compound is a compound of formula **II-hh**:



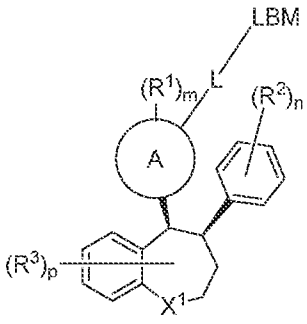
II-hh

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

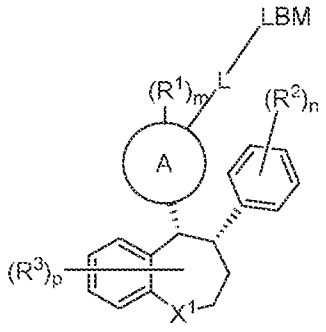
Embodiment 128. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-m-1**, **II-n-1**, **II-o-1**, **II-p-1**, **II-q-1**, **II-r-1**, **II-s-1**, **II-t-1**, **II-u-1**, **II-v-1**, **II-w-1**, **II-x-1**, **II-y-1**, **II-z-1**, or **II-aa-1**:



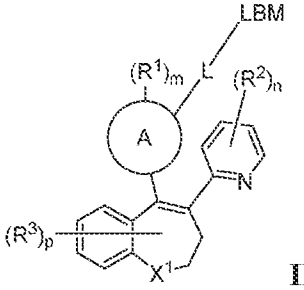
II-m-1



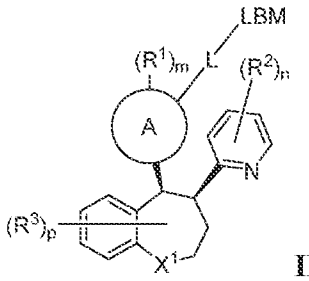
II-n-1



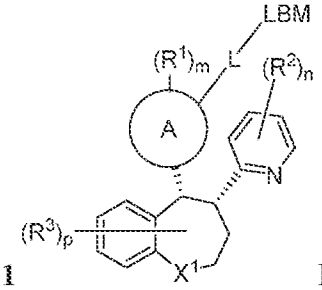
II-o-1



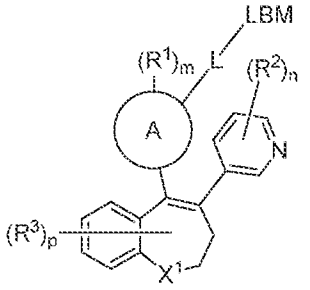
II-p-1



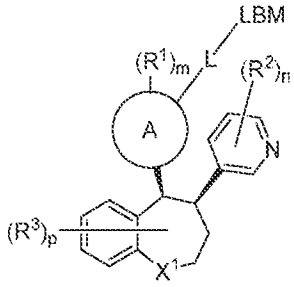
II-q-1



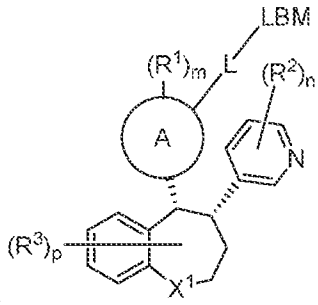
II-r-1



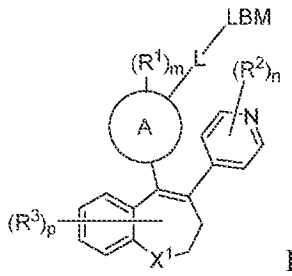
II-s-1



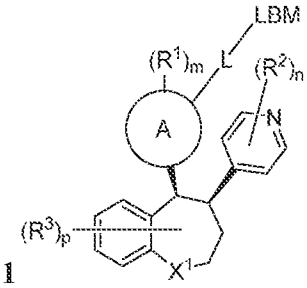
II-t-1



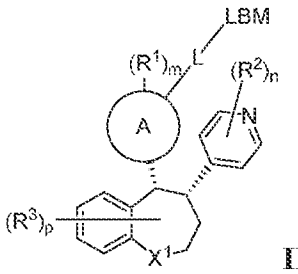
II-u-1



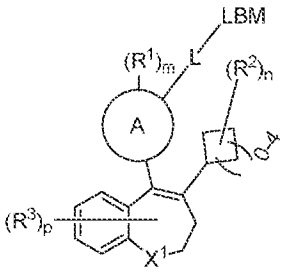
II-v-1



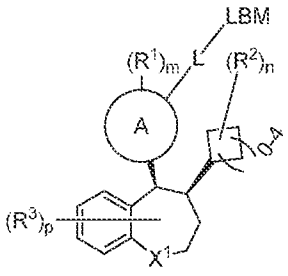
II-w-1



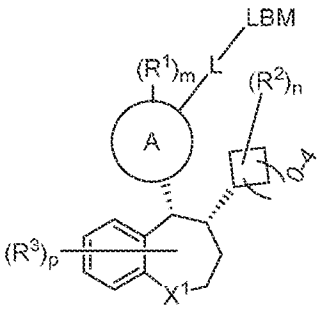
II-x-1



II-y-1



II-z-1



II-aa-1

or a pharmaceutically acceptable salt thereof.

Embodiment 129. The compound of embodiment 128, wherein the compound is a compound of formula **II-m-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 130. The compound of embodiment 128, wherein the compound is a compound of formula **II-n-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 131. The compound of embodiment 128, wherein the compound is a compound of formula **II-o-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 132. The compound of embodiment 128, wherein the compound is a compound of formula **II-p-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 133. The compound of embodiment 128, wherein the compound is a compound of formula **II-q-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 134. The compound of embodiment 128, wherein the compound is a compound of formula **II-r-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 135. The compound of embodiment 128, wherein the compound is a compound of formula **II-s-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 136. The compound of embodiment 128, wherein the compound is a compound of formula **II-t-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 137. The compound of embodiment 128, wherein the compound is a compound of formula **II-u-1** or a pharmaceutically acceptable salt thereof.

Embodiment 138. The compound of embodiment 128, wherein the compound is a compound of formula **II-v-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 139. The compound of embodiment 128, wherein the compound is a compound of formula **II-w-1**, or a pharmaceutically acceptable salt thereof.

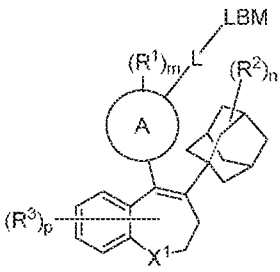
Embodiment 140. The compound of embodiment 128, wherein the compound is a compound of formula **II-x-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 141. The compound of embodiment 128, wherein the compound is a compound of formula **II-y-1**, or a pharmaceutically acceptable salt thereof.

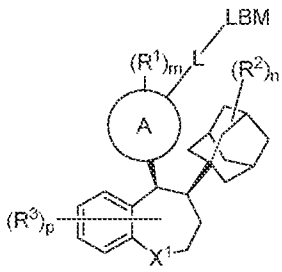
Embodiment 142. The compound of embodiment 128, wherein the compound is a compound of formula **II-z-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 143. The compound of embodiment 128, wherein the compound is a compound of formula **II-aa-1**, or a pharmaceutically acceptable salt thereof.

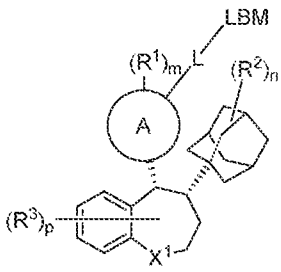
Embodiment 144. The compound of embodiment 1, wherein the compound is a compound of one of formulas **II-bb-1**, **II-cc-1**, **II-dd-1**, **II-ee-1**, **II-ff-1** or **II-gg-1**:



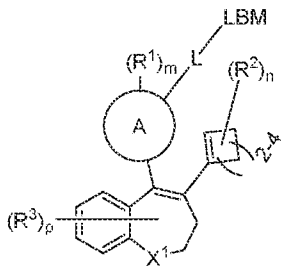
II-bb-1



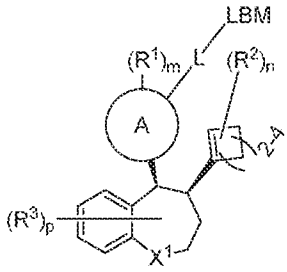
II-cc-1



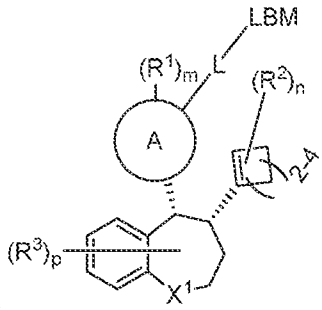
II-dd-1



II-ee-1



II-ff-1



II-gg-1

or a pharmaceutically acceptable salt thereof.

Embodiment 145. The compound of embodiment 144, wherein the compound is a compound of formula **II-bb-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 146. The compound of embodiment 144, wherein the compound is a compound of formula **II-cc-1**, or a pharmaceutically acceptable salt thereof.

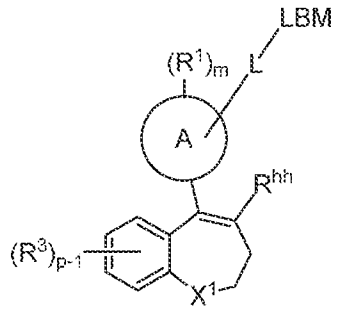
Embodiment 147. The compound of embodiment 144, wherein the compound is a compound of formula **II-dd-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 148. The compound of embodiment 144, wherein the compound is a compound of formula **II-ee-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 149. The compound of embodiment 144, wherein the compound is a compound of formula **II-ff-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 150. The compound of embodiment 144, wherein the compound is a compound of formula **II-gg-1**, or a pharmaceutically acceptable salt thereof.

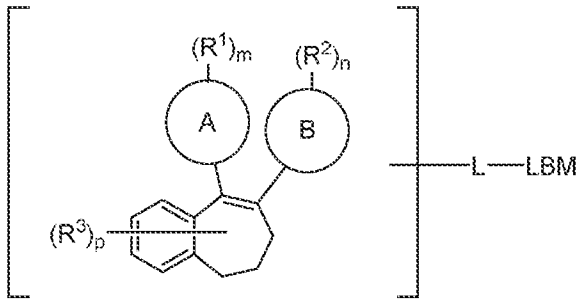
Embodiment 151. The compound of embodiment 1, wherein the compound is a compound of formula **II-hh-1**:



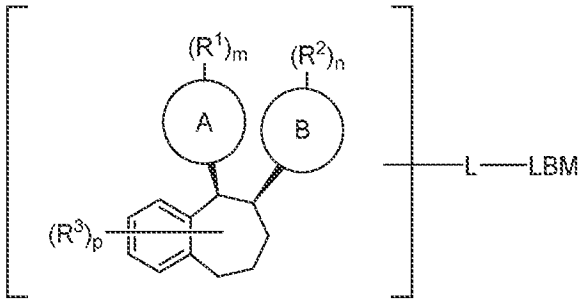
II-hh-1

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

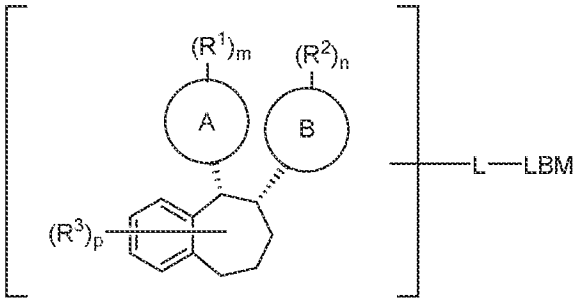
Embodiment 152. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, or **III-f**:



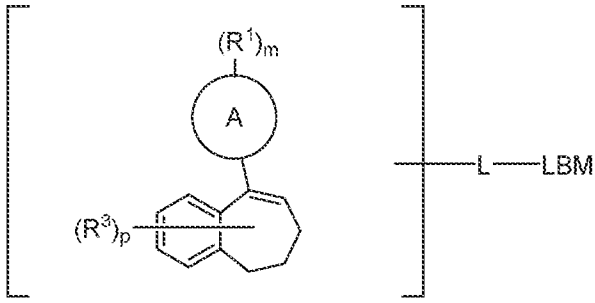
III-a



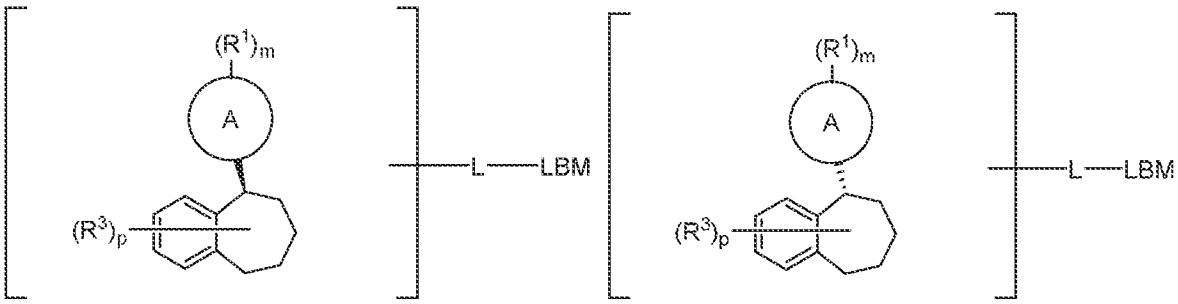
III-b



III-c



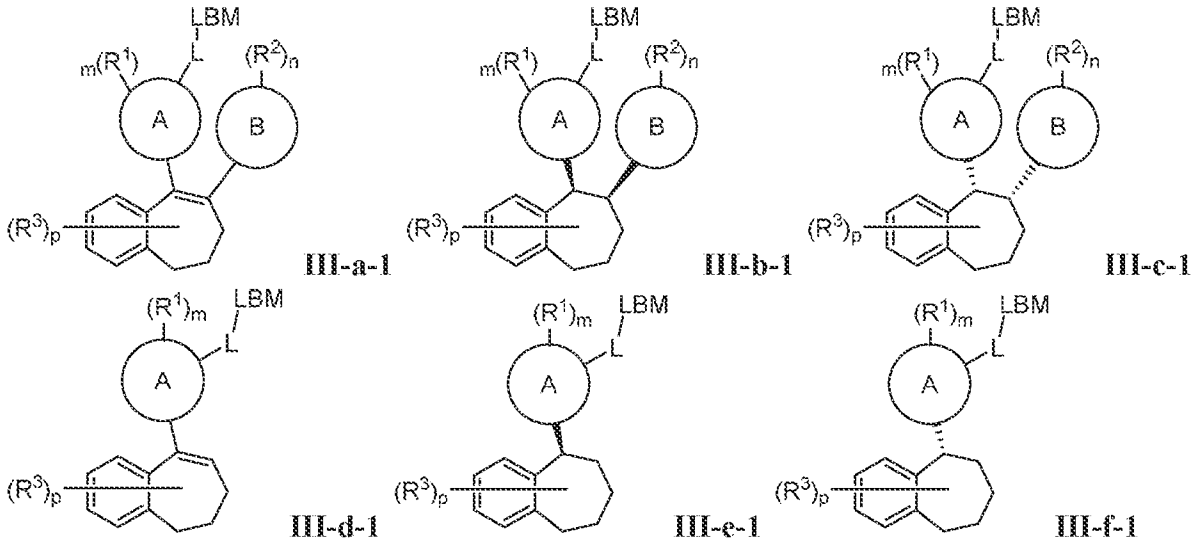
III-d



III-e **III-f**

or a pharmaceutically acceptable salt thereof.

Embodiment 153. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-a-1**, **III-b-1**, **III-c-1**, **III-d-1**, **III-e-1**, or **III-f-1**:



III-a-1 **III-b-1** **III-c-1**

III-d-1 **III-e-1** **III-f-1**

or a pharmaceutically acceptable salt thereof.

Embodiment 154. The compound of embodiment 153, wherein the compound is a compound of formula **III-a-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 155. The compound of embodiment 153, wherein the compound is a compound of formula **III-b-1**, or a pharmaceutically acceptable salt thereof.

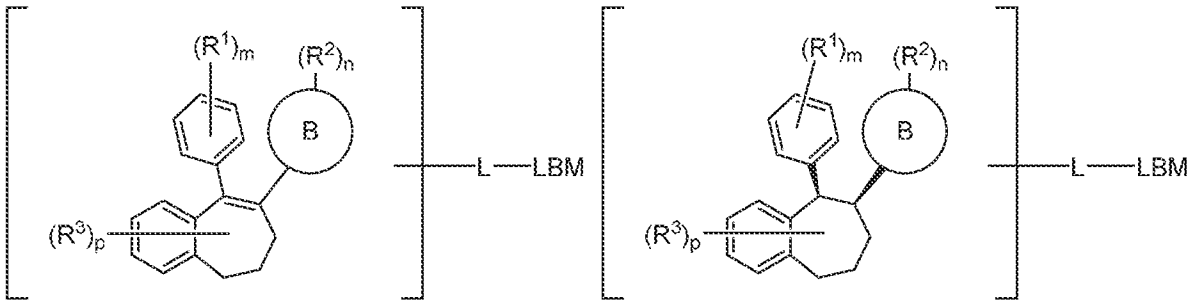
Embodiment 156. The compound of embodiment 153, wherein the compound is a compound of formula **III-c-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 157. The compound of embodiment 153, wherein the compound is a compound of formula **III-d-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 158. The compound of embodiment 153, wherein the compound is a compound of formula **III-e-1**, or a pharmaceutically acceptable salt thereof.

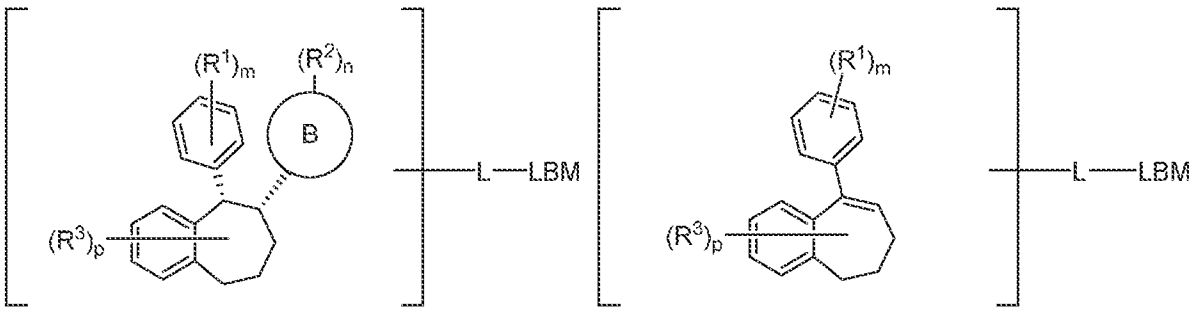
Embodiment 159. The compound of embodiment 153, wherein the compound is a compound of formula **III-f-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 160. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-g**, **III-h**, **III-i**, **III-j**, **III-k**, or **III-l**:



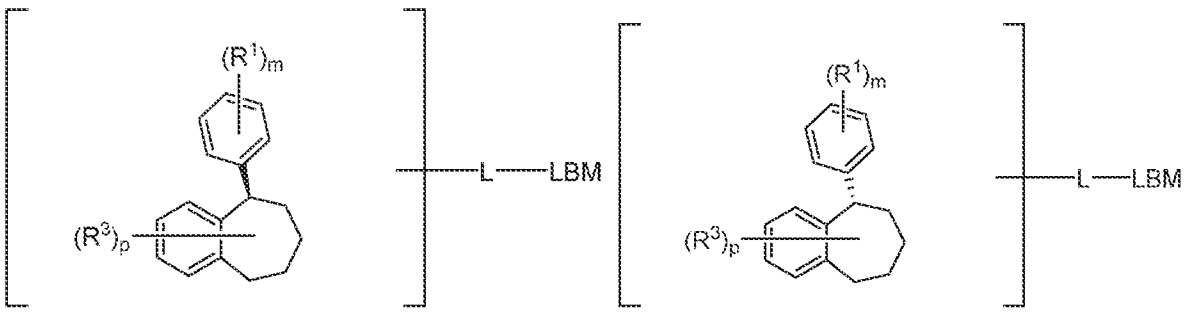
III-g

III-h



III-i

III-j

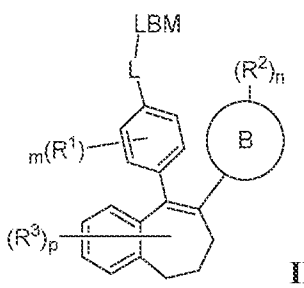


III-k

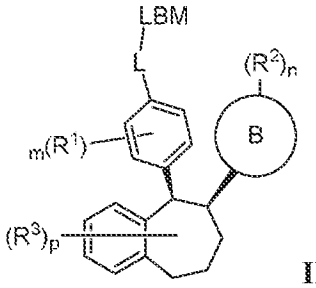
III-l

or a pharmaceutically acceptable salt thereof.

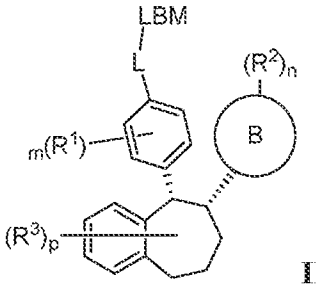
Embodiment 161. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-g-1**, **III-h-1**, **III-i-1**, **V-f**, **III-k-1**, or **III-l-1**:



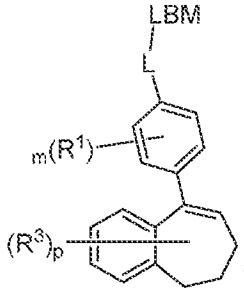
III-g-1



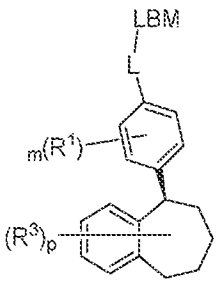
III-h-1



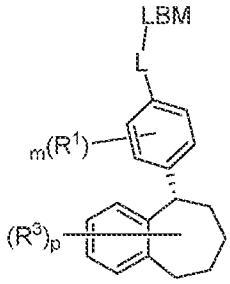
III-i-1



V-f



III-k-1



III-l-1, or a pharmaceutically acceptable salt thereof.

Embodiment 162. The compound of embodiment 161, wherein the compound is a compound of formula **III-g-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 163. The compound of embodiment 161, wherein the compound is a compound of formula **III-h-1**, or a pharmaceutically acceptable salt thereof.

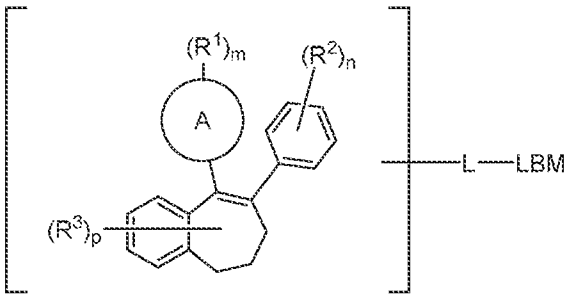
Embodiment 164. The compound of embodiment 161, wherein the compound is a compound of formula **III-i-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 165. The compound of embodiment 161, wherein the compound is a compound of formula **V-f**, or a pharmaceutically acceptable salt thereof.

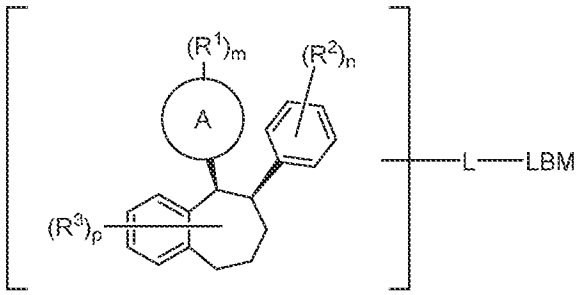
Embodiment 166. The compound of embodiment 161, wherein the compound is a compound of formula **III-k-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 167. The compound of embodiment 161, wherein the compound is a compound of formula **III-l-1**, or a pharmaceutically acceptable salt thereof.

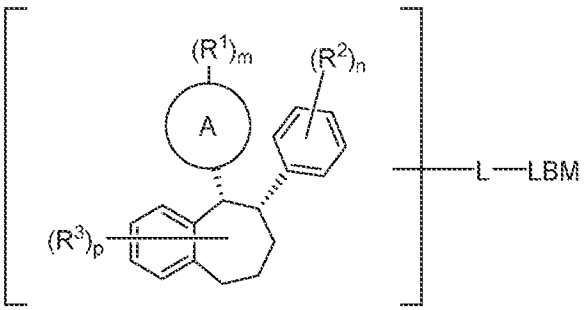
Embodiment 168. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-m**, **III-n**, **III-o**, **III-p**, **III-q**, **III-r**, **III-s**, **III-t**, **III-u**, **III-v**, **III-w**, **III-x**, **III-y**, **III-z**, or **III-aa**:



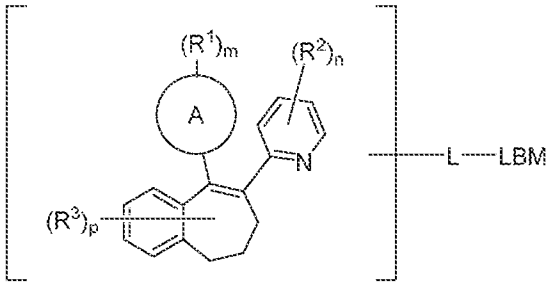
III-m



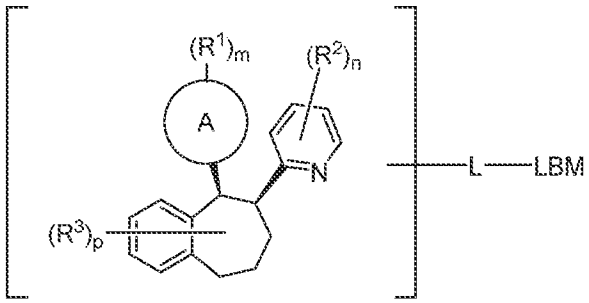
III-n



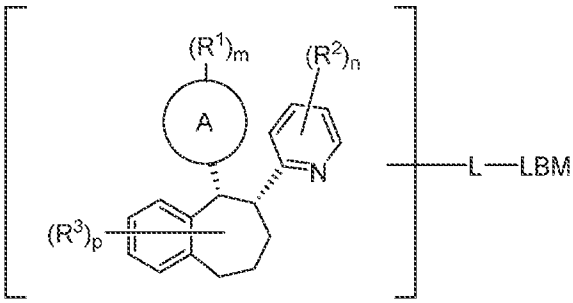
III-o



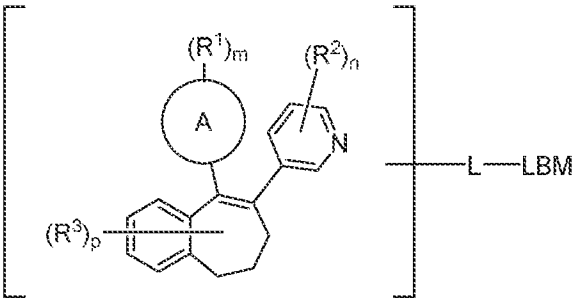
III-p



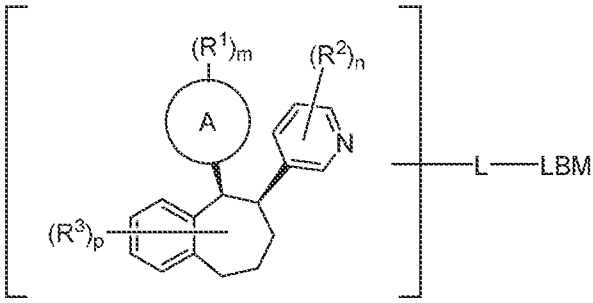
III-q



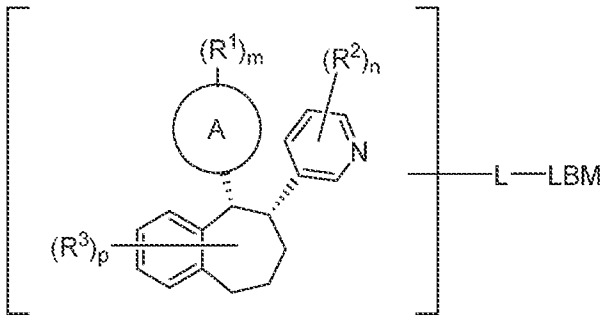
III-r

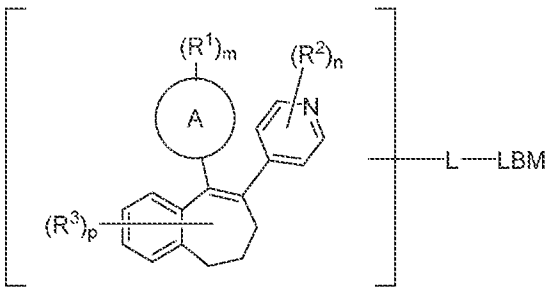


III-s

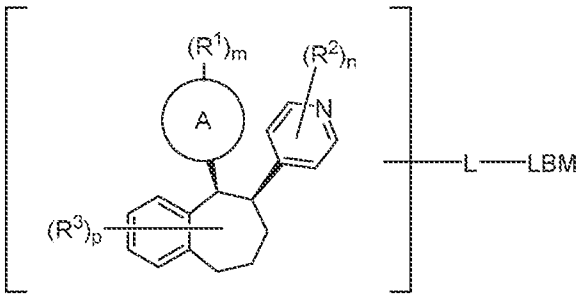


III-t

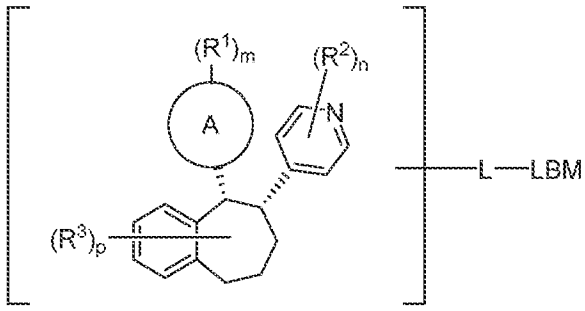




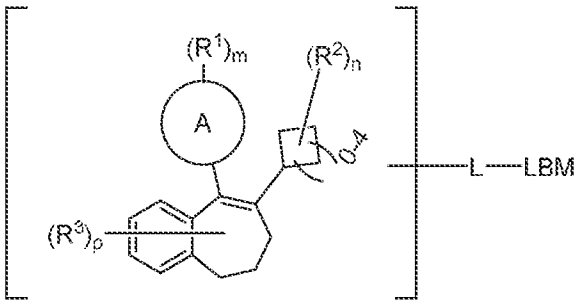
III-u



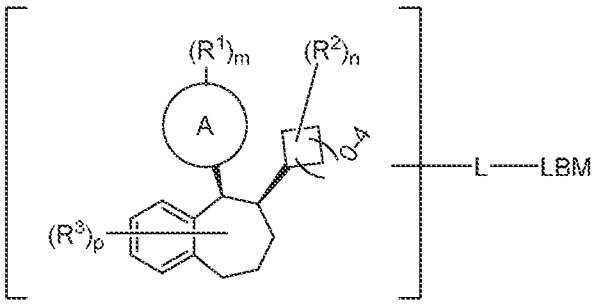
III-v



III-w

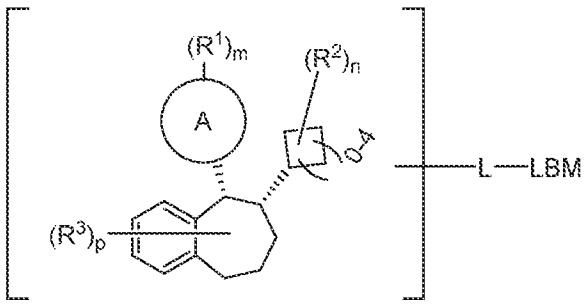


III-x



III-y

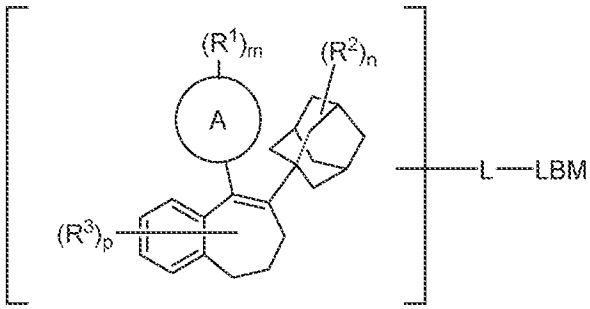
III-z



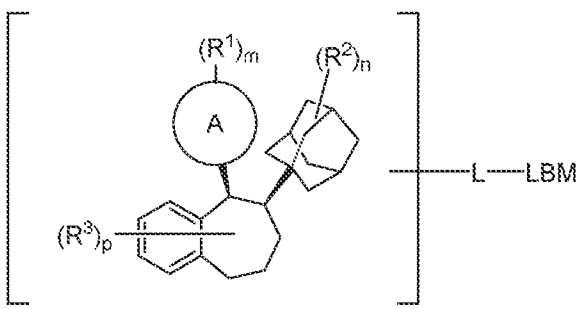
III-aa

or a pharmaceutically acceptable salt thereof.

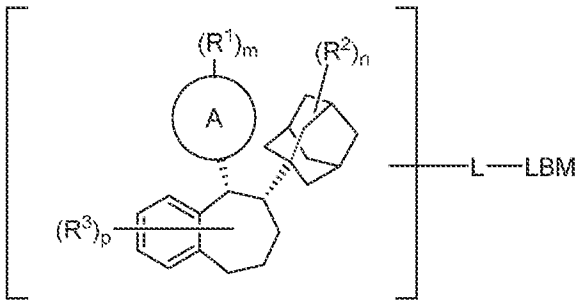
Embodiment 169. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-bb**, **III-cc**, **III-dd**, **III-ee**, **III-ff**, or **III-gg**:



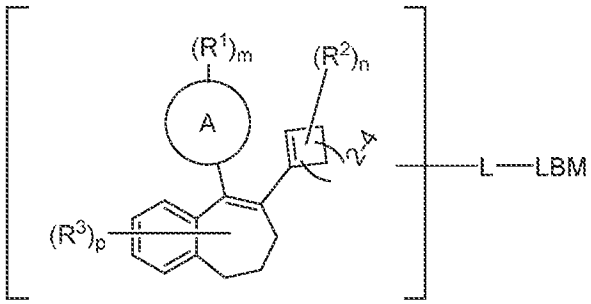
III-bb



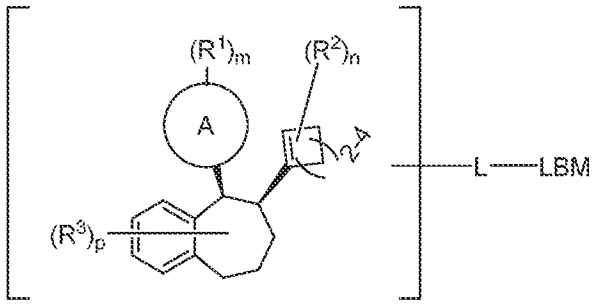
III-cc



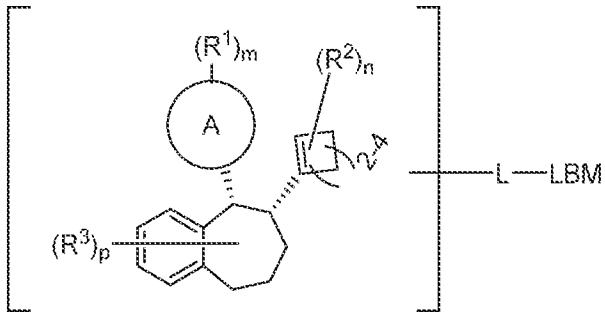
III-dd



III-ee



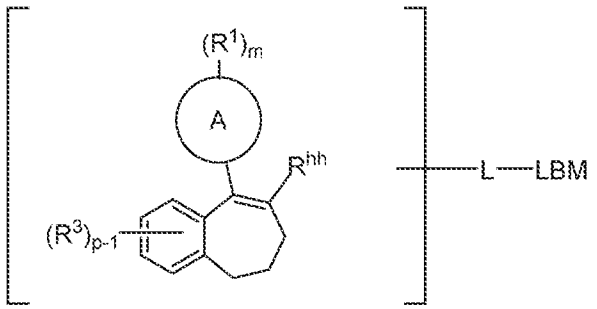
III-ff



III-gg

or a pharmaceutically acceptable salt thereof.

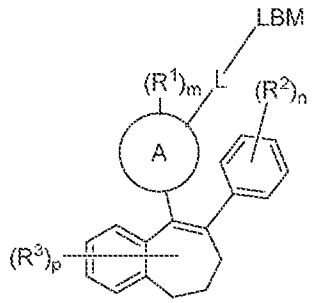
Embodiment 170. The compound of embodiment 1, wherein the compound is a compound of formula **III-hh**:



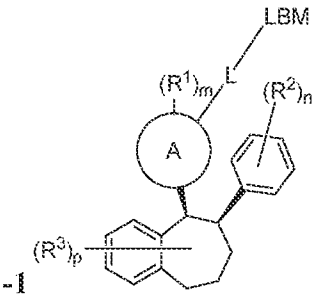
III-hh

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

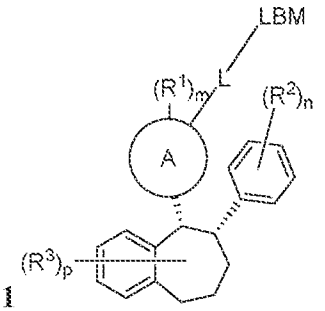
Embodiment 171. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-m-1**, **III-n-1**, **III-o-1**, **III-p-1**, **III-q-1**, **III-r-1**, **III-s-1**, **III-t-1**, **III-u-1**, **III-v-1**, **III-w-1**, **III-x-1**, **III-y-1**, **III-z-1**, or **III-aa-1**:



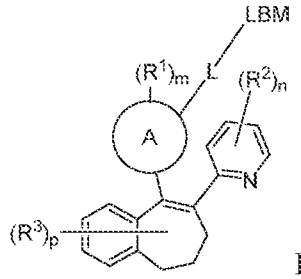
III-m-1



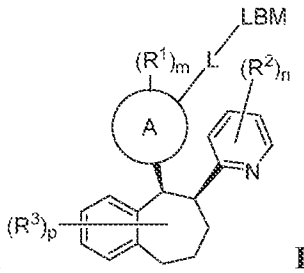
III-n-1



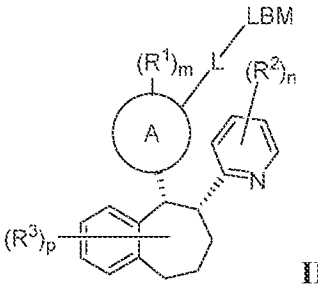
III-o-1



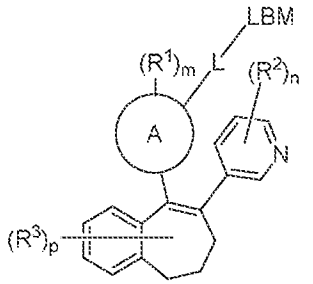
III-p-1



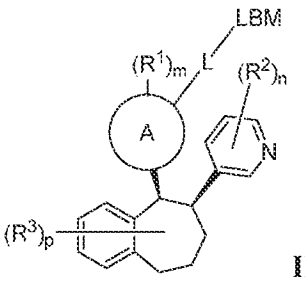
III-q-1



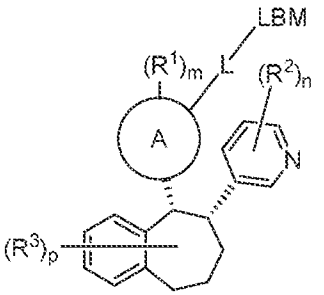
III-r-1



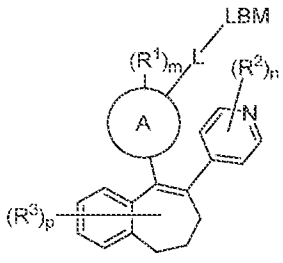
III-s-1



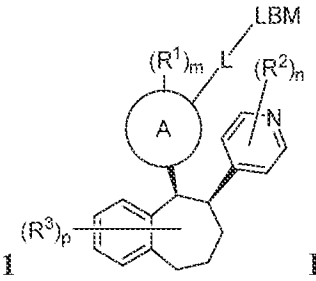
III-t-1



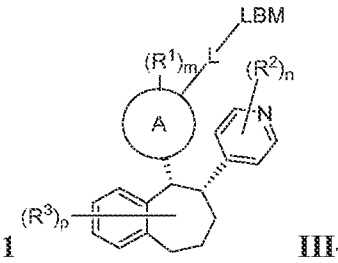
III-u-1



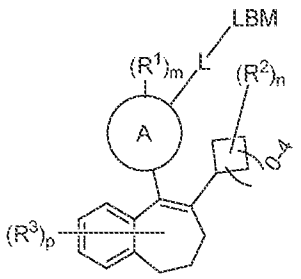
III-v-1



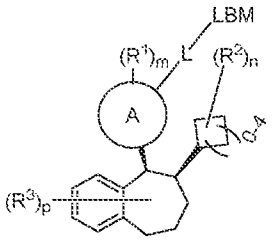
III-w-1



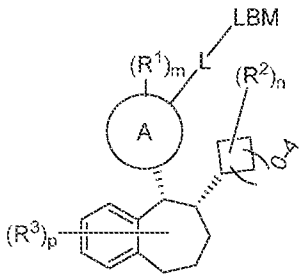
III-x-1



III-y-1



III-z-1



III-aa-1

or a pharmaceutically acceptable salt thereof.

Embodiment 172. The compound of embodiment 171, wherein the compound is a compound of formula **III-m-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 173. The compound of embodiment 171, wherein the compound is a compound of formula **III-n-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 174. The compound of embodiment 171, wherein the compound is a compound of formula **III-o-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 175. The compound of embodiment 171, wherein the compound is a compound of formula **III-p-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 176. The compound of embodiment 171, wherein the compound is a compound of formula **III-q-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 177. The compound of embodiment 171, wherein the compound is a compound of formula **III-r-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 178. The compound of embodiment 171, wherein the compound is a compound of formula **III-s-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 179. The compound of embodiment 171, wherein the compound is a compound of formula **III-t-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 180. The compound of embodiment 171, wherein the compound is a compound of formula **III-u-1** or a pharmaceutically acceptable salt thereof.

Embodiment 181. The compound of embodiment 171, wherein the compound is a compound of formula **III-v-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 182. The compound of embodiment 171, wherein the compound is a compound of formula **III-w-1**, or a pharmaceutically acceptable salt thereof.

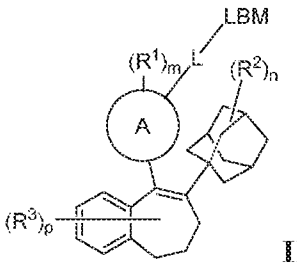
Embodiment 183. The compound of embodiment 171, wherein the compound is a compound of formula **III-x-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 184. The compound of embodiment 171, wherein the compound is a compound of formula **III-y-1**, or a pharmaceutically acceptable salt thereof.

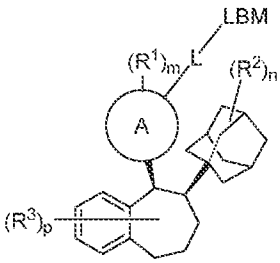
Embodiment 185. The compound of embodiment 171, wherein the compound is a compound of formula **III-z-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 186. The compound of embodiment 171, wherein the compound is a compound of formula **III-aa-1**, or a pharmaceutically acceptable salt thereof.

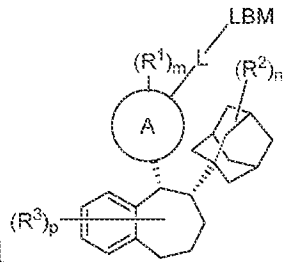
Embodiment 187. The compound of embodiment 1, wherein the compound is a compound of one of formulas **III-bb-1**, **III-cc-1**, **III-dd-1**, **III-ee-1**, **III-ff-1** or **III-gg-1**:



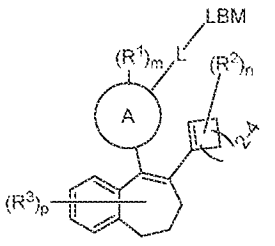
III-bb-1



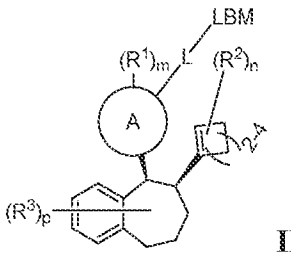
III-cc-1



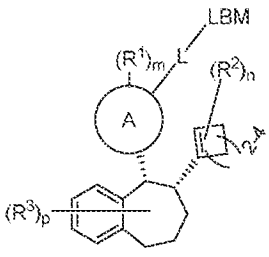
III-dd-1



III-ee-1



III-ff-1



III-gg-1

or a pharmaceutically acceptable salt thereof.

Embodiment 188. The compound of embodiment 187, wherein the compound is a compound of formula **III-bb-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 189. The compound of embodiment 187, wherein the compound is a compound of formula **III-cc-1**, or a pharmaceutically acceptable salt thereof.

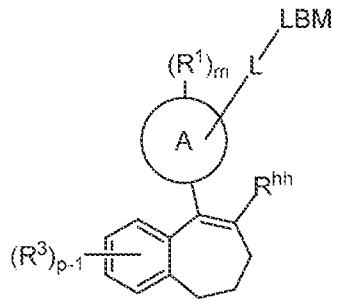
Embodiment 190. The compound of embodiment 187, wherein the compound is a compound of formula **III-dd-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 191. The compound of embodiment 187, wherein the compound is a compound of formula **III-ee-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 192. The compound of embodiment 187, wherein the compound is a compound of formula **III-ff-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 193. The compound of embodiment 187, wherein the compound is a compound of formula **III-gg-1**, or a pharmaceutically acceptable salt thereof.

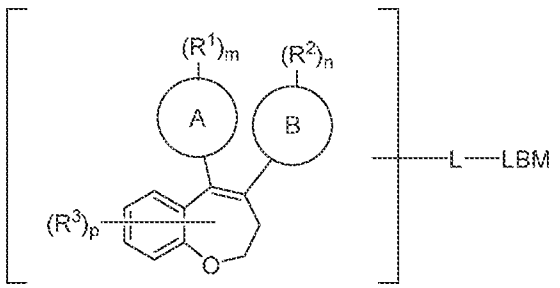
Embodiment 194. The compound of embodiment 1, wherein the compound is a compound of formula **III-hh-1**:



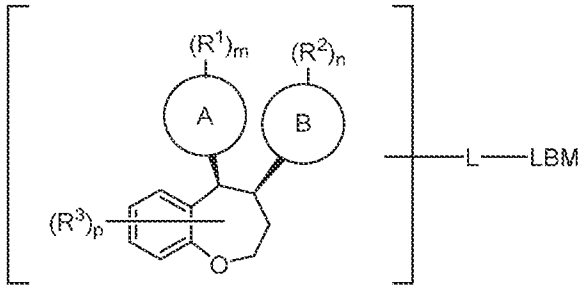
II-hh-1

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1$–C_6 alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

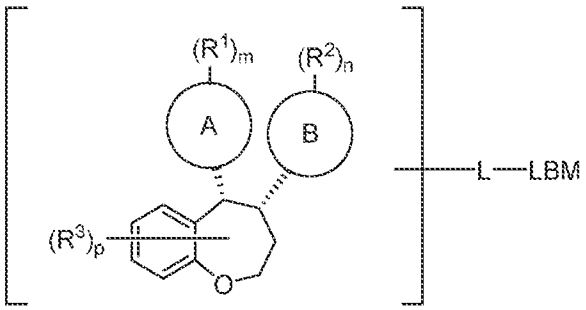
Embodiment 195. The compound of embodiment 1, wherein the compound is a compound of one of formulas **IV-a**, **IV-b**, **IV-c**, **IV-d**, **IV-e**, or **IV-f**:



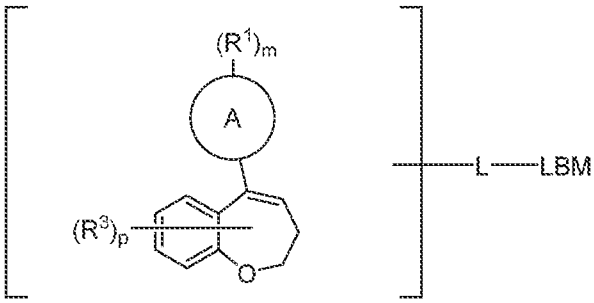
IV-a



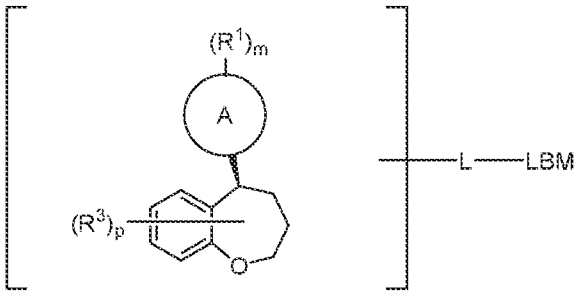
IV-b



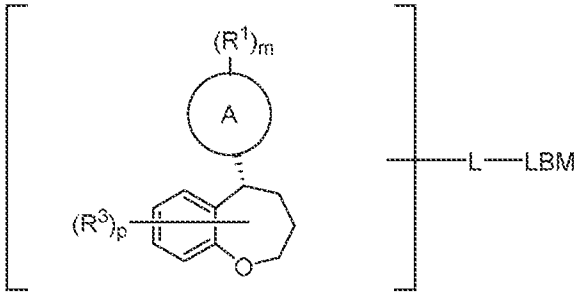
IV-c



IV-d



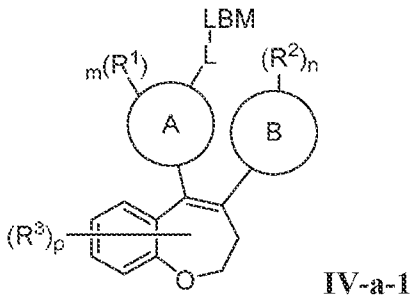
IV-e



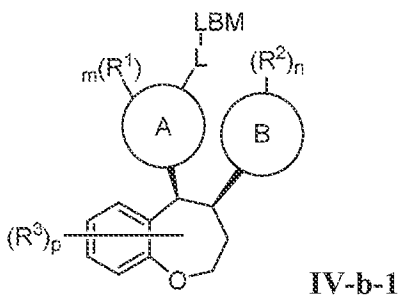
IV-f

or a pharmaceutically acceptable salt thereof.

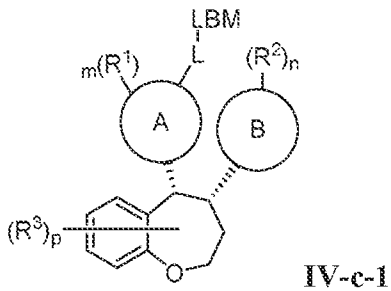
Embodiment 196. The compound of of embodiment 1, wherein the compound is a compound of one of formulas **IV-a-1**, **IV-b-1**, **IV-c-1**, **IV-d-1**, **IV-e-1**, or **IV-f-1**:



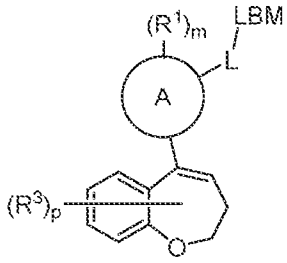
IV-a-1



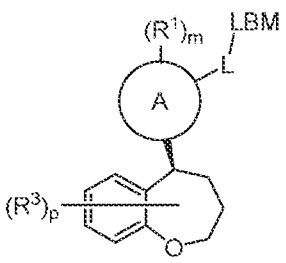
IV-b-1



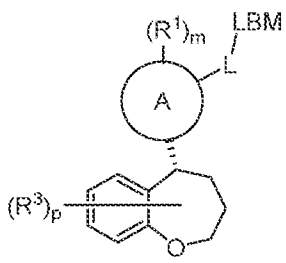
IV-c-1



IV-d-1



IV-e-1



IV-f-1

or a pharmaceutically acceptable salt thereof.

Embodiment 197. The compound of embodiment 196, wherein the compound is a compound of formula **IV-a-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 198. The compound of embodiment 196, wherein the compound is a compound of formula **IV-b-1**, or a pharmaceutically acceptable salt thereof.

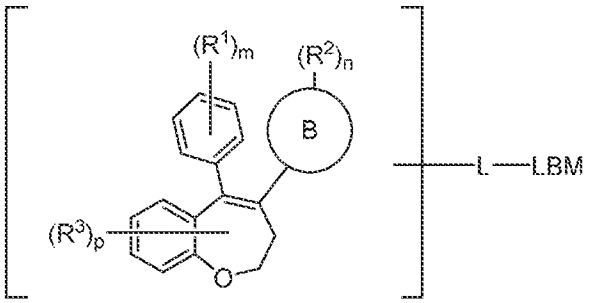
Embodiment 199. The compound of embodiment 196, wherein the compound is a compound of formula **IV-c-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 200. The compound of embodiment 196, wherein the compound is a compound of formula **IV-d-1**, or a pharmaceutically acceptable salt thereof.

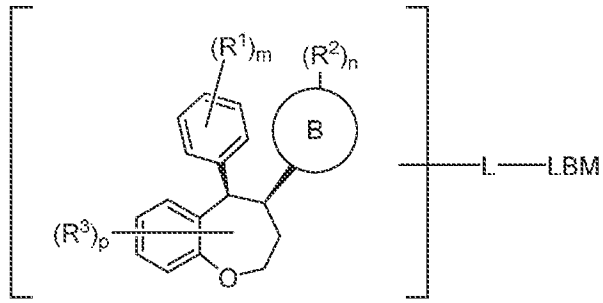
Embodiment 201. The compound of embodiment 196, wherein the compound is a compound of formula **IV-e-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 202. The compound of embodiment 196, wherein the compound is a compound of formula **IV-f-1**, or a pharmaceutically acceptable salt thereof.

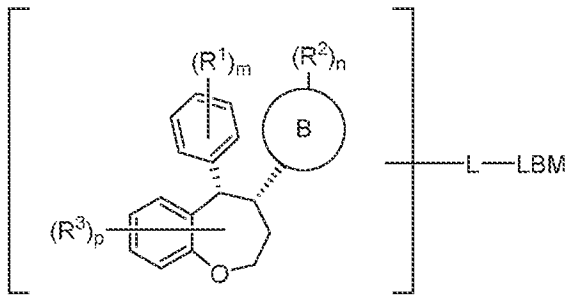
Embodiment 203. The compound of of embodiment 1, wherein the compound is a compound of one of formulas **IV-g**, **IV-h**, **IV-i**, **IV-j**, **IV-k**, or **IV-l**:



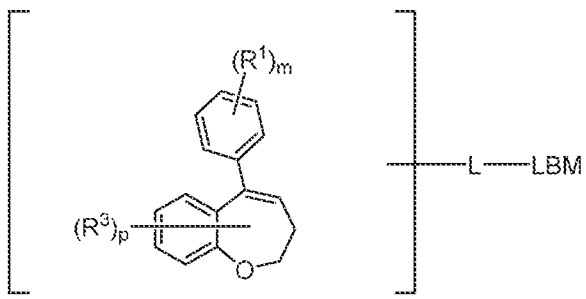
IV-g



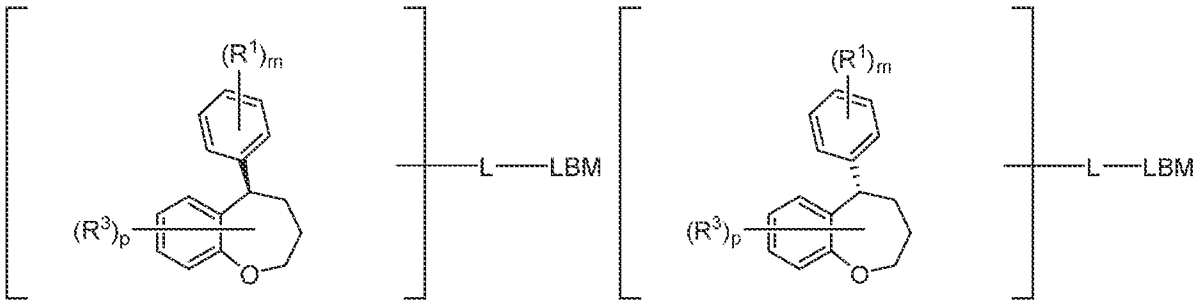
IV-h



IV-i



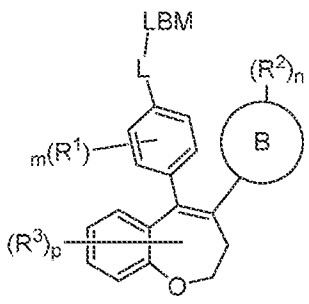
IV-j



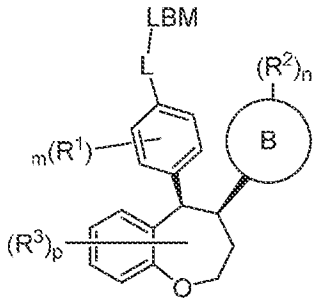
IV-k IV-l

or a pharmaceutically acceptable salt thereof.

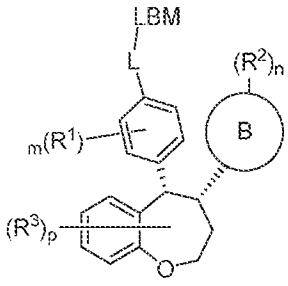
Embodiment 204. The compound of of embodiment 1, wherein the compound is a compound of one of formulas **IV-g-1**, **IV-h-1**, **IV-i-1**, **V-e**, **IV-k-1** or **IV-l-1**:



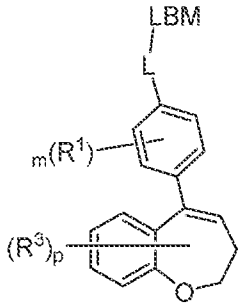
IV-g-1



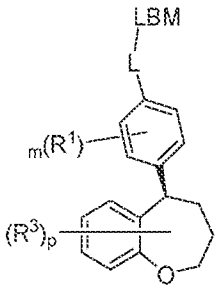
IV-h-1



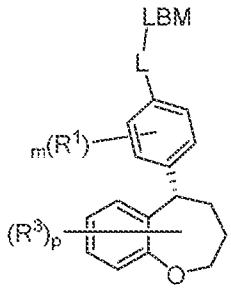
IV-i-1



V-e



IV-k-1



IV-l-1, or a pharmaceutically acceptable salt thereof.

Embodiment 205. The compound of embodiment 204, wherein the compound is a compound of formula **IV-g-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 206. The compound of embodiment 204, wherein the compound is a compound of formula **IV-h-1**, or a pharmaceutically acceptable salt thereof.

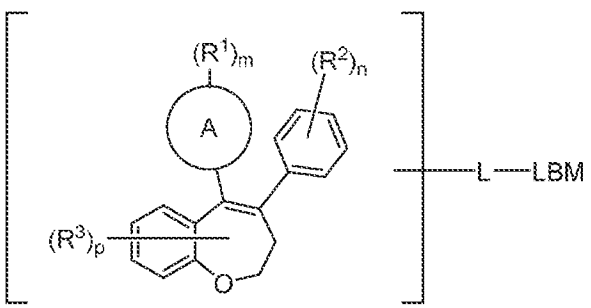
Embodiment 207. The compound of embodiment 204, wherein the compound is a compound of formula **IV-i-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 208. The compound of embodiment 204, wherein the compound is a compound of formula **IV-e-1**, or a pharmaceutically acceptable salt thereof.

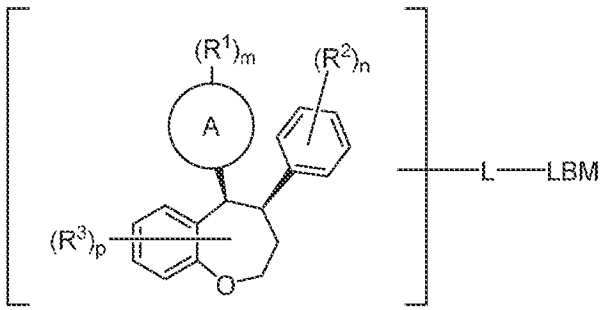
Embodiment 209. The compound of embodiment 204, wherein the compound is a compound of formula **V-k**, or a pharmaceutically acceptable salt thereof.

Embodiment 210. The compound of embodiment 204, wherein the compound is a compound of formula **IV-l-1**, or a pharmaceutically acceptable salt thereof.

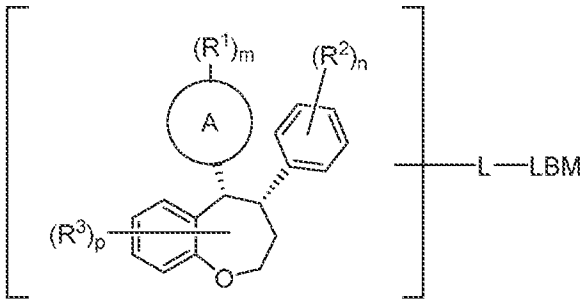
Embodiment 211. The compound of embodiment 1, wherein the compound is a compound of one of formulas **IV-m**, **IV-n**, **IV-o**, **IV-p**, **IV-q**, **IV-r**, **IV-s**, **IV-t**, **IV-u**, **IV-v**, **IV-w**, **IV-x**, **IV-y**, **IV-z**, or **IV-aa**:



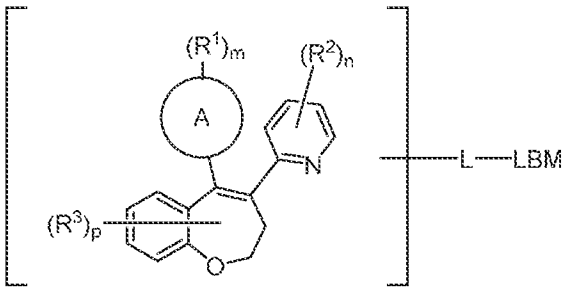
IV-m



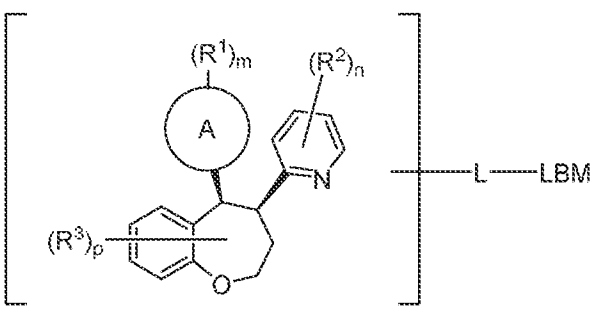
IV-n



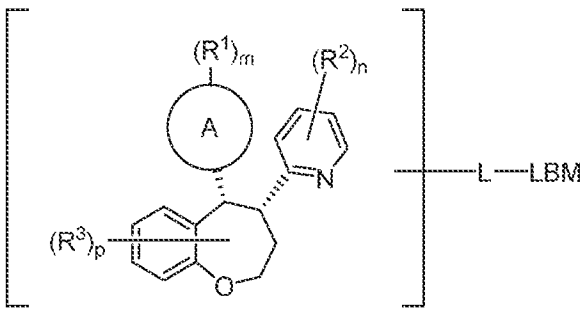
IV-o



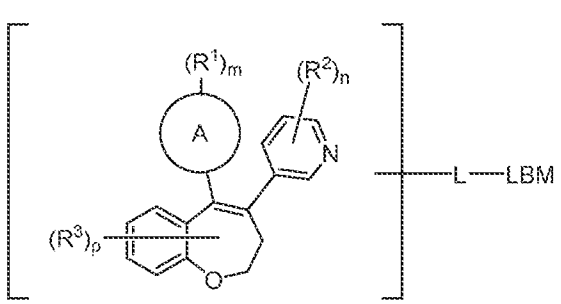
IV-p



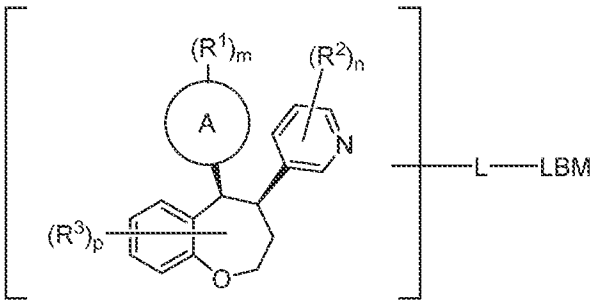
IV-q



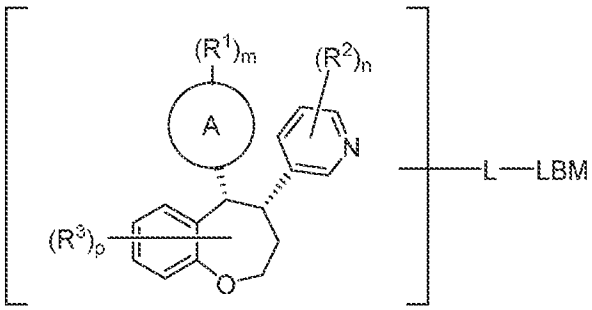
IV-r



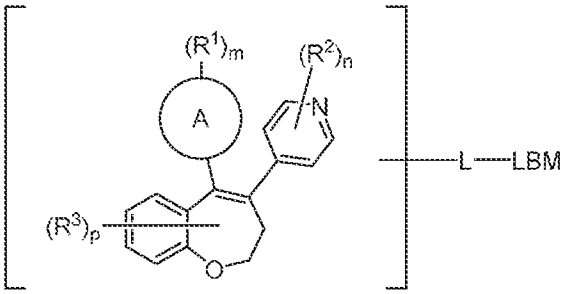
IV-s



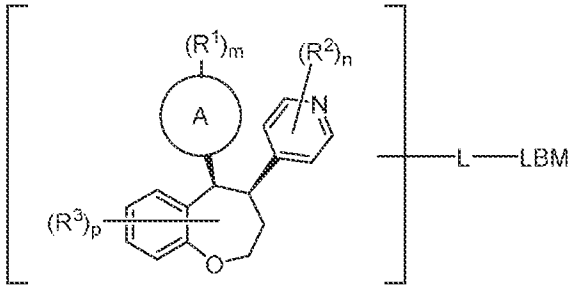
IV-t



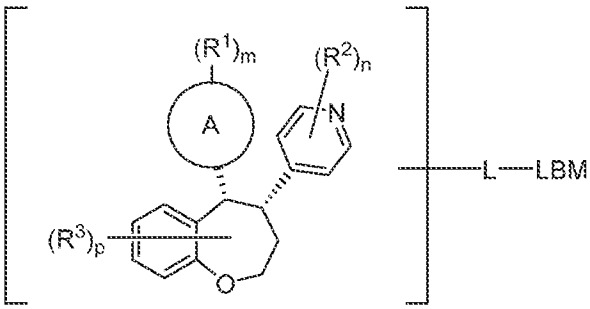
IV-u



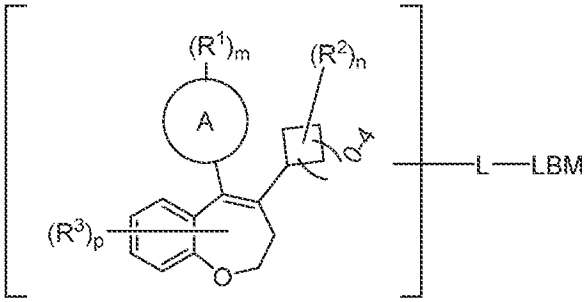
IV-v



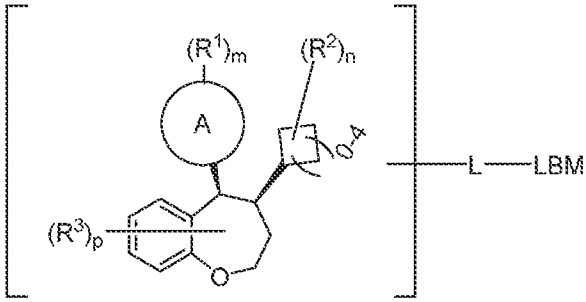
IV-w



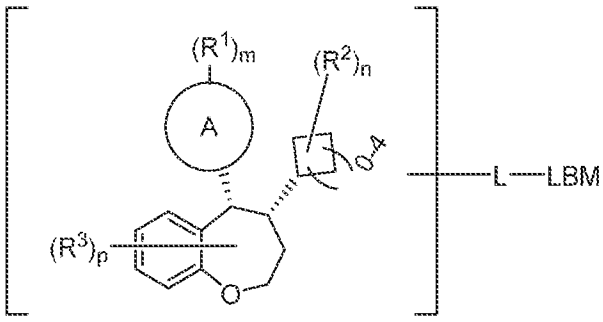
IV-x



IV-y



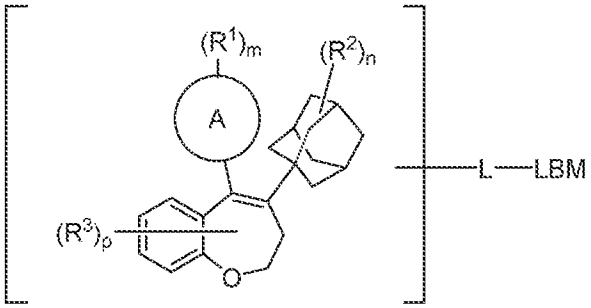
IV-z



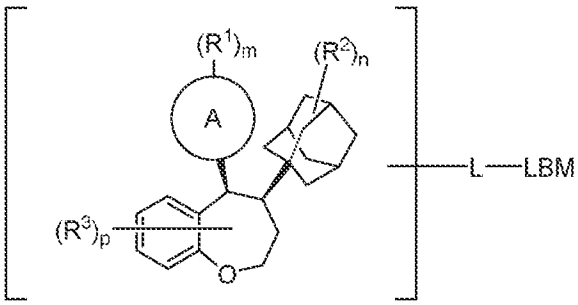
IV-aa

or a pharmaceutically acceptable salt thereof.

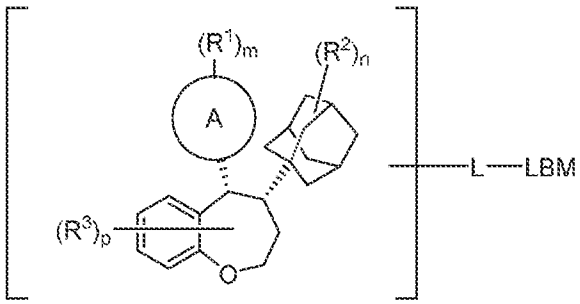
Embodiment 212. The compound of embodiment 1, wherein the compound is a compound of one of formulas **IV-bb**, **IV-cc**, **IV-dd**, **IV-ee**, **IV-ff**, or **IV-gg**:



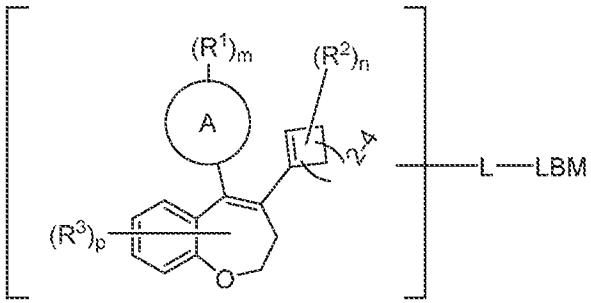
IV-bb



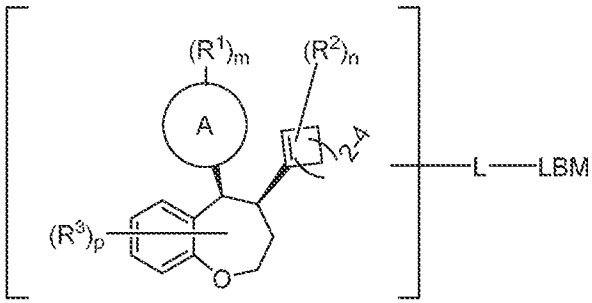
IV-cc



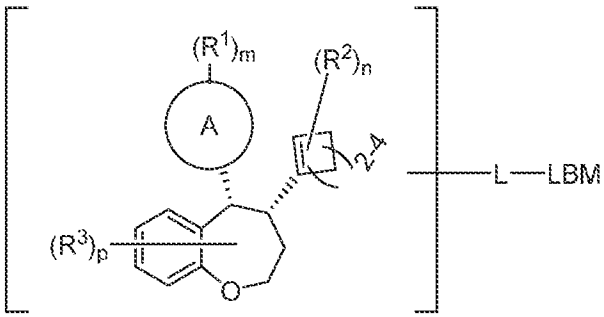
IV-dd



IV-ee



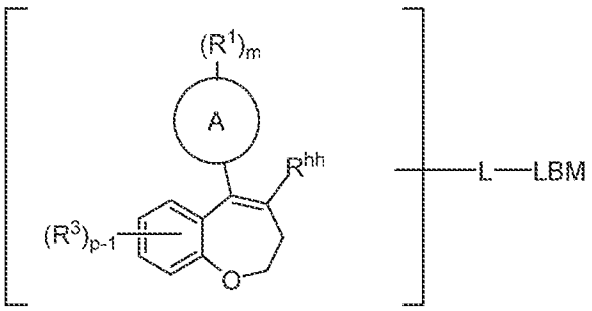
IV-ff



IV-gg

or a pharmaceutically acceptable salt thereof.

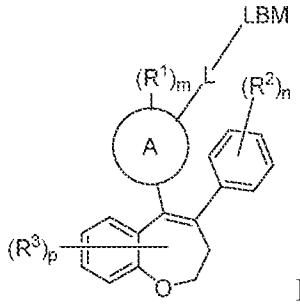
Embodiment 213. The compound of embodiment 1, wherein the compound is a compound of formula **IV-hh**:



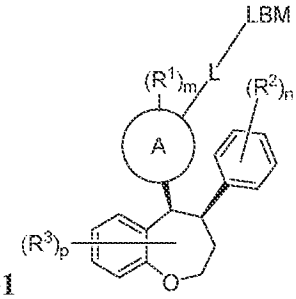
IV-hh

or a pharmaceutically acceptable salt thereof, wherein wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

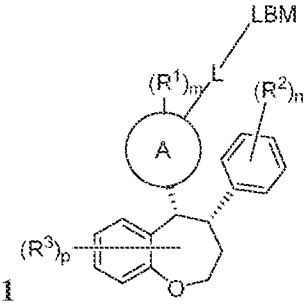
Embodiment 214. The compound of embodiment 1, wherein the compound is a compound of one of formulas **IV-m-1**, **IV-n-1**, **IV-o-1**, **IV-p-1**, **IV-q-1**, **IV-r-1**, **IV-s-1**, **IV-t-1**, **IV-u-1**, **IV-v-1**, **IV-w-1**, **IV-x-1**, **IV-y-1**, **IV-z-1**, or **IV-aa-1**:



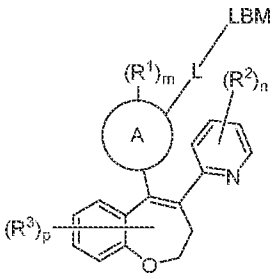
IV-m-1



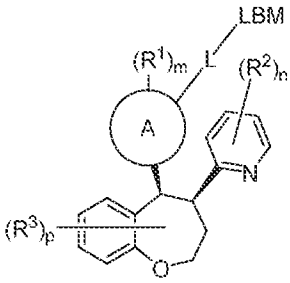
IV-n-1



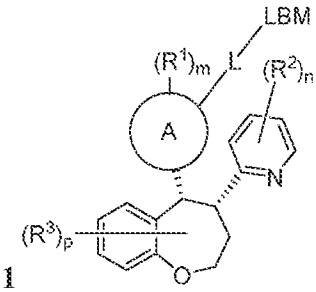
IV-o-1



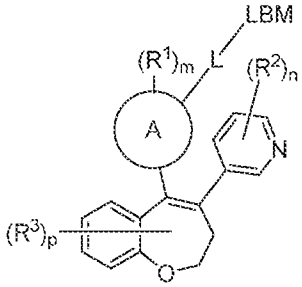
IV-p-1



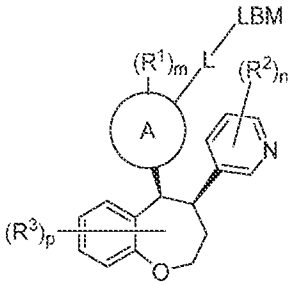
IV-q-1



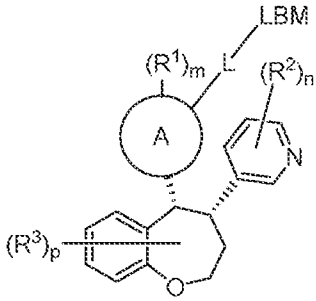
IV-r-1



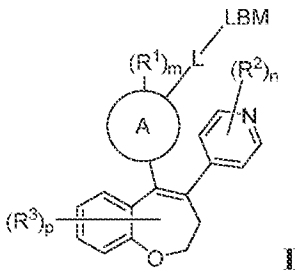
IV-s-1



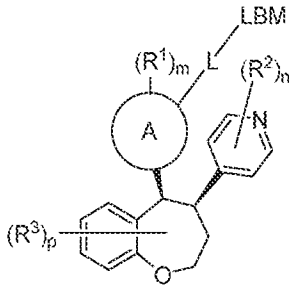
IV-t-1



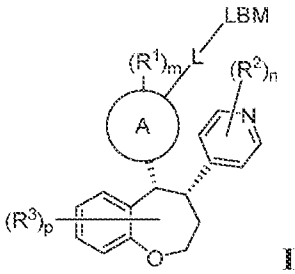
IV-u-1



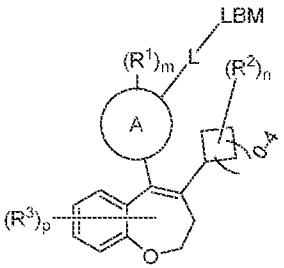
IV-v-1



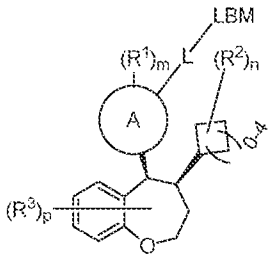
IV-w-1



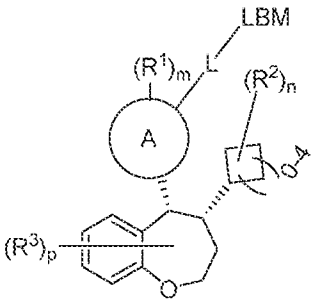
IV-x-1



IV-y-1



IV-z-1



IV-aa-1

or a pharmaceutically acceptable salt thereof.

Embodiment 215. The compound of embodiment 214, wherein the compound is a compound of formula **IV-m-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 216. The compound of embodiment 214, wherein the compound is a compound of formula **IV-n-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 217. The compound of embodiment 214, wherein the compound is a compound of formula **IV-o-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 218. The compound of embodiment 214, wherein the compound is a compound of formula **IV-p-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 219. The compound of embodiment 214, wherein the compound is a compound of formula **IV-q-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 220. The compound of embodiment 214, wherein the compound is a compound of formula **IV-r-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 221. The compound of embodiment 214, wherein the compound is a compound of formula **IV-s-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 222. The compound of embodiment 214, wherein the compound is a compound of formula **IV-t-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 223. The compound of embodiment 214, wherein the compound is a compound of formula **IV-u-1** or a pharmaceutically acceptable salt thereof.

Embodiment 224. The compound of embodiment 214, wherein the compound is a compound of formula **IV-v-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 225. The compound of embodiment 214, wherein the compound is a compound of formula **IV-w-1**, or a pharmaceutically acceptable salt thereof.

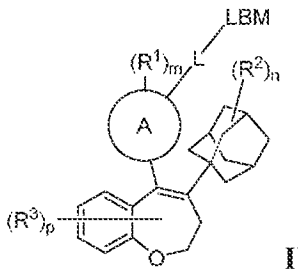
Embodiment 226. The compound of embodiment 214, wherein the compound is a compound of formula **IV-x-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 227. The compound of embodiment 214, wherein the compound is a compound of formula **IV-y-1**, or a pharmaceutically acceptable salt thereof.

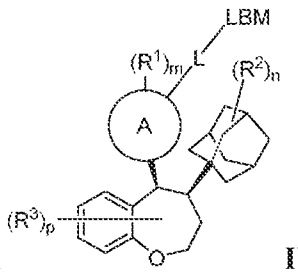
Embodiment 228. The compound of embodiment 214, wherein the compound is a compound of formula **IV-z-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 229. The compound of embodiment 214, wherein the compound is a compound of formula **IV-aa-1**, or a pharmaceutically acceptable salt thereof.

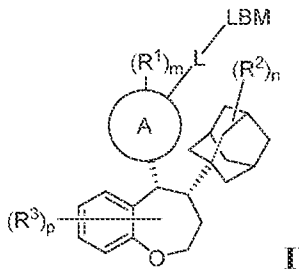
Embodiment 230. The compound of embodiment 1, wherein the compound is a compound of one of formulas **IV-bb-1**, **IV-cc-1**, **IV-dd-1**, **IV-ee-1**, **IV-ff-1** or **IV-gg-1**:



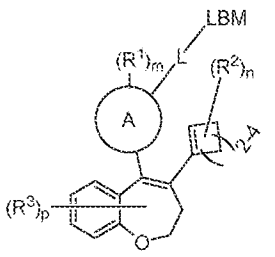
IV-bb-1



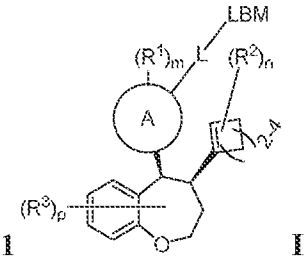
IV-cc-1



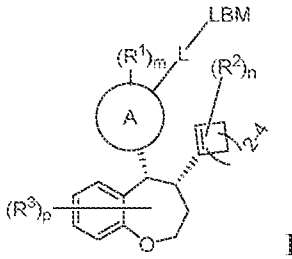
IV-dd-1



IV-ee-1



IV-ff-1



IV-gg-1

or a pharmaceutically acceptable salt thereof.

Embodiment 231. The compound of embodiment 230, wherein the compound is a compound of formula **IV-bb-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 232. The compound of embodiment 230, wherein the compound is a compound of formula **IV-cc-1**, or a pharmaceutically acceptable salt thereof.

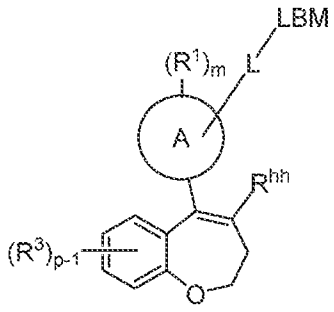
Embodiment 233. The compound of embodiment 230, wherein the compound is a compound of formula **IV-dd-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 234. The compound of embodiment 230, wherein the compound is a compound of formula **IV-ee-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 235. The compound of embodiment 230, wherein the compound is a compound of formula **IV-ff-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 236. The compound of embodiment 230, wherein the compound is a compound of formula **IV-gg-1**, or a pharmaceutically acceptable salt thereof.

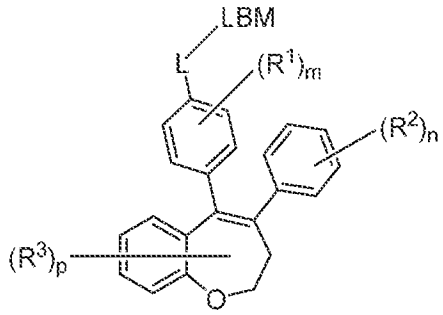
Embodiment 237. The compound of embodiment 1, wherein the compound is a compound of formula **IV-hh-1**:



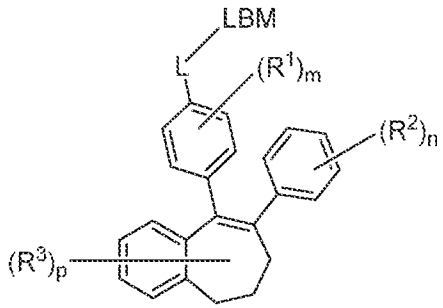
IV-hh-1

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, or 3 instances of –F.

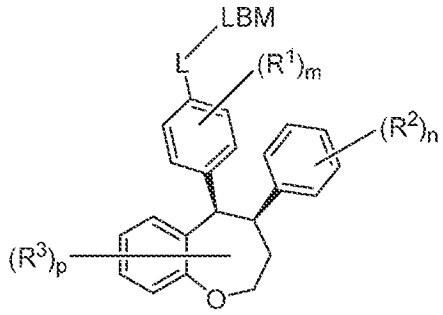
Embodiment 238. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-a**, **V-b**, **V-c**, **V-d**, **V-e**, or **V-f**:



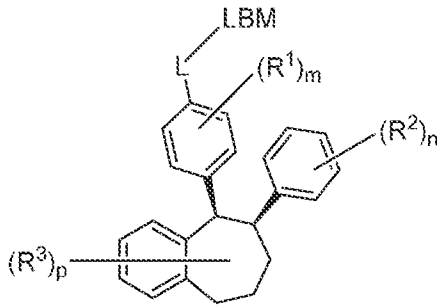
V-a



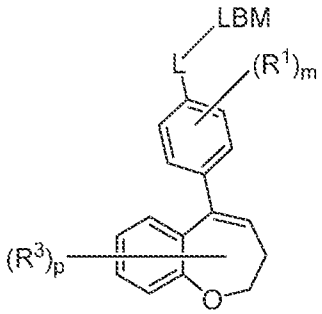
V-b



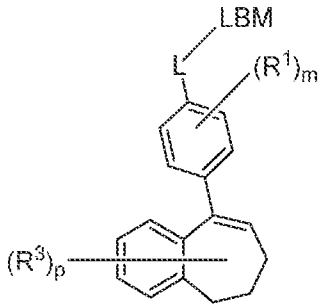
V-c



V-d



V-e



V-f

or a pharmaceutically acceptable salt thereof.

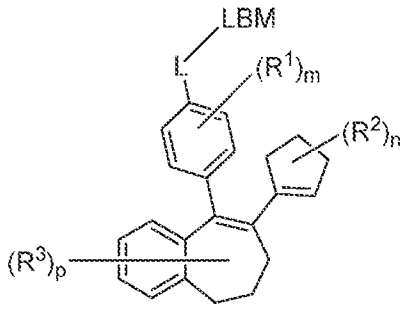
Embodiment 239. The compound of embodiment 238, wherein the compound is a compound of formula **V-a**, or a pharmaceutically acceptable salt thereof.

Embodiment 240. The compound of embodiment 238, wherein the compound is a compound of formula **V-b**, or a pharmaceutically acceptable salt thereof.

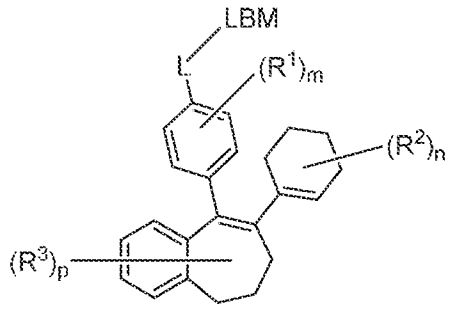
Embodiment 241. The compound of embodiment 238, wherein the compound is a compound of formula **V-c**, or a pharmaceutically acceptable salt thereof.

Embodiment 242. The compound of embodiment 238, wherein the compound is a compound of formula **V-d**, or a pharmaceutically acceptable salt thereof.

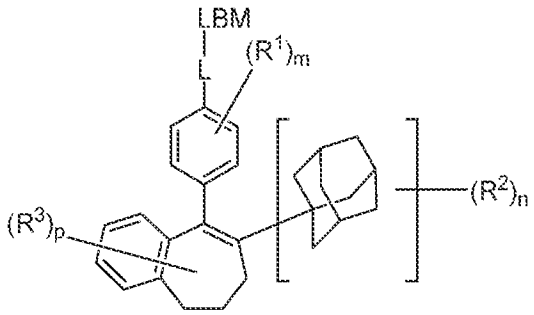
Embodiment 243. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-g**, **V-h**, **V-i**, **V-j**, **V-k**, **V-l**, or **V-m**:



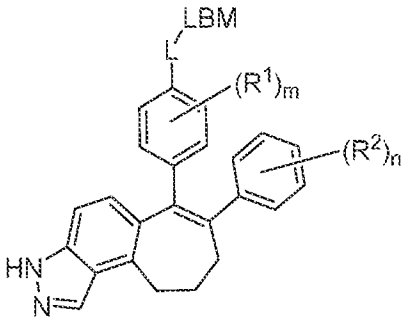
V-g



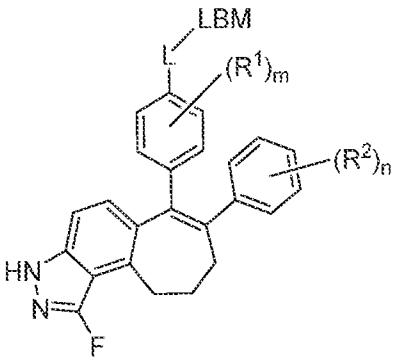
V-h



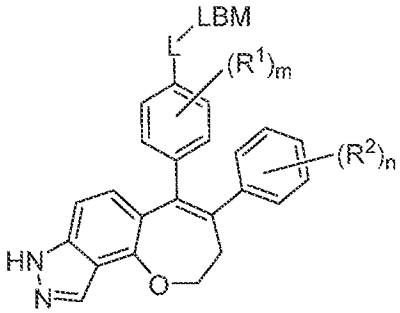
V-i



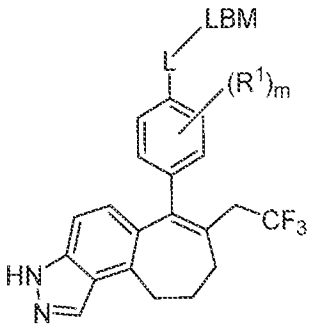
V-j



V-k



V-l



V-m

or a pharmaceutically acceptable salt thereof.

Embodiment 244. The compound of embodiment 243, wherein the compound is a compound of formula **V-g**, or a pharmaceutically acceptable salt thereof.

Embodiment 245. The compound of embodiment 243, wherein the compound is a compound of formula **V-h**, or a pharmaceutically acceptable salt thereof.

Embodiment 246. The compound of embodiment 243, wherein the compound is a compound of formula **V-i**, or a pharmaceutically acceptable salt thereof.

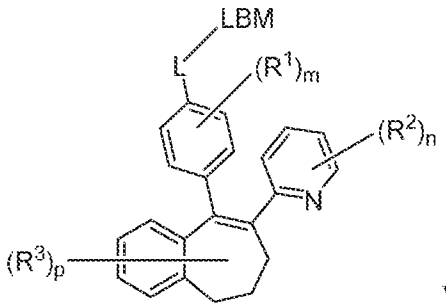
Embodiment 247. The compound of embodiment 243, wherein the compound is a compound of formula **V-j**, or a pharmaceutically acceptable salt thereof.

Embodiment 248. The compound of embodiment 243, wherein the compound is a compound of formula **V-k**, or a pharmaceutically acceptable salt thereof.

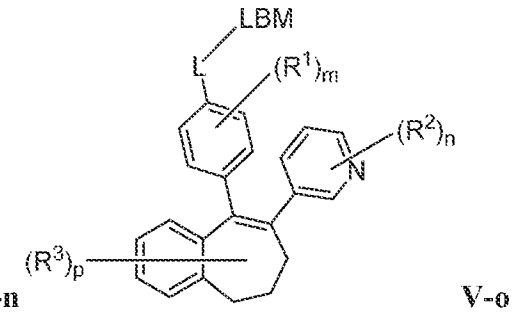
Embodiment 249. The compound of embodiment 243, wherein the compound is a compound of formula **V-l**, or a pharmaceutically acceptable salt thereof.

Embodiment 250. The compound of embodiment 243, wherein the compound is a compound of formula **V-m**, or a pharmaceutically acceptable salt thereof.

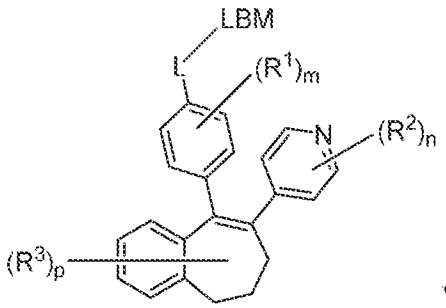
Embodiment 251. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-n**, **V-o**, **V-p**, **V-q** or **V-r**:



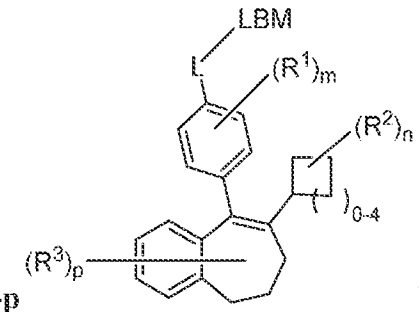
V-n



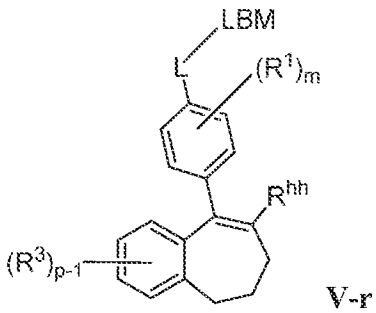
V-o



V-p



V-q



V-r

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, or 3 instances of –F.

Embodiment 252. The compound of embodiment 251, wherein the compound is a compound of formula **V-n**, or a pharmaceutically acceptable salt thereof.

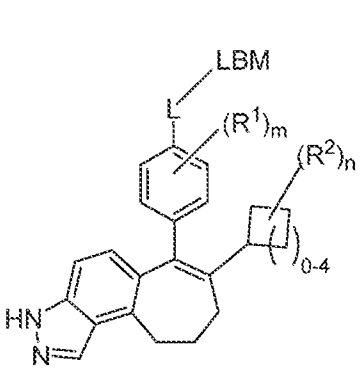
Embodiment 253. The compound of embodiment 251, wherein the compound is a compound of formula **V-o**, or a pharmaceutically acceptable salt thereof.

Embodiment 254. The compound of embodiment 251, wherein the compound is a compound of formula **V-p**, or a pharmaceutically acceptable salt thereof.

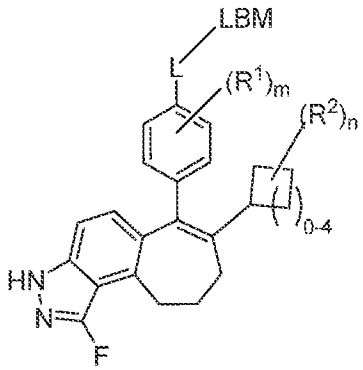
Embodiment 255. The compound of embodiment 251, wherein the compound is a compound of formula **V-q**, or a pharmaceutically acceptable salt thereof.

Embodiment 256. The compound of embodiment 251, wherein the compound is a compound of formula **V-r**, or a pharmaceutically acceptable salt thereof.

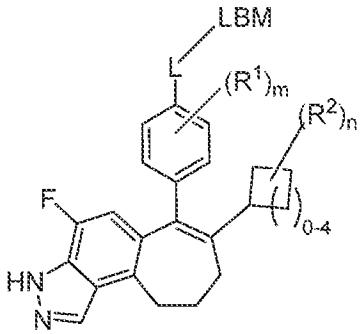
Embodiment 257. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-s**, **V-t**, **V-u**, **V-v**, **V-w**, **V-x** or **V-y**:



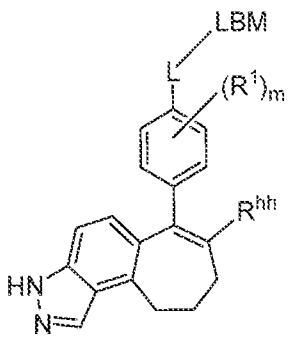
V-s

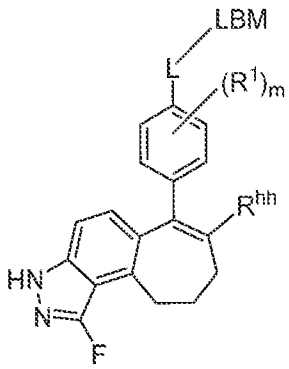


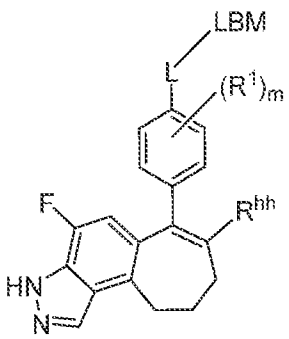
V-t



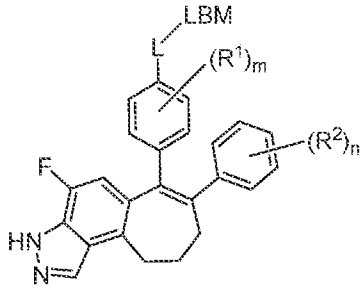
V-u







V-v V-w V-x



V-y

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, or 3 instances of –F.

Embodiment 258. The compound of embodiment 257, wherein the compound is a compound of formula **V-s**, or a pharmaceutically acceptable salt thereof.

Embodiment 259. The compound of embodiment 257, wherein the compound is a compound of formula **V-t**, or a pharmaceutically acceptable salt thereof.

Embodiment 260. The compound of embodiment 257, wherein the compound is a compound of formula **V-u**, or a pharmaceutically acceptable salt thereof.

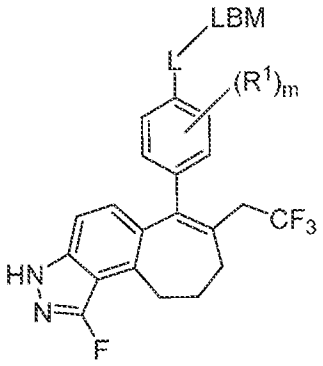
Embodiment 261. The compound of embodiment 257, wherein the compound is a compound of formula **V-v**, or a pharmaceutically acceptable salt thereof.

Embodiment 262. The compound of embodiment 257, wherein the compound is a compound of formula **V-w**, or a pharmaceutically acceptable salt thereof.

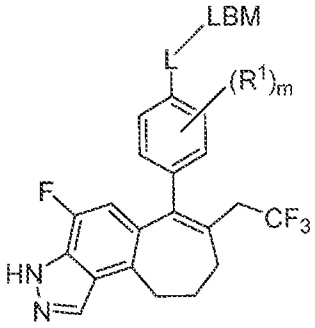
Embodiment 263. The compound of embodiment 257, wherein the compound is a compound of formula **V-x**, or a pharmaceutically acceptable salt thereof.

Embodiment 264. The compound of embodiment 257, wherein the compound is a compound of formula **V-y**, or a pharmaceutically acceptable salt thereof.

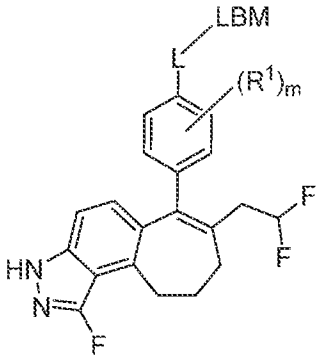
Embodiment 265. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-z**, **V-aa**, **V-bb**, **V-cc**, **V-dd**, **V-ee**, **V-ff**, **V-gg** or **V-hh**:



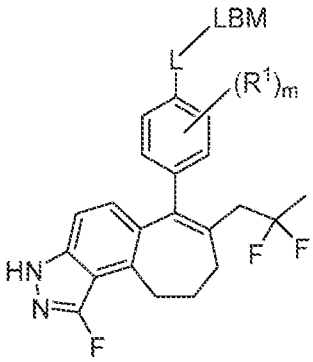
V-z



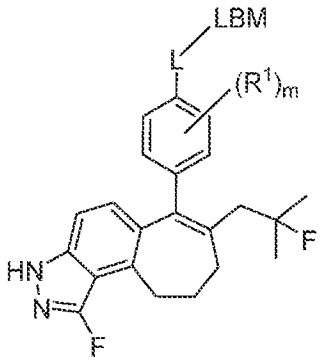
V-aa



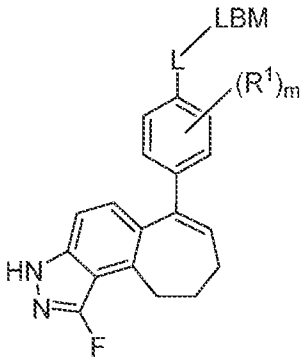
V-bb



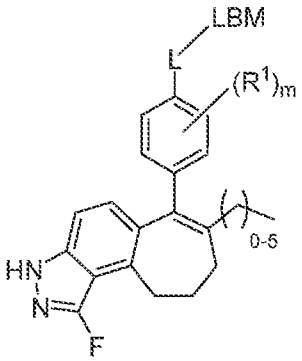
V-cc



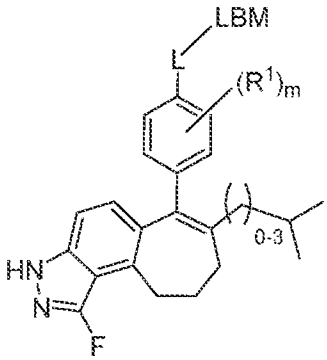
V-dd



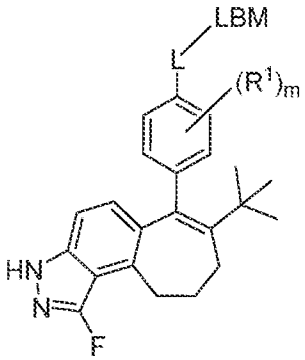
V-ee



V-ff



V-gg



V-hh

or a pharmaceutically acceptable salt thereof.

Embodiment 266. The compound of embodiment 265, wherein the compound is a compound of formula **V-z**, or a pharmaceutically acceptable salt thereof.

Embodiment 267. The compound of embodiment 265, wherein the compound is a compound of formula **V-aa**, or a pharmaceutically acceptable salt thereof.

Embodiment 268. The compound of embodiment 265, wherein the compound is a compound of formula **V-bb** or a pharmaceutically acceptable salt thereof.

Embodiment 269. The compound of embodiment 265, wherein the compound is a compound of formula **V-cc**, or a pharmaceutically acceptable salt thereof.

Embodiment 270. The compound of embodiment 265, wherein the compound is a compound of formula **V-dd**, or a pharmaceutically acceptable salt thereof.

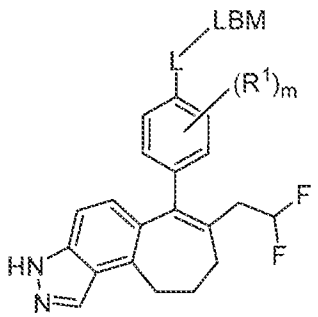
Embodiment 271. The compound of embodiment 265, wherein the compound is a compound of formula **V-ee**, or a pharmaceutically acceptable salt thereof.

Embodiment 272. The compound of embodiment 265, wherein the compound is a compound of formula **V-ff** or a pharmaceutically acceptable salt thereof.

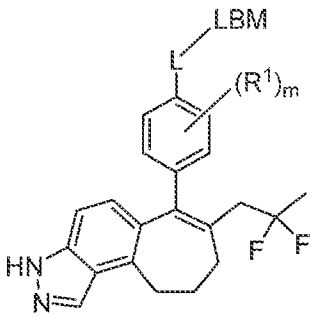
Embodiment 273. The compound of embodiment 265, wherein the compound is a compound of formula **V-gg**, or a pharmaceutically acceptable salt thereof.

Embodiment 274. The compound of embodiment 265, wherein the compound is a compound of formula **V-hh**, or a pharmaceutically acceptable salt thereof.

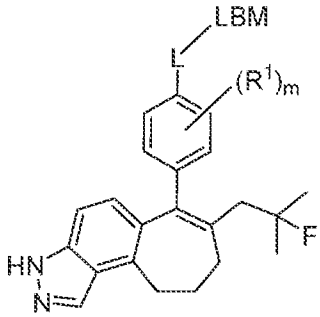
Embodiment 275. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-ii**, **V-jj**, **V-kk**, **V-ll**, **V-mm**, **V-nn**, **V-oo**, **V-pp**, **V-qq**, **V-rr**, **V-ss**, **V-tt**, **V-uu**, or **V-vv**:



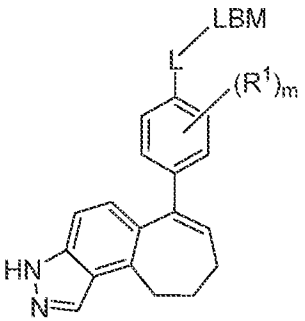
V-ii



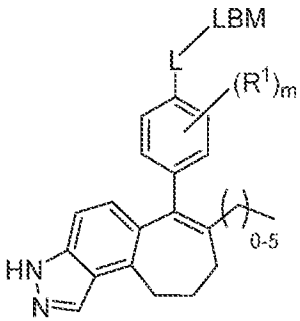
V-jj



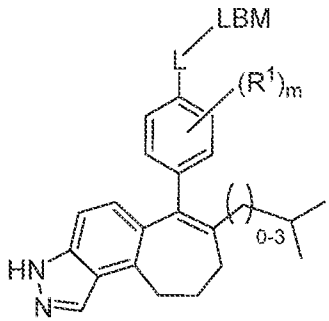
V-kk



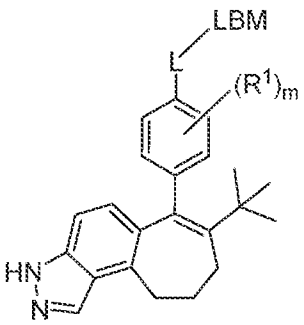
V-ll



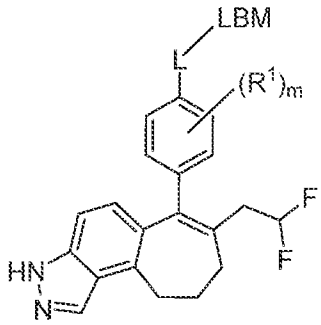
V-mm



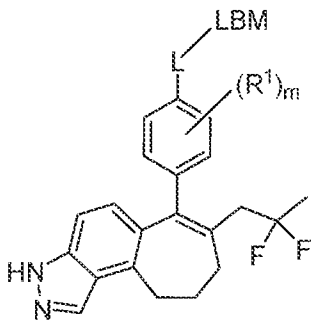
V-nn



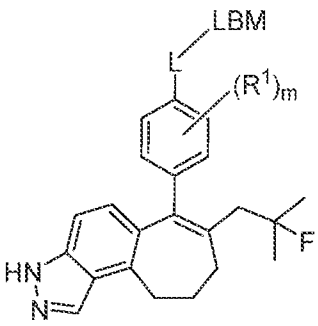
V-oo



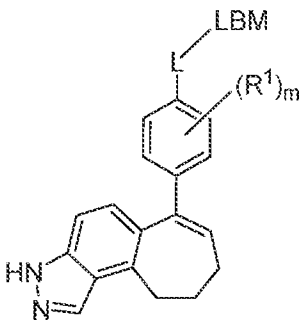
V-pp



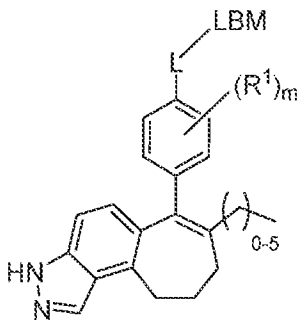
V-qq



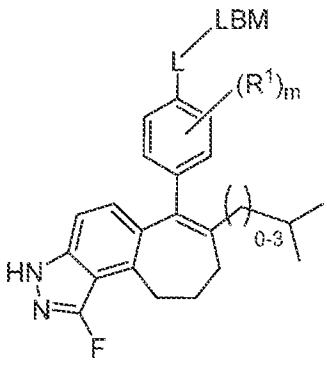
V-rr



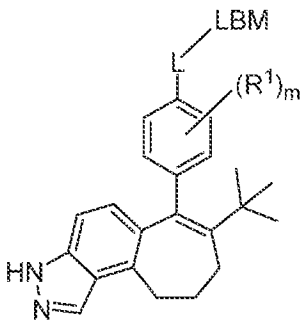
V-ss



V-tt



V-uu



V-vv

or a pharmaceutically acceptable salt thereof.

Embodiment 276. The compound of embodiment 275, wherein the compound is a compound of formula **V-ii**, or a pharmaceutically acceptable salt thereof.

Embodiment 277. The compound of embodiment 275, wherein the compound is a compound of formula **V-jj**, or a pharmaceutically acceptable salt thereof.

Embodiment 278. The compound of embodiment 275, wherein the compound is a compound of formula **V-kk** or a pharmaceutically acceptable salt thereof.

Embodiment 279. The compound of embodiment 275, wherein the compound is a compound of formula **V-ll**, or a pharmaceutically acceptable salt thereof.

Embodiment 280. The compound of embodiment 275, wherein the compound is a compound of formula **V-mm**, or a pharmaceutically acceptable salt thereof.

Embodiment 281. The compound of embodiment 275, wherein the compound is a compound of formula **V-nn**, or a pharmaceutically acceptable salt thereof.

Embodiment 282. The compound of embodiment 275, wherein the compound is a compound of formula **V-oo** or a pharmaceutically acceptable salt thereof.

Embodiment 283. The compound of embodiment 275, wherein the compound is a compound of formula **V-pp**, or a pharmaceutically acceptable salt thereof.

Embodiment 284. The compound of embodiment 275, wherein the compound is a compound of formula **V-qq**, or a pharmaceutically acceptable salt thereof.

Embodiment 285. The compound of embodiment 275, wherein the compound is a compound of formula **V-rr**, or a pharmaceutically acceptable salt thereof.

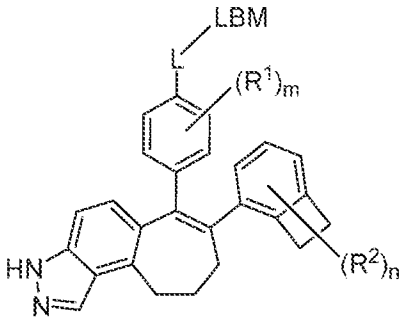
Embodiment 286. The compound of embodiment 275, wherein the compound is a compound of formula **V-ss**, or a pharmaceutically acceptable salt thereof.

Embodiment 287. The compound of embodiment 275, wherein the compound is a compound of formula **V-tt** or a pharmaceutically acceptable salt thereof.

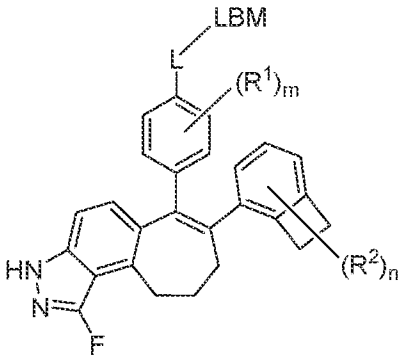
Embodiment 288. The compound of embodiment 275, wherein the compound is a compound of formula **V-uu**, or a pharmaceutically acceptable salt thereof.

Embodiment 289. The compound of embodiment 275, wherein the compound is a compound of formula **V-vv**, or a pharmaceutically acceptable salt thereof.

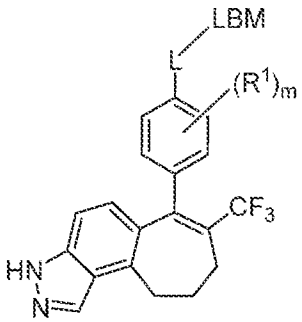
Embodiment 290. The compound of embodiment 1, wherein the compound is a compound of one of formulas **V-ww**, **V-xx**, **V-yy**, **V-zz**, **V-aa-1**, **V-bb-1**, **V-cc-1**, **V-dd-1**, **V-ee-1**, **V-ff-1**, **V-gg-1**, **V-hh-1**, **V-ii-1**, **V-jj-1**, **V-kk-1**, or **V-ll-1**:



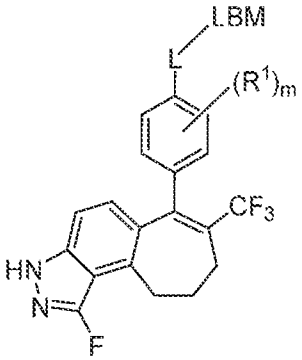
V-ww



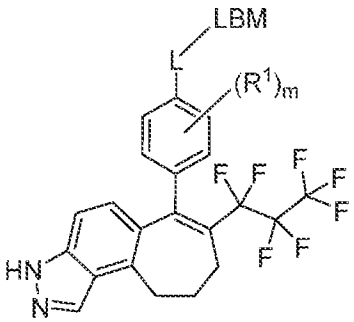
V-xx



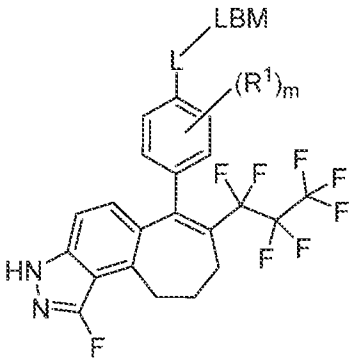
V-yy



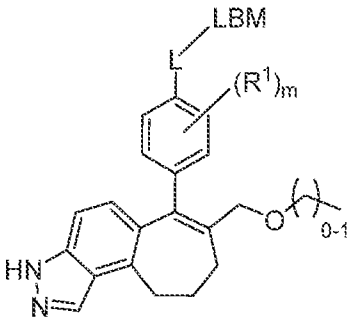
V-zz



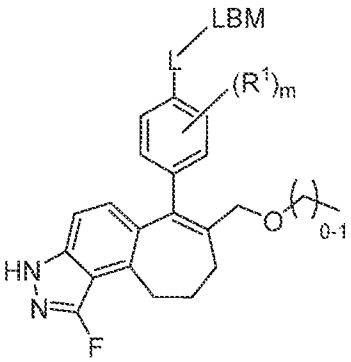
V-aa-1



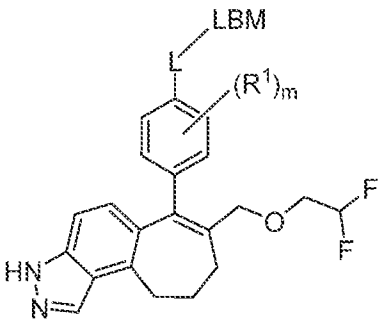
V-bb-1



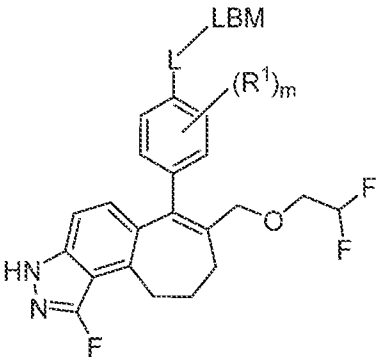
V-cc-1



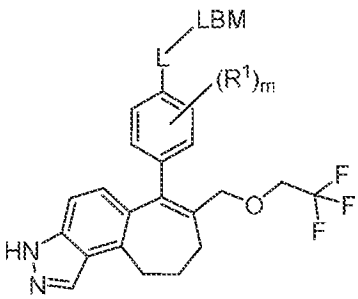
V-dd-1



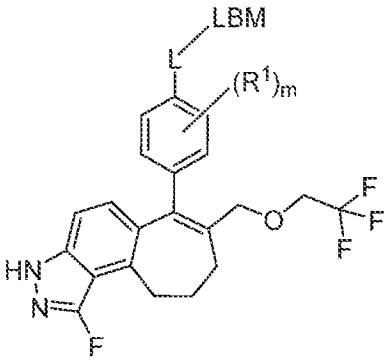
V-ee-1



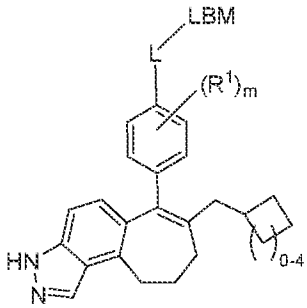
V-ff-1



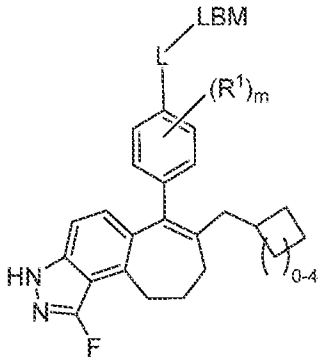
V-gg-1



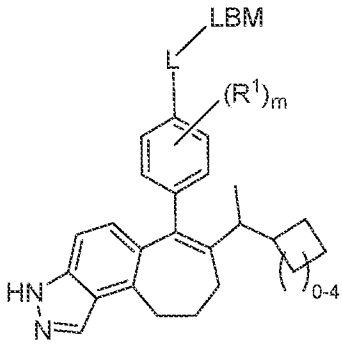
V-hh-1



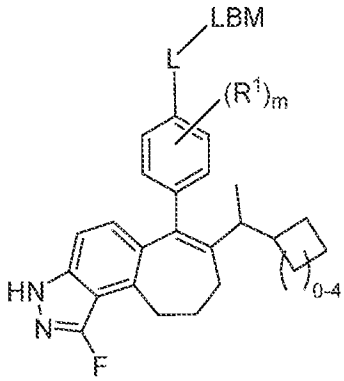
V-ii-1



V-jj-1



V-kk-1



V-ll-1

Embodiment 291. or a pharmaceutically acceptable salt thereof.

Embodiment 292. The compound of embodiment 290, wherein the compound is a compound of formula **V-ww**, or a pharmaceutically acceptable salt thereof.

Embodiment 293. The compound of embodiment 290, wherein the compound is a compound of formula **V-xx**, or a pharmaceutically acceptable salt thereof.

Embodiment 294. The compound of embodiment 290, wherein the compound is a compound of formula **V-zz** or a pharmaceutically acceptable salt thereof.

Embodiment 295. The compound of embodiment 290, wherein the compound is a compound of formula **V-aa-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 296. The compound of embodiment 290, wherein the compound is a compound of formula **V-bb-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 297. The compound of embodiment 290, wherein the compound is a compound of formula **V-cc-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 298. The compound of embodiment 290, wherein the compound is a compound of formula **V-dd-1** or a pharmaceutically acceptable salt thereof.

Embodiment 299. The compound of embodiment 290, wherein the compound is a compound of formula **V-ee-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 300. The compound of embodiment 290, wherein the compound is a compound of formula **V-ff-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 301. The compound of embodiment 290, wherein the compound is a compound of formula **V-gg-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 302. The compound of embodiment 290, wherein the compound is a compound of formula **V-hh-1**, or a pharmaceutically acceptable salt thereof.

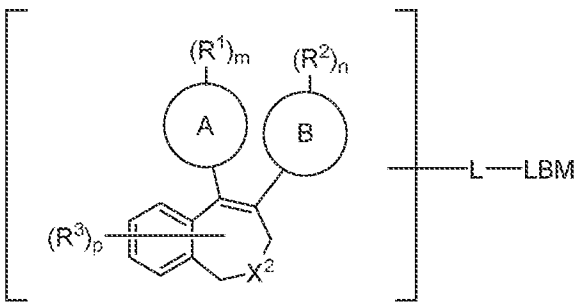
Embodiment 303. The compound of embodiment 290, wherein the compound is a compound of formula **V-ii-1** or a pharmaceutically acceptable salt thereof.

Embodiment 304. The compound of embodiment 290, wherein the compound is a compound of formula **V-jj-1**, or a pharmaceutically acceptable salt thereof.

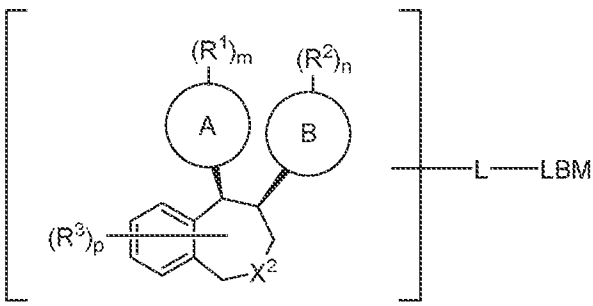
Embodiment 305. The compound of embodiment 290, wherein the compound is a compound of formula **V-kk-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 306. The compound of embodiment 290, wherein the compound is a compound of formula **V-ll-1**, or a pharmaceutically acceptable salt thereof.

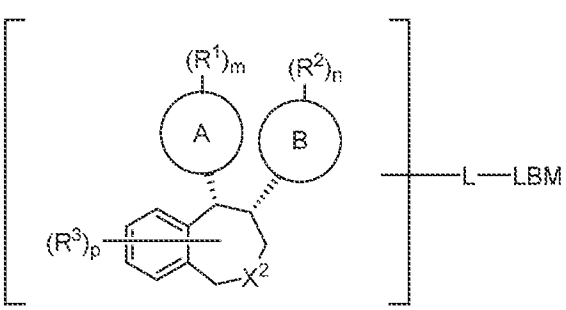
Embodiment 307. The compound of embodiment 1, wherein the compound is a compound of one of formulas **VI-a**, **VI -b**, **VI -c**, **VI -d**, **VI -e**, or **VI -f**:



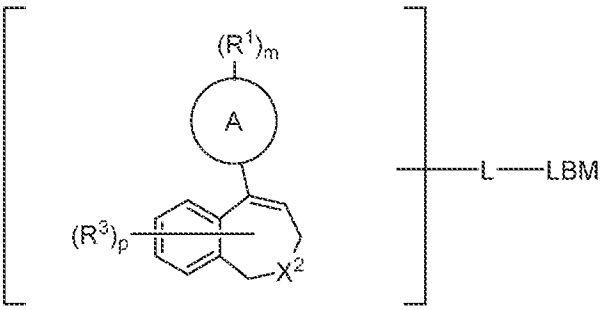
VI-a



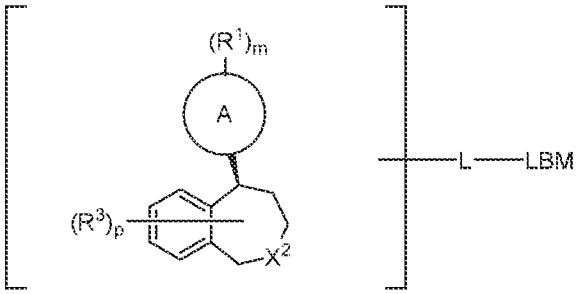
VI-b



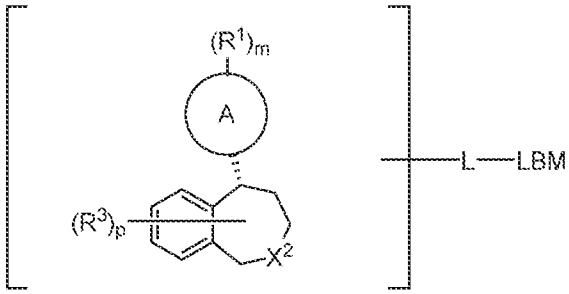
VI-c



VI-d



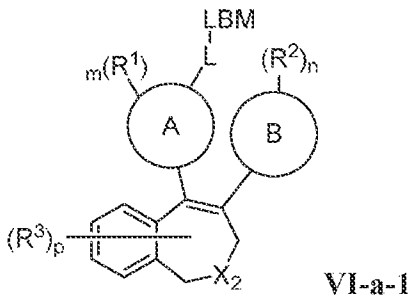
VI-e



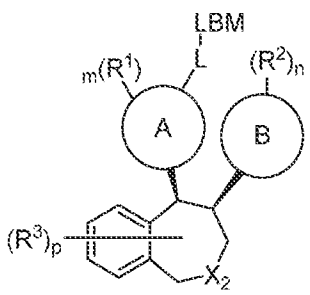
VI-f

or a pharmaceutically acceptable salt thereof.

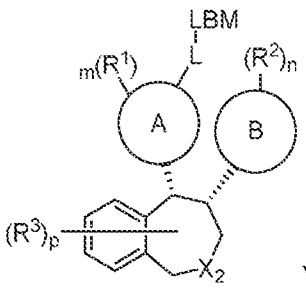
Embodiment 308. The compound of embodiment 1, wherein the compound is a compound of one of formulas **VI-a-1**, **VI-b-1**, **VI-c-1**, **VI-d-1**, **VI-e-1**, or **VI-f-1**:



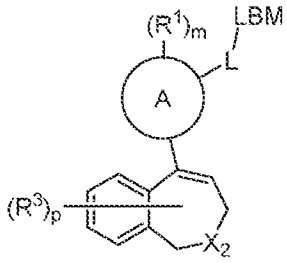
VI-a-1



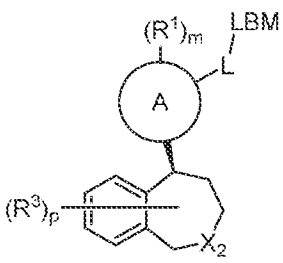
VI-b-1



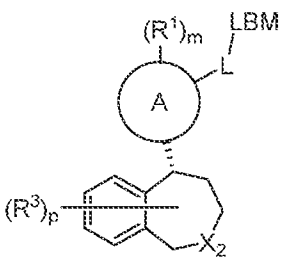
VI-c-1



VI-d-1



VI-e-1



VI-f-1

or a pharmaceutically acceptable salt thereof.

Embodiment 309. The compound of embodiment 307, wherein the compound is a compound of formula **VI-a-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 310. The compound of embodiment 307, wherein the compound is a compound of formula **VI-b-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 311. The compound of embodiment 307, wherein the compound is a compound of formula **VI-c-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 312. The compound of embodiment 307, wherein the compound is a compound of formula **VI-d-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 313. The compound of embodiment 307, wherein the compound is a compound of formula **VI-e-1**, or a pharmaceutically acceptable salt thereof.

Embodiment 314. The compound of embodiment 307, wherein the compound is a compound of formula **VI-f-1**, or a pharmaceutically acceptable salt thereof.

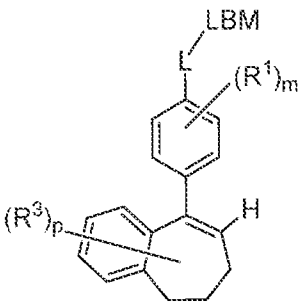
Embodiment 315. The compound of any one of embodiments 1-313, wherein X^2 is selected from –$CH(R^{A1})$–, –$C(R^{A1})_2$–, –O–, –S–, –$S(O)_2$–, and –$N(R^{A2})$–.

Embodiment 316. The compound of any one of embodiments 1-313, wherein X^2 is selected from –$CH(R^{A1})$–, –$C(R^{A1})_2$– and –O–.

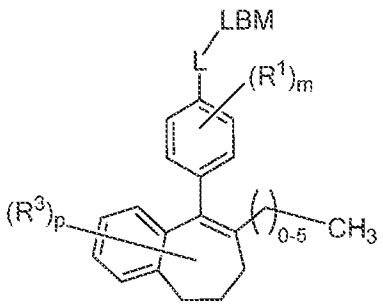
Embodiment 317. The compound of any one of embodiments 1-313, wherein X^2 is –$CH(R^{A1})$– or –$C(R^{A1})_2$–.

Embodiment 318. The compound of any one of embodiments 1-313, wherein X^2 is –O–.

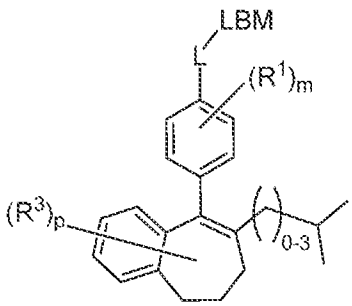
Embodiment 319. The compound of embodiment 1, wherein the compound is a compound of one of formulas **VII-a**, **VII-b**, **VII-c**, **VII-d**, **VII-e**, **VII-f**, **VII-g**, or **VII-h**:



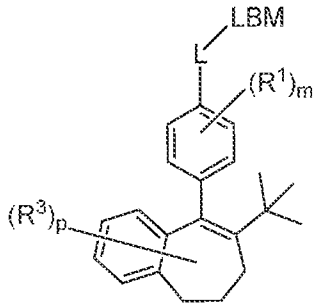
VII-a



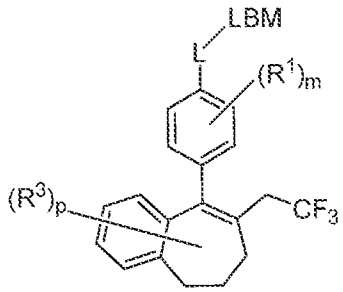
VII-b



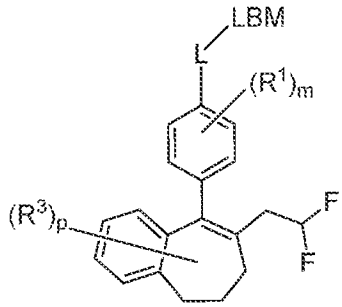
VII-c



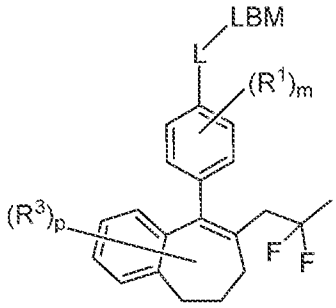
VII-d



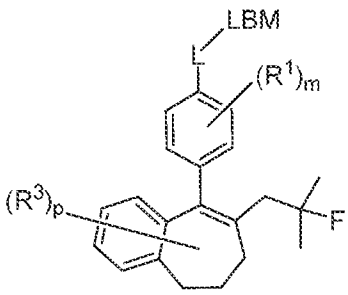
VII-e



VII-f



VII-g



VII-h

or a pharmaceutically acceptable salt thereof.

Embodiment 320. The compound of embodiment 318, wherein the compound is a compound of formula **VII-a**, or a pharmaceutically acceptable salt thereof.

Embodiment 321. The compound of embodiment 318, wherein the compound is a compound of formula **VII-b**, or a pharmaceutically acceptable salt thereof.

Embodiment 322. The compound of embodiment 318, wherein the compound is a compound of formula **VII-c** or a pharmaceutically acceptable salt thereof.

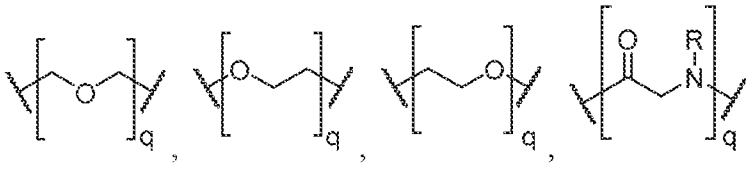
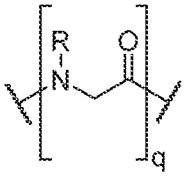
Embodiment 323. The compound of embodiment 318, wherein the compound is a compound of formula **VII-d**, or a pharmaceutically acceptable salt thereof.

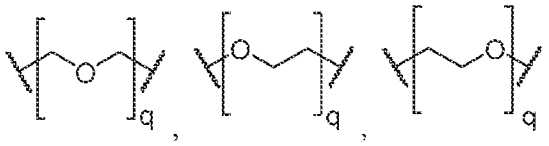
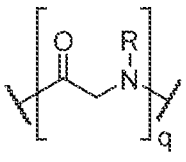
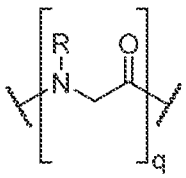
Embodiment 324. The compound of embodiment 318, wherein the compound is a compound of formula **VII-e**, or a pharmaceutically acceptable salt thereof.

Embodiment 325. The compound of embodiment 318, wherein the compound is a compound of formula **VII-f** or a pharmaceutically acceptable salt thereof.

Embodiment 326. The compound of embodiment 318, wherein the compound is a compound of formula **VII-g**, or a pharmaceutically acceptable salt thereof.

Embodiment 327. The compound of embodiment 318, wherein the compound is a compound of formula **VII-h**, or a pharmaceutically acceptable salt thereof.

Embodiment 328. The compound of any one of embodiments 1-326, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, –C(R)$_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –S(O)$_2$–, –NRS(O)$_2$–, –S(O)$_2$NR–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  , or  .

Embodiment 329. The compound of any one of embodiments 1-326, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 0, 1, 2 or 3 methylene units of L are independently replaced by –Cy–, –CH(R)–, –C(R)$_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –S(O)$_2$–, –NRS(O)$_2$–, –S(O)$_2$NR–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,  , or  .

Embodiment 330. The compound of any one of embodiments 1-326, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 1, 2 or 3 methylene units of L are independently replaced by –Cy–, –CH(R)–, –C(R)$_2$–, –O– or–NR– .

Embodiment 331. The compound of any one of embodiments 1-326, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 1, 2 or 3 methylene units of L are independently replaced by –Cy– or–NR– .

Embodiment 332. The compound of any one of embodiments 1-330, wherein each –Cy– is independently an optionally substituted bivalent ring selected from a 4-7 membered saturated or partially unsaturated monocyclic carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated monocyclic heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered monocyclic saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1185-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

Embodiment 333. The compound of any one of embodiments 1-330, wherein each –Cy– is independently an optionally substituted bivalent ring selected from a 4-7 membered saturated or partially unsaturated monocyclic carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated monocyclic heterocyclylenyl containing 1-2 nitrogen atoms, a 5-11 membered monocyclic saturated or partially unsaturated spiro heterocyclylenyl containing 1-2 nitrogen atoms, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl containing 1-2 nitrogen atoms, and a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl containing 1-2 nitrogen atoms.

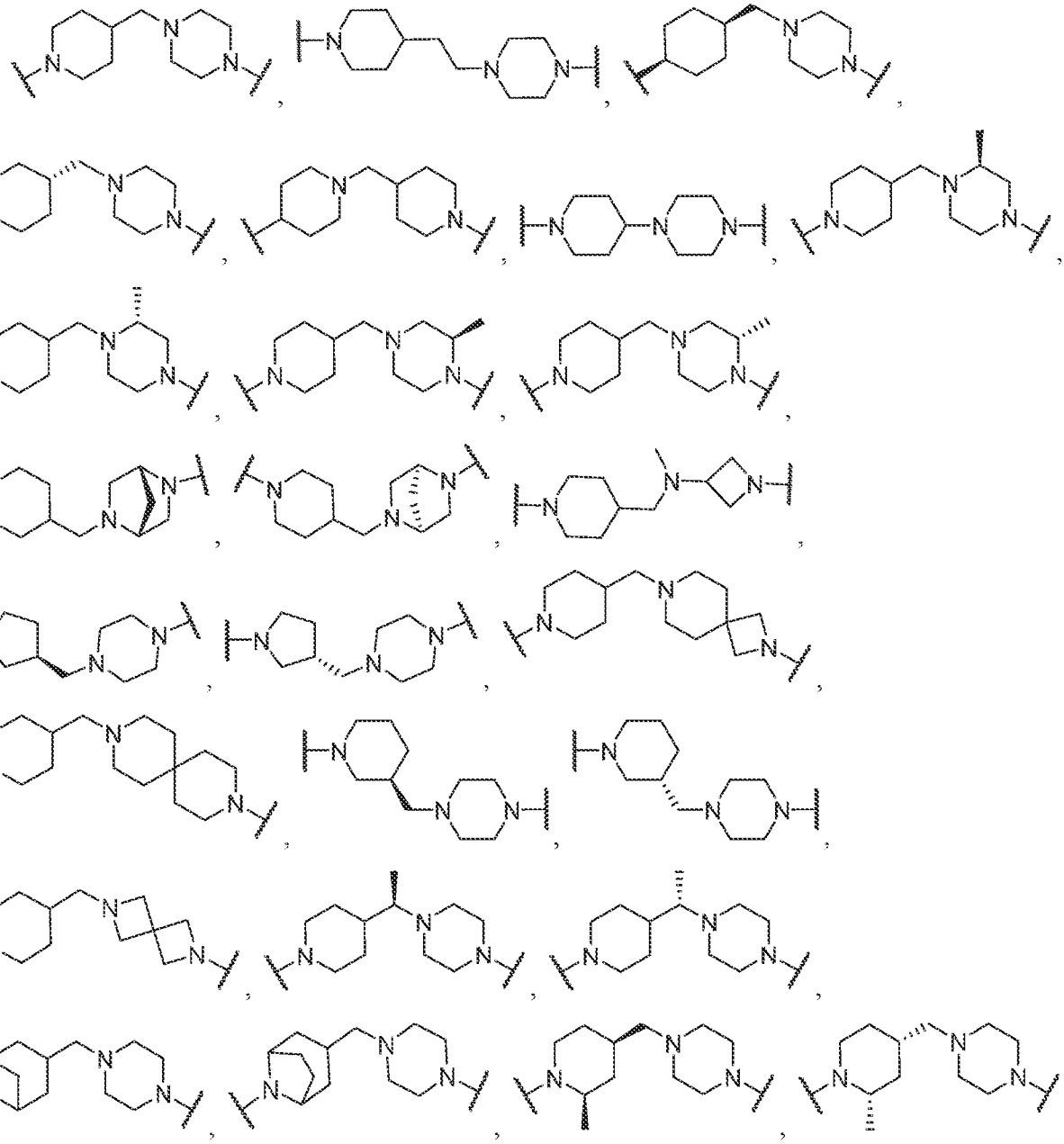
Embodiment 334. The compound of any one of embodiments 1-330, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from –C_1–C_4 alkyl, –C_1–C_4 haloalkyl, –C_3–C_7 cycloalkyl, –O–C_1–C_4 alkyl, halo, cyano, –OH, –NH_2, –N(H)(C_1–C_4 alkyl) and –N(C_1–C_4 alkyl)$_2$.

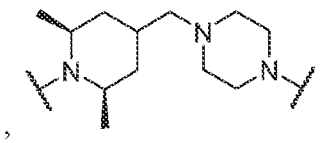
Embodiment 335. The compound of any one of embodiments 1-330, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from –Me, –Et, –Pr, –^{i}Pr, cyclopropyl, –CF_3, –OMe, –F, –Cl, –CN, –NH_2, –NHMe and –NMe_2.

Embodiment 336. The compound of any one of embodiments 1-330, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from Me, –OMe and –F.

Embodiment 337. The compound of any one of embodiments 1-330, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 instances of Me.

Embodiment 338. The compound of any one of embodiments 1-330, wherein the bivalent ring of each –Cy– is unsubstituted.

Embodiment 339. The compound of any one of embodiments 1-337, wherein L is selected from 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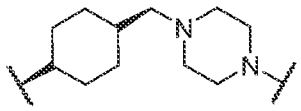
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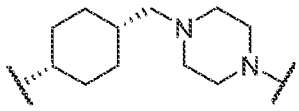
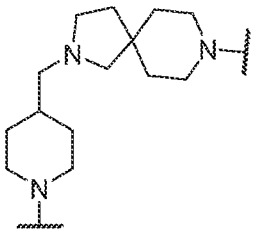
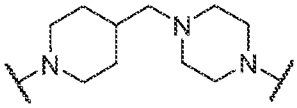
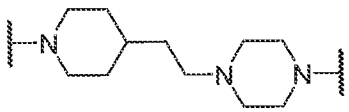
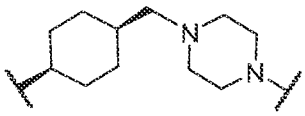
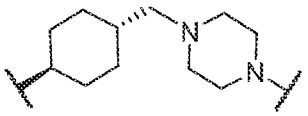
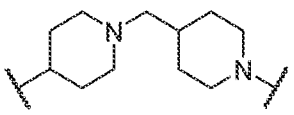

, and


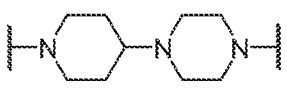
Embodiment 340. The compound of any one of embodiments 1-337, wherein L is


Embodiment 341. The compound of any one of embodiments 1-337, wherein L is


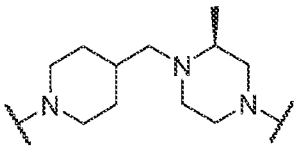
Embodiment 342. The compound of any one of embodiments 1-337, wherein L is


Embodiment 343. The compound of any one of embodiments 1-337, wherein L is


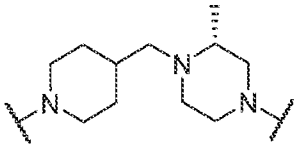
Embodiment 344. The compound of any one of embodiments 1-337, wherein L is


Embodiment 345. The compound of any one of embodiments 1-337, wherein L is


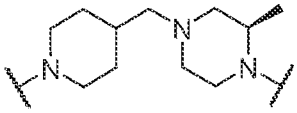
Embodiment 346. The compound of any one of embodiments 1-337, wherein L is



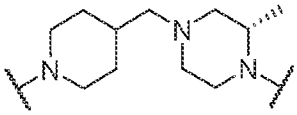
Embodiment 347. The compound of any one of embodiments 1-337, wherein L is



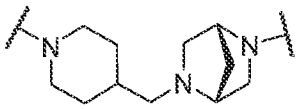
Embodiment 348. The compound of any one of embodiments 1-337, wherein L is



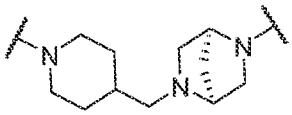
Embodiment 349. The compound of any one of embodiments 1-337, wherein L is



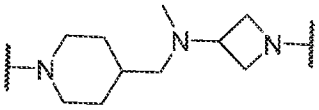
Embodiment 350. The compound of any one of embodiments 1-337, wherein L is



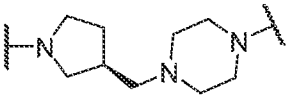
Embodiment 351. The compound of any one of embodiments 1-337, wherein L is



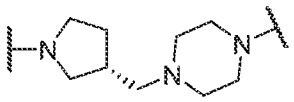
Embodiment 352. The compound of any one of embodiments 1-337, wherein L is



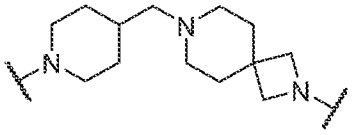
Embodiment 353. The compound of any one of embodiments 1-337, wherein L is



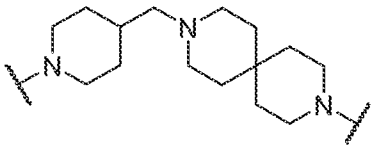
Embodiment 354. The compound of any one of embodiments 1-337, wherein L is



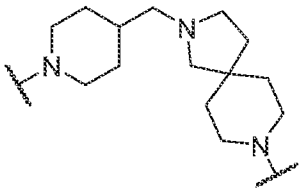
Embodiment 355. The compound of any one of embodiments 1-337, wherein L is



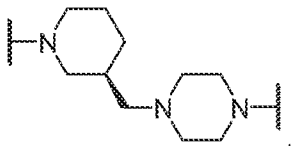
Embodiment 356. The compound of any one of embodiments 1-337, wherein L is



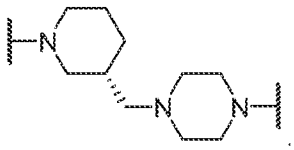
Embodiment 356a. The compoudn of any one of embodiments 1-337, wherein L is



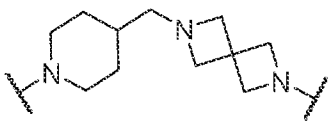
Embodiment 357. The compound of any one of embodiments 1-337, wherein L is



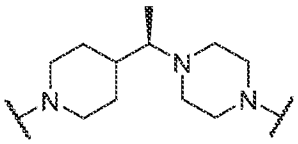
Embodiment 358. The compound of any one of embodiments 1-337, wherein L is



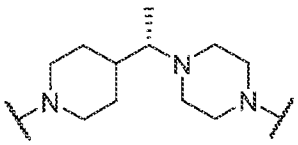
Embodiment 359. The compound of any one of embodiments 1-337, wherein L is



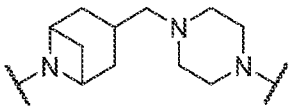
Embodiment 360. The compound of any one of embodiments 1-337, wherein L is



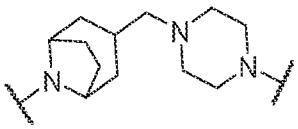
Embodiment 361. The compound of any one of embodiments 1-337, wherein L is



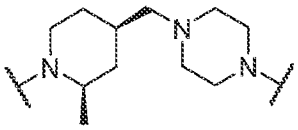
Embodiment 362. The compound of any one of embodiments 1-337, wherein L is



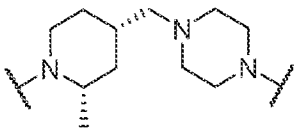
Embodiment 363. The compound of any one of embodiments 1-337, wherein L is



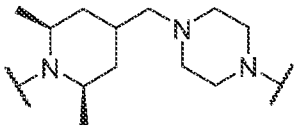
Embodiment 364. The compound of any one of embodiments 1-337, wherein L is



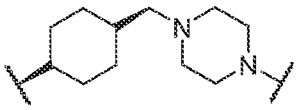
Embodiment 365. The compound of any one of embodiments 1-337, wherein L is



Embodiment 366. The compound of any one of embodiments 1-337, wherein L is

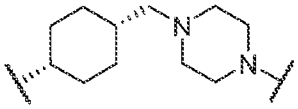


Embodiment 367. The compound of any one of embodiments 1-337, wherein L is



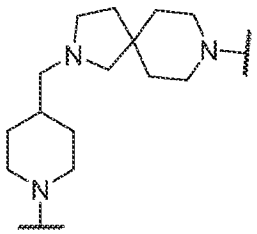
.

Embodiment 368. The compound of any one of embodiments 1-337, wherein L is



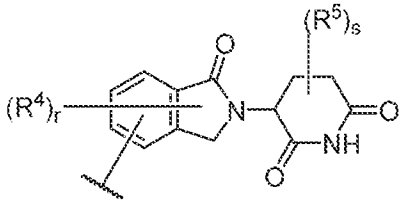
.

Embodiment 369. The compound of any one of embodiments 1-337, wherein L is



.

Embodiment 370. The compound of any one of embodiments 1-368, wherein LBM is selected from



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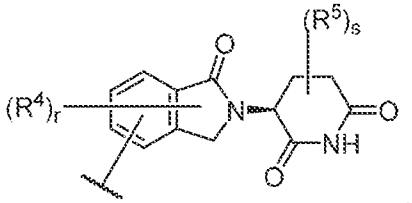

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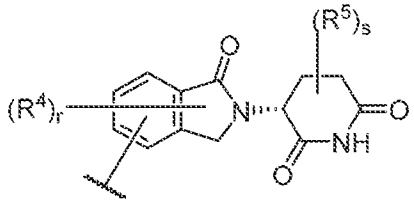

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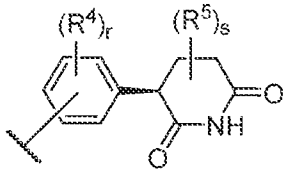
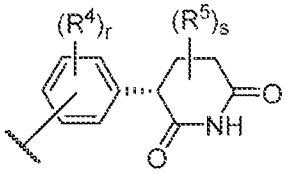
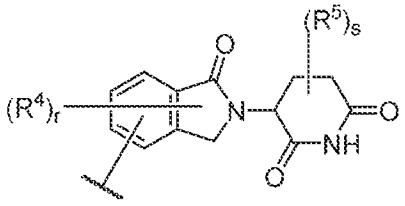
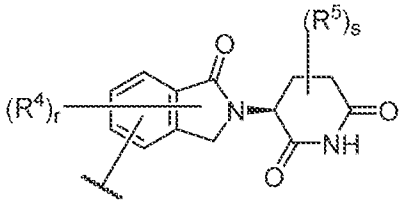
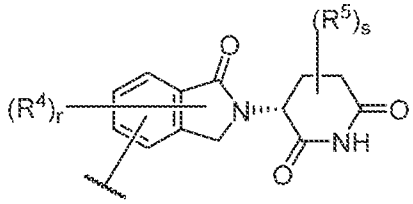


, and



.

Embodiment 371. The compound of any one of embodiments 1-368, wherein LBM is selected from  ,  , and  .

Embodiment 372. The compound of any one of embodiments 1-370, wherein each R^4 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –$C(O)NR_2$, –C(O)N(R)OR, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)S(O)_2NR_2$ and –$N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

Embodiment 373. The compound of any one of embodiments 1-370, wherein each R^4 is independently selected from –Me, –Et, –F, –Cl, –CF_3, –CN, –OH, –OMe, –NH_2, –NHMe and –NMe_2.

Embodiment 374. The compound of any one of embodiments 1-372, wherein each R^5 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –$C(O)NR_2$, –C(O)N(R)OR, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)S(O)_2NR_2$ and –$N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

Embodiment 375. The compound of any one of embodiments 1-372, wherein each R^5 is independently selected from –Me, –Et, –F, –Cl, –CF_3, –CN, –OH, –OMe, –NH_2, –NHMe and –NMe_2.

Embodiment 376. The compound of any one of embodiments 1-372, wherein each R^5 is independently selected from –Me and –F.

Embodiment 377. The compound of any one of embodiments 1-375, wherein r is 0, 1 or 2.

Embodiment 378. The compound of any one of embodiments 1-375, wherein r is 0.

Embodiment 379. The compound of any one of embodiments 1-375, wherein r is 1.

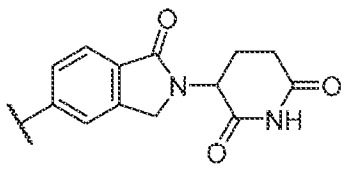
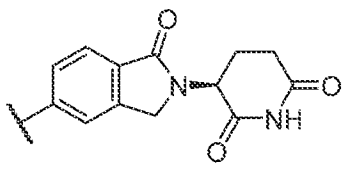
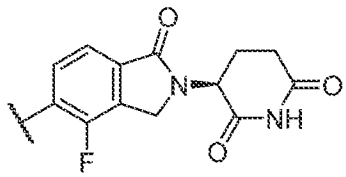
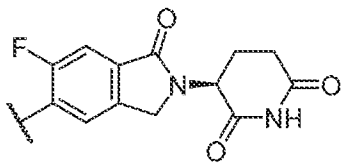
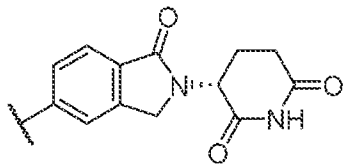
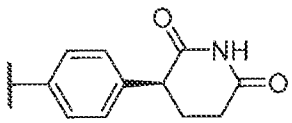
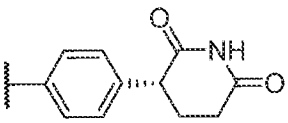
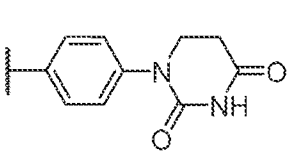
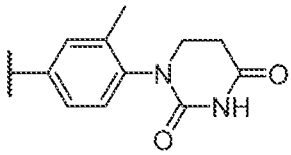
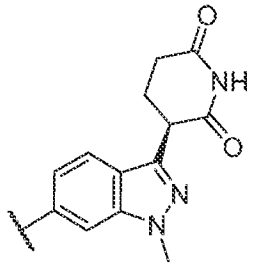
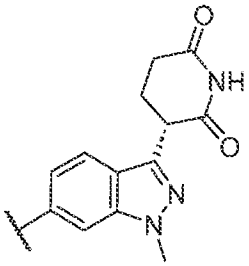
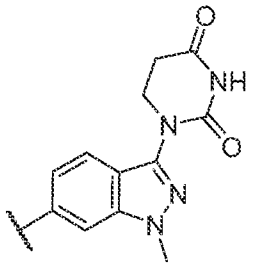
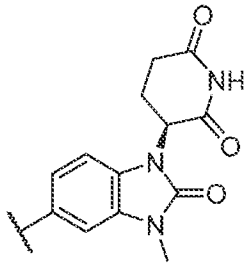
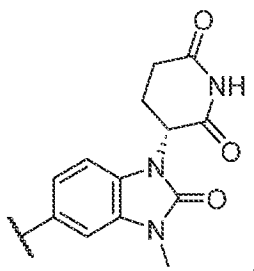
Embodiment 380. The compound of any one of embodiments 1-375, wherein r is 2.

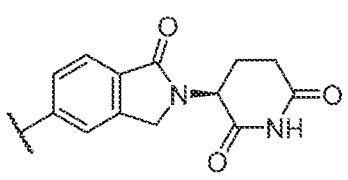
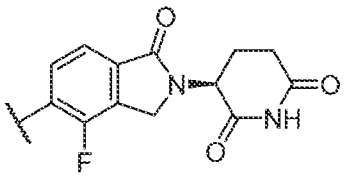
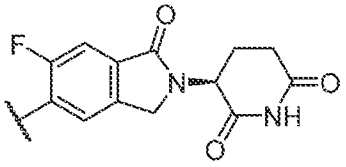
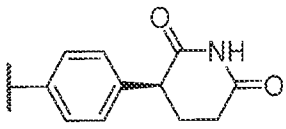
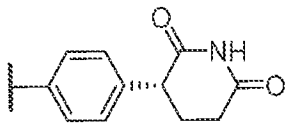
Embodiment 381. The compound of any one of embodiments 1-379, wherein s is 0, 1 or 2.

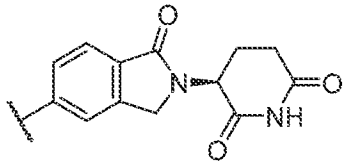
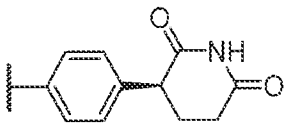
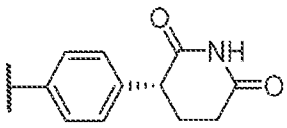
Embodiment 382. The compound of any one of embodiments 1-379, wherein s is 0.

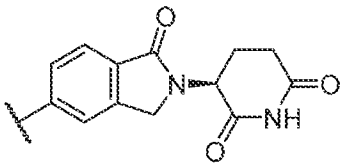
Embodiment 383. The compound of any one of embodiments 1-379, wherein s is 1.

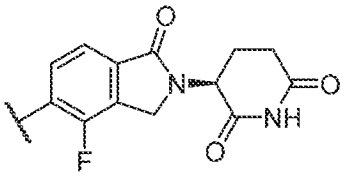
Embodiment 384. The compound of any one of embodiments 1-379, wherein s is 2.

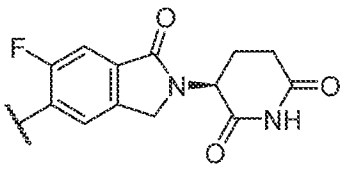
Embodiment 385. The compound of any one of embodiments 1-383, wherein LBM is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

Embodiment 386. The compound of any one of embodiments 1-338, wherein LBM is selected from  ,  ,  ,  and  .

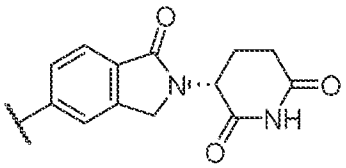
Embodiment 387. The compound of any one of embodiments 1-338, wherein LBM is selected from  ,  and  .

Embodiment 388. The compound of any one of embodiments 1-338, wherein LBM is  .

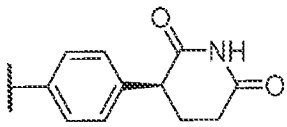
Embodiment 389. The compound of any one of embodiments 1-338, wherein LBM is  .

Embodiment 390. The compound of any one of embodiments 1-338, wherein LBM is  .

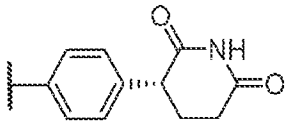
Embodiment 391. The compound of any one of embodiments 1-338, wherein LBM is



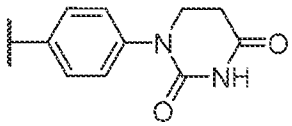
Embodiment 392. The compound of any one of embodiments 1-338, wherein LBM is



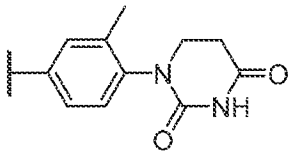
Embodiment 393. The compound of any one of embodiments 1-338, wherein LBM is



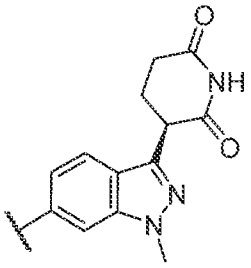
Embodiment 394. The compound of any one of embodiments 1-338, wherein LBM is



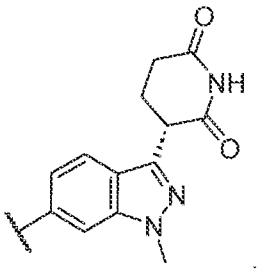
Embodiment 395. The compound of any one of embodiments 1-338, wherein LBM is



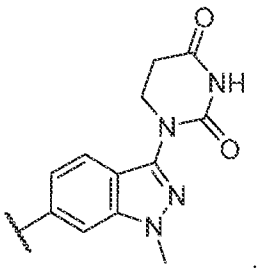
Embodiment 396. The compound of any one of embodiments 1-338, wherein LBM is



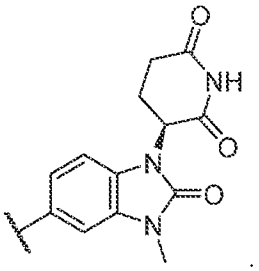
Embodiment 397. The compound of any one of embodiments 1-338, wherein LBM is



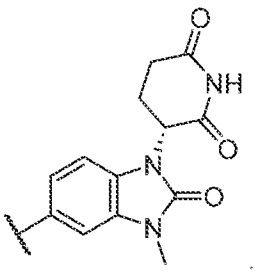
Embodiment 398. The compound of any one of embodiments 1-338, wherein LBM is



Embodiment 399. The compound of any one of embodiments 1-338, wherein LBM is



Embodiment 400. The compound of any embodiments 1-338, wherein LBM is



Embodiment 401. The compound of any one of embodiments 1-399, wherein each R^1 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –SR, –OR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –

$N(R)C(O)NR_2$, $-N(R)S(O)_2NR_2$ and $-N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain substituted with 0-3 instances of halo.

Embodiment 402. The compound of any one of embodiments 1-399, wherein each R^1 is independently selected from –Me, –Et, –F, –Cl, $-SCF_3$, $-OCF_3$, $-CF_3$, –CN, –OH, –OMe, $-NH_2$, –NHMe and $-NMe_2$.

Embodiment 403. The compound of any one of embodiments 1-399, wherein R^1 is –F.

Embodiment 404. The compound of any one of embodiments 1-402, wherein each R^2 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, –S(O)R, $-S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $-C(O)NR_2$, –C(O)N(R)OR, $-OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2NR_2$ and $-N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

Embodiment 405. The compound of any one of embodiments 1-402, wherein each R^2 is independently selected from –Me, –Et, –F, –Cl, $-CF_3$, $-CHF_2$, –CN, –OH, –OMe, $-OCF_3$, $-NH_2$, –NHMe and $-NMe_2$.

Embodiment 406. The compound of any one of embodiments 1-402, wherein each R^2 is independently selected from –Me, –Et, –F, –Cl, $-CF_3$, –CN, –OH, –OMe, $-NH_2$, –NHMe and $-NMe_2$.

Embodiment 407. The compound of any one of embodiments 1-402, wherein each R^2 is independently selected from –F, –Cl, $-CF_3$, $-CHF_2$, –OH, $-OCF_3$ and $-SCF_3$.

Embodiment 408. The compound of any one of embodiments 1-402, wherein each R^2 is independently selected from –F, –Cl and $-SCF_3$.

Embodiment 409. The compound of any one of embodiments 1-407, wherein m is 0, 1 or 2.

Embodiment 410. The compound of any one of embodiments 1-407, wherein m is 0.

Embodiment 411. The compound of any one of embodiments 1-407, wherein m is 1.

Embodiment 412. The compound of any one of embodiments 1-407, wherein m is 2.

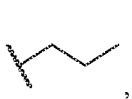
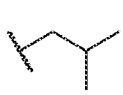
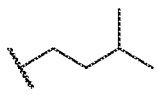
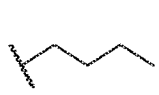
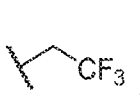
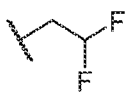
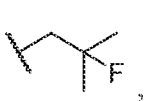
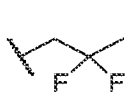
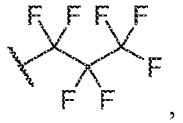
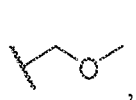
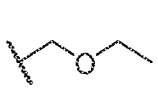
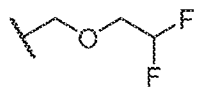
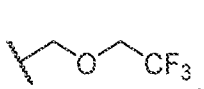
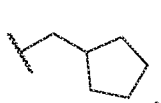
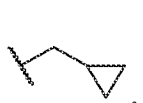
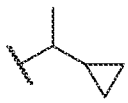
Embodiment 413. The compound of any one of embodiments 1-411, wherein n is 0, 1 or 2.

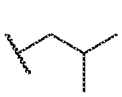
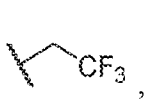
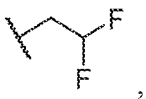
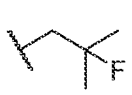
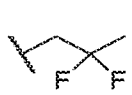
Embodiment 414. The compound of any one of embodiments 1-411, wherein n is 0.

Embodiment 415. The compound of any one of embodiments 1-411, wherein n is 1.

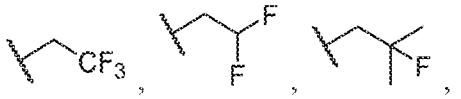
Embodiment 416. The compound of any one of embodiments 1-411, wherein n is 2.

Embodiment 417. The compound of any one of embodiments 1-415, wherein each R^3 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$ and –$B(OR)_2$, wherein R is –H or a C_{1-6} aliphatic chain.

Embodiment 418. The compound of any one of embodiments 1-415, wherein each R^3 is independently selected from –Me, –Et,  , ,  ,  ,  , , –F, –CF_3,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , –CO_2H, –OH, –OMe, and –$B(OH)_2$.

Embodiment 419. The compound of any one of embodiments 1-415, wherein each R^3 is independently selected from –Me, –Et, , ,  , , –F, –Cl, –CF_3,  ,  ,  ,  , –CO_2H, –CN, –OH, –OMe, –NH_2, –NHMe, –NMe_2 and –$B(OH)_2$.

Embodiment 420. The compound of any one of embodiments 1-415, wherein each R^3 is independently selected from –Me, –Et, –F, –Cl, –CF_3,-CO_2H, –CN, –OH, –OMe, –NH_2, –NHMe and –NMe_2.

Embodiment 421. The compound of any one of embodiments 1-415, wherein each R^3 is independently selected from –Me, –Et, , –F, –CF_3,  , –CO_2H, –OH, –OMe, and –$B(OH)_2$.

Embodiment 422. The compound of any one of embodiments 1-415, wherein R^3 is selected from –F, –OH, and –CO_2H.

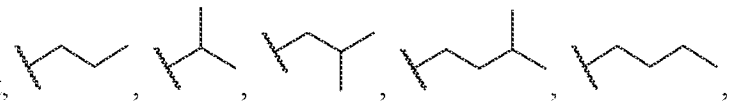
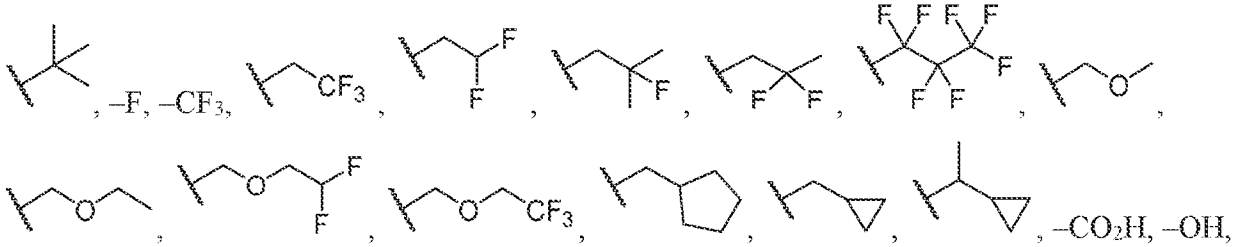
Embodiment 423. The compound of any one of embodiments 1-415, wherein R^3 is selected from –OH and –CO_2H.

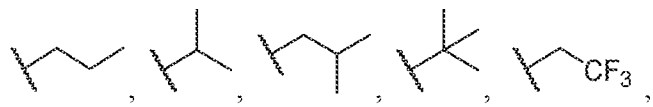
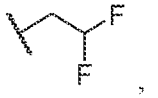
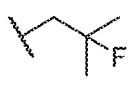
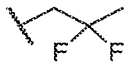
Embodiment 424. The compound of any one of embodiments 1-422 wherein p is 0, 1 or 2.

Embodiment 425. The compound of any one of embodiments 1-422 wherein p is 0.

Embodiment 426. The compound of any one of embodiments 1-422 wherein p is 1.

Embodiment 427. The compound of any one of embodiments 1-422 wherein p is 2.

Embodiment 428. The compound of any one of embodiments 1-426, wherein each R^{hh} is independently selected from–Me, –Et,  , –F, –CF_3,  , –CO_2H, –OH, –OMe, and –$B(OH)_2$.

Embodiment 429. The compound of any one of embodiments 1-426, wherein each R^{hh} is independently selected from –Me, –Et,  ,  ,  and  .

Embodiment 430. The compound of any one of embodiments 1-428, wherein the compound is a compound shown in **Table 1** or a pharmaceutically acceptable salt thereof.

Embodiment 431. A pharmaceutical composition comprising a compound of any one of embodiments 1-429, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

Embodiment 432. A method of inhibiting ERα signaling in a sample, e.g., in vivo or in vitro, by contacting ERα with a compound of any one of embodiments 1-428, or a pharmaceutically acceptable salt thereof, or a composition of embodiment 429.

Embodiment 433. The method of embodiment 431, wherein the inhibiting of ERα signaling comprises reducing the signaling activity of ERα by at least 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, e.g., relative to a reference standard.

Embodiment 434. The method of embodiment 431, wherein the inhibiting of ERα signaling comprises reducing the signaling activity of ERα by at least 1-fold, 1.5-fold, 2-fold, 3-fold, 5-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold, or more, e.g., relative to a reference standard.

Embodiment 435. A method of treating an ERα-mediated disorder in a patient in need thereof, comprising administering to the patient a compound of any one of embodiments 1-428, or a pharmaceutically acceptable salt thereof, or a composition of embodiment 429.

Embodiment 436. The method of embodiment 434, wherein the ERα-mediated disorder is associated with estrogen receptor accumulation and aggregation.

Embodiment 437. The method of any embodiments 434 or 435, wherein the ERα-mediated disorder is cancer or a neoplasia associated with estrogen receptor accumulation and aggregation.

Embodiment 438. The method of embodiment 436, wherein the ERα-mediated disorder is a disorder mediated by a ERα containing a D538G, Y537S, or L536R mutation.

Embodiment 439. The method of any one of embodiments 431-437, wherein the ERα-mediated disorder is a disorder described herein.

Embodiment 440. The method of any one of embodiments 431-437, wherein the method comprises the steps of:

(i) identifying a subject in need of such treatment;

(ii) providing a disclosed compound, or a pharmaceutically acceptable salt thereof; and

(iii) administering said provided compound in a therapeutically effective amount to treat, suppress and/or prevent the disease state or condition in a subject in need of such treatment.

Embodiment 441. The method of any one of embodiments 431-437, wherein the ERα-mediated disorder is breast cancer or uterine cancer.

Embodiment 442. The method of embodiment 438, wherein the breast cancer is selected from the group consisting of ER+ breast cancer, ER+/HER2- breast cancer, ER+ advanced/metastatic breast cancer, and ER+/HER2- advanced/metastatic breast cancer.

Embodiment 443. The method of any one of embodiments 431-437, wherein the ERα-mediated disorder is endometriosis.

Embodiment 444. A compound or pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, according to any one of embodiments 1-429 or a pharmaceutical composition of embodiment 430, for use as a medicament.

Embodiment 445. A compound or pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, according to any one of embodiments 1-429 or a pharmaceutical composition of embodiment 430, for use in the treatment of an ERα-mediated disorder.

EXAMPLES

[0606] Examples are provided herein to facilitate a more complete understanding of the disclosure. The following examples serve to illustrate the exemplary modes of making and practicing the subject matter of the disclosure. However, the scope of the disclosure is not to be construed as limited to specific embodiments disclosed in these examples, which are illustrative only.

[0607] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to other classes and subclasses and species of each of these compounds, as described herein. Additional compounds of the disclosure were prepared by methods substantially similar to those described herein in the Examples and methods known to one skilled in the art.

[0608] In the description of the synthetic methods described below, unless otherwise stated, it is to be understood that all reaction conditions (for example, reaction solvent, atmosphere, temperature, duration, and workup procedures) are selected from the standard conditions for that reaction, unless otherwise indicated. The starting materials for the Examples are either commercially available or are readily prepared by standard methods from known materials.

General Methods

[0609] The parameters used for the HPLC measurement in the synthesis procedures below are as follows: Mobile Phase: 2.75ML/4LTFA in water (solvent A) and 2.5ML/4LTFA in acetonitrile (solvent B), using the elution gradient 10%-80% (solvent B) over 6 minutes and holding at 80% for 2 minutes at a flow rate of 1.2 ml/min; Column: Ultimate C18 3.0*50mm,3um Wavelength:UV220nm,215nm,254nm; Column temperature: 40°C.

[0610] The parameters for the LCMS (acidic) measurement in the synthesis procedures below are one of the following: (1) Mobile Phase: 1.5ML/4LTFA in water (solvent A) and 0.75ML/4LTFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over0.7 minutes and holding at 95%; for 0.4 minutes at a flow rate of 1.5 ml/min; Column: MerckChromolith®FlashRP-183*25mm,3um; Wavelength:UV 220nm,254nm; Column temperature: 50°C; MS ionization: ESI. (2) Mobile Phase: 1.5ML/4LTFA in water (solvent A) and 0.75ML/4LTFA in acetonitrile (solvent B), using the elution gradient 10%-80% (solvent B)

over 3 minutes and holding at 80%; for 0.5 minutes at a flow rate of 0.8 ml/min; column: Xtimate C18 2.1*30mm,3um.

[0611] The parameters for the LCMS (basic) measurement in the synthesis procedures below are as follows: Mobile Phase: 0.8mL/4L $NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B), using the elution gradient 30%-90% (solvent B) over 2 minutes and holding at 90%; for 0.48minutes at a flow rate of 1.2 ml/min; Column: Xbridge Shield RP-18,5um,2.1*50mm; Wavelength:UV 220nm & 254nm ; Column temperature: 50°C; MS ionization:ESI. Wavelength:UV 220nm & 254nm; Column temperature: 50°C; MS ionization:ESI.

List of Abbreviations

aq: aqueous

Ac: acetyl

ACN or MeCN: acetonitrile

AmF: ammonium formate

anhyd.: anhydrous

BINAP: (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene

Bn: Benzyl

conc.: concentrated

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE: Dichloroethane

DCM: Dichloromethane

DIPEA: Diisopropylamine

DMF: N,N-dimethylformamide

DMP: Dess-Martin periodinane

DMPU: N,N′-Dimethylpropyleneurea

DMSO: dimethylsulfoxide

DIPEA: diisopropylethylamine

EA or EtOAc: ethyl acetate

EDCI, EDC, or EDAC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

equiv or eq: molar equivalents

Et: ethyl

HATU: 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid Hexafluorophosphate

HPLC: high pressure liquid chromatography

LCMS or LC-MS: liquid chromatography-mass spectrometry

Ms: methanesulfonyl

NBS: N-bromosuccinimide

NMR: nuclear magnetic resonance

PE: petroleum ether

PMB: *p*-methoxybenzyl

rt or RT: room temperature

sat: saturated

TBS: *tert*-butyldimethylsilyl

TEA: triethylamine

Tf: trifluoromethanesulfonate

TFA: trifluoroacetic acid

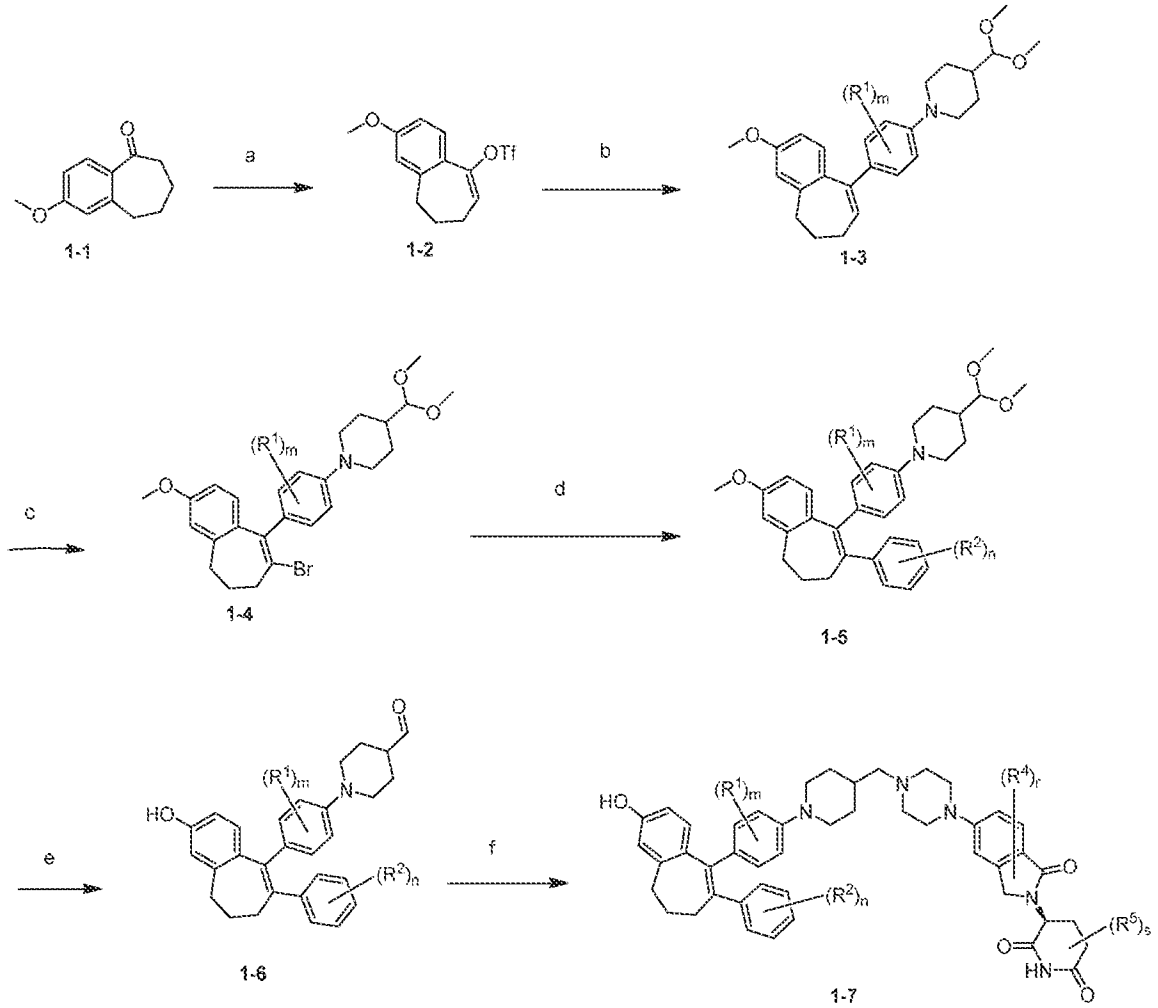
THF: tetrahydrofuran

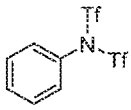
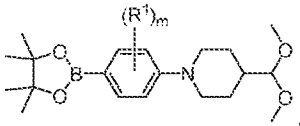
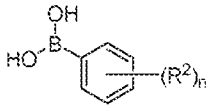
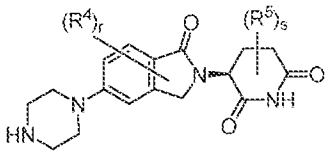
TLC: thin layer chromatography

Tol: toluene

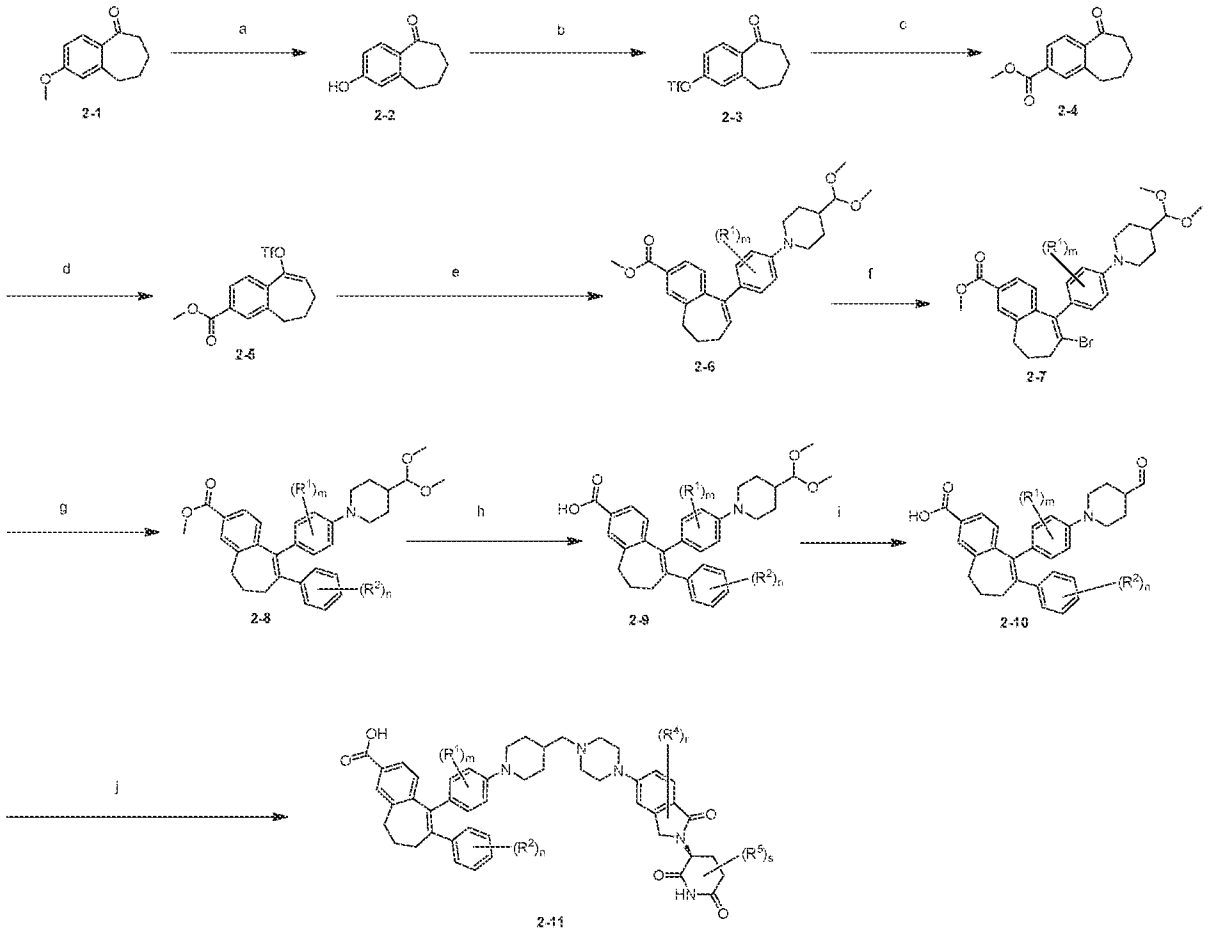
UV: ultraviolet

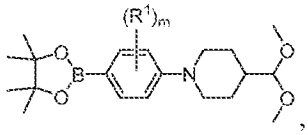
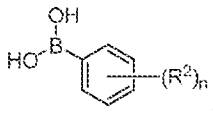
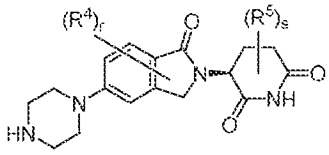
General Synthetic Scheme 1



[0612] Reagents and conditions: (a)  , LDA, THF, -78 °C - r.t., 12 h; (b)  , Pd-118, Na_2CO_3, dioxane/H_2O = 4:1, 70 °C, 16 h; (c) $PyHBr_3$, DIEA, DCM, 0 °C – 25 °C, 0.5 h; (d)  , $Pd(dppf)Cl_2$, Na_2CO_3, dioxane/H_2O = 4:1, 100 °C, 16 h; (e) BBr_3, DCM, 0 – 25 °C, overnight; (f)  , DCM/MeOH, NaOAc, AcOH, 1 h, then $NaBH_3CN$, r.t., overnight

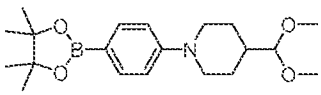
General Synthetic Scheme 2



[0613] Reagents and conditions : (a) $AlCl_3$, Tol, 90 °C, 1 h; (b) Phenyl triflimide, TEA, DMAP, DCM 20 °C, 16 h; (c) $Pd(dppf)Cl_2$, CO, DIEA, DMF, MeOH, 50 psi, 80 °C, 48 h; (d) Tf_2O, Py, DCM, 0 – r.t., 16 h; (e)  , Pd-118, Na_2CO_3, dioxane/H_2O = 4:1, 85 °C, 16 h; (f) $PyHBr_3$, DIEA, DCM, 0 °C, 0.5 h; (g)  , $Pd(dppf)Cl_2$, Na_2CO_3, dioxane/H_2O = 4:1, 100 °C, 16 h; (h) 2M LiOH, THF/MeOH = 1:1, 50 °C, 16 h; (i) 10% H_2SO_4, THF, 70 °C, 16 h; (j)  , AcONa, DCM/MeOH, 0.5 h, then AcOH, $NaBH(OAc)_3$, r.t., overnight.

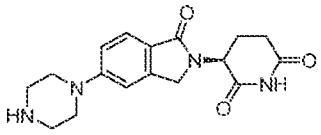
Intermediates

[Intermediate 1] – 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine - Commercially available



[Intermediate 1]

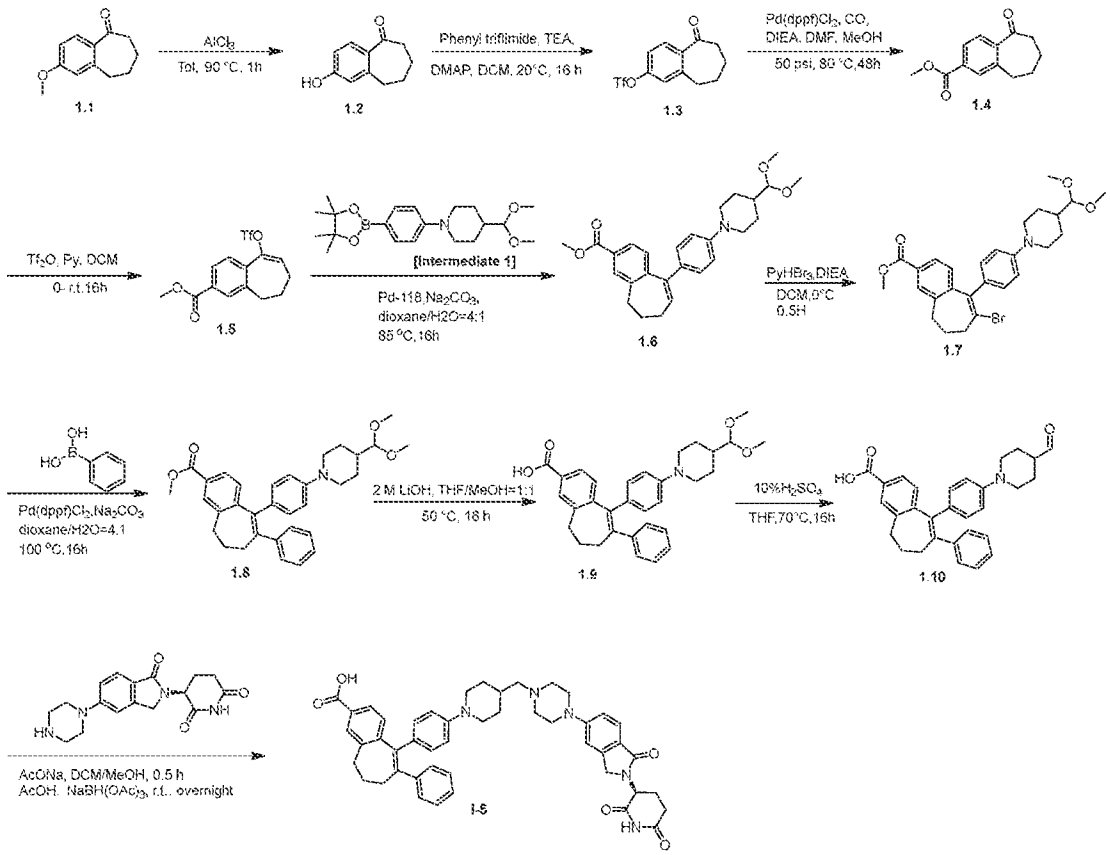
[Intermediate 2] – (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione – Commercially available



[Intermediate 2]

Example 1. Synthesis of (S)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-5

Synthetic scheme:



Synthesis of compound 1.2

[0614] Synthesis of compound **1.2**. To a solution of 2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (10 g, 1 Eq, 53 mmol) in toluene (200 ml) was added aluminum chloride (17 g, 6.1 mL, 2.4 Eq, 0.13 mol) at 0 °C. The reaction vessel was removed from the ice bath and allowed to gradually warm to r.t. over the course of 5 min. Then the reaction mixture was stirred at 90° C for 2 h. The reaction was cooled to room temperature and poured onto ice (500 g). The slurry was stirred overnight and the solid formed was filtered, the filter cake was washed with water (200 ml), and then was concentrated to dryness in vacuo to give **1.2** as a yellow solid (9.15 g, 98% yield)

[0615] LC-MS (ESI^+) m/z: 177.1 $(M+H)^+$

Synthesis of compound 1.3

[0616] To a stirred solution of 2-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one **1.2** (8.77 g , 1 Eq, 49.5 mmol)and phenyl triflimide (19.6 g, 1.11 Eq, 54.9 mmol)in DCM (80 mL) at 20°C was added Triethylamine (6.01 g, 8.28 mL, 1.2 Eq, 59.4 mmol) and a catalytic amount of DMAP (605 mg, 0.1 Eq, 4.95 mmol) was then added to the mixture and stirring was continued at 20°C for 16 hours. The reaction was concentrated to dryness in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 10% EtOAc in petroleum ether). The desired fractions were collected, and concentrated to dryness in vacuo to give **1.3** as a yellow oil (15 g, 83% yield).

[0617] TLC: petroleum ether/ethyl acetate=5:1, R_f=0.7

[0618] LC-MS (ESI^+) *m/z*: 309.1 $(M+H)^+$

Synthesis of compound 1.4

[0619] To a solution of 5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl trifluoromethanesulfonate **1.3** (15 g, 1 Eq, 41 mmol) in DMF (80 ml) and MeOH (40 ml), were added [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with dichloromethane (2.0 g, 0.06 Eq, 2.5 mmol) and diisopropylethylamine (12 g, 16 mL, 2.2 Eq, 91 mmol). The black suspension was carbonylated in a hydrogenated bottle at 80° C under 50 psi of CO for 48 hours. 300 mL H_2O was added, and the mixture was extracted with ethyl acetate (2×80 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a black solution (17 g, crude). The black solution was subjected to column chromatography over silica gel (gradient elution: 0 – 12% EtOAc in petroleum ether). The desired fractions were collected, and concentrated to dryness in vacuo to give **1.4** as a yellow solution (9.34 g, 100% purity).

[0620] TLC: petroleum ether/ethyl acetate=5:1, R_f=0.6

[0621] LC-MS (ESI^+) m/z: 219.2 $(M+H)^+$

Synthesis of compound 1.5

[0622] To a solution of methyl 5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate **1.4** (9.34 g, 1 Eq, 42.0 mmol)in DCM (100 mL) and pyridine (5.21 g, 5.34 mL, 1.57 Eq, 65.9 mmol), was added dropwise trifluoromethanesulfonic anhydride (29.6 g, 17.6 mL, 2.5 Eq, 105 mmol) at 0 ° C for 10 min. The reaction vessel was removed from the ice bath and allowed to gradually warm to 20 ° C over the course of 5 min, after which time stirring was continued for 16 h. Then

ice (100 g) was added and the slurry partitioned between water and DCM. The organic phase was concentrated to dryness in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 18% EtOAc in petroleum ether).The pure fractions were collected and concentrated to dryness in vacuo to give **1.5** as a brown oil (14.83 g, 98.3% purity).

[0623] TLC=petroleum ether/ethyl acetate=5:1, R_f=0.8

[0624] LC-MS (ESI^+) m/z: 351.0 $(M+H)^+$

Synthesis of compound 1.6

[0625] A 100 mL round-bottomed flask was equipped with magnetic stirrer.1,1'-bis(di-t-butylphosphino)ferrocene palladium dichloride (589 mg, 0.1 Eq, 903 μmol) was added to the mixture of , methyl 9-(((trifluoromethyl)sulfonyl)oxy)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate **1.5** (3.28 g, 96.476% purity, 1 Eq, 9.03 mmol) 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine **[Intermediate 1]** (3.92 g, 1.2 Eq, 10.8 mmol) and sodium carbonate (2.87 g, 1.67 mL, 3 Eq, 27.1 mmol) in dioxane (24 mL) and H_2O (6 mL) at r.t.. The 100 mL round-bottomed flask was equipped with a reflux condenser, and tee-junction with a N_2 balloon. The suspension was degassed in vacuo and purged with N_2 several times. The reaction mixture was heated at 85 °C for 16 hour. Then the reaction was cooled to room temperature. 150 mL H_2O was added, and the mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a black oil. The black oil was subjected to column chromatography over silica gel (gradient elution: 0 – 7% EtOAc in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuo to give **1.6** as a yellow solid (2.21 g, 47.7% yield). TLC: petroleum ether/ethyl acetate=5:1, R_f=0.5.

[0626] LC-MS (ESI^+) m/z: 436.3 $(M+H)^+$

Synthesis of compound 1.7

[0627] To a mixture of methyl 9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate **1.6** (2.11 g, 1 Eq, 4.11 mmol)in DCM (20 mL) and DIEA (797 mg, 1.07 mL, 1.5 Eq, 6.17 mmol), pyridinium bromide perbromide (1.38 g, 1.05 Eq, 4.32 mmol) were added at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. 100 mL H_2O was

added, and the mixture was extracted with DCM (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 20% EtOAc in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuo to give **1.7** as a yellow oil (2.5 g, 90% yield).

[0628] TLC: petroleum ether/ethyl acetate=5:1, R_f=0.5.

[0629] LC-MS (ESI^+) m/z: 514.1 $(M+H)^+$

Synthesis of compound 1.8

[0630] 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride (32.5 mg, 0.1 Eq, 44.4 µmol) was added to the mixture of methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate **1.7** (300 mg, 76.115 % purity, 1 Eq, 444 umol) benzeneboronic acid (64.9 mg, 1.2 Eq, 533 umol) and sodium carbonate (141 mg, 3 Eq, 1.33 mmol) in dioxane (3 mL) and H_2O (0.3 mL) at r.t. The suspension was degassed in vacuo and purged with N_2 several times. The reaction mixture was heated at 100 °C for 16 hours. Then the reaction was cooled to room temperature. 15 mL H_2O was added, and the mixture was extracted with ethyl acetate (2×20 mL).The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a black solid. The black solid was subjected to column chromatography over silica gel (gradient elution: 0 – 20% EtOAc in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuo to give **1.8** as a yellow solid (230 mg, 84.053 % purity, 85.1 % yield).

[0631] TLC: petroleum ether/ethyl acetate=5:1, R_f=0.6.

[0632] LC-MS (ESI^+) m/z: 512.3 $(M+H)^+$

Synthesis of compound 1.9

[0633] To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-phenyl-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate **1.8** (220 mg, 361.41 umol, 84.053% purity, 1 *eq*) in THF (2 mL) and MeOH (2 mL) was added lithium hydroxide (2 M, 1.81 mL, 10 *eq*) . The mixture was stirred at 50 °C for 16 hr . The reaction was concentrated to dryness in vacuo to give a yellow oil. Ethyl acetate (7 mL) was added, the mixture was adjust to *p*H =5 with 1N HCl. 50 mL water was added and the mixture was extracted with ethyl acetate (25 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo to give 5-

[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-phenyl-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid **1.9** (259 mg, crude) as a yellow solid.

[0634] LC-MS (ESI^+) m/z: 498.4 $(M+H)^+$

Synthesis of compound 1.10

[0635] To a solution of 9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid **1.9** (130 mg, 216.89 umol, 83.023% purity, 1 *eq*) in THF (3 mL) was added 10% H_2SO_4 (3 mL). The mixture was stirred at 70 °C for 16 hr . The reaction was adjust to *p*H = 8 with aq. $NaHCO_3$ (15 mL). Then the mixture was added water (20 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 9-(4-(4-formylpiperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid **1.10** (120 mg, crude) as a yellow solid.

[0636] LC-MS (ESI^+) m/z: 452.2 $(M+H)^+$

Synthesis of compound I-5

[0637] A solution of (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione **[Intermediate 2]** (83 mg, 1 Eq, 0.25 mmol，p-TSA salt)，9-(4-(4-formylpiperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid **1.10** (0.10 g, 0.9 Eq, 0.23 mmol) and sodium acetate (0.10 g, 5 Eq, 1.3 mmol) in DCM (1.5 mL) and MeOH (1.5 mL) was stirred at 20 °C for 30 mins, Then acetic acid (30 mg, 29 μL, 2 Eq, 0.51 mmol) and sodium triacetoxyborohydride (0.11 g, 75 μL, 2 Eq, 0.51 mmol) was added. The mixture was stirred at 20°C for 16 h. The reaction was concentrated to dryness in vacuo to give a yellow oil. The yellow oil was purified by prep-HPLC (Xtimate C18 100*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 10%-50%, 8min). The pure fractions were collected and concentrated in vacuo to remove organic solvent. The aqueous phase was lyophilized to dryness to give the product of (S)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid **I-5** (39.4 mg, 7.2% yield, 0.132 eq FA salt)

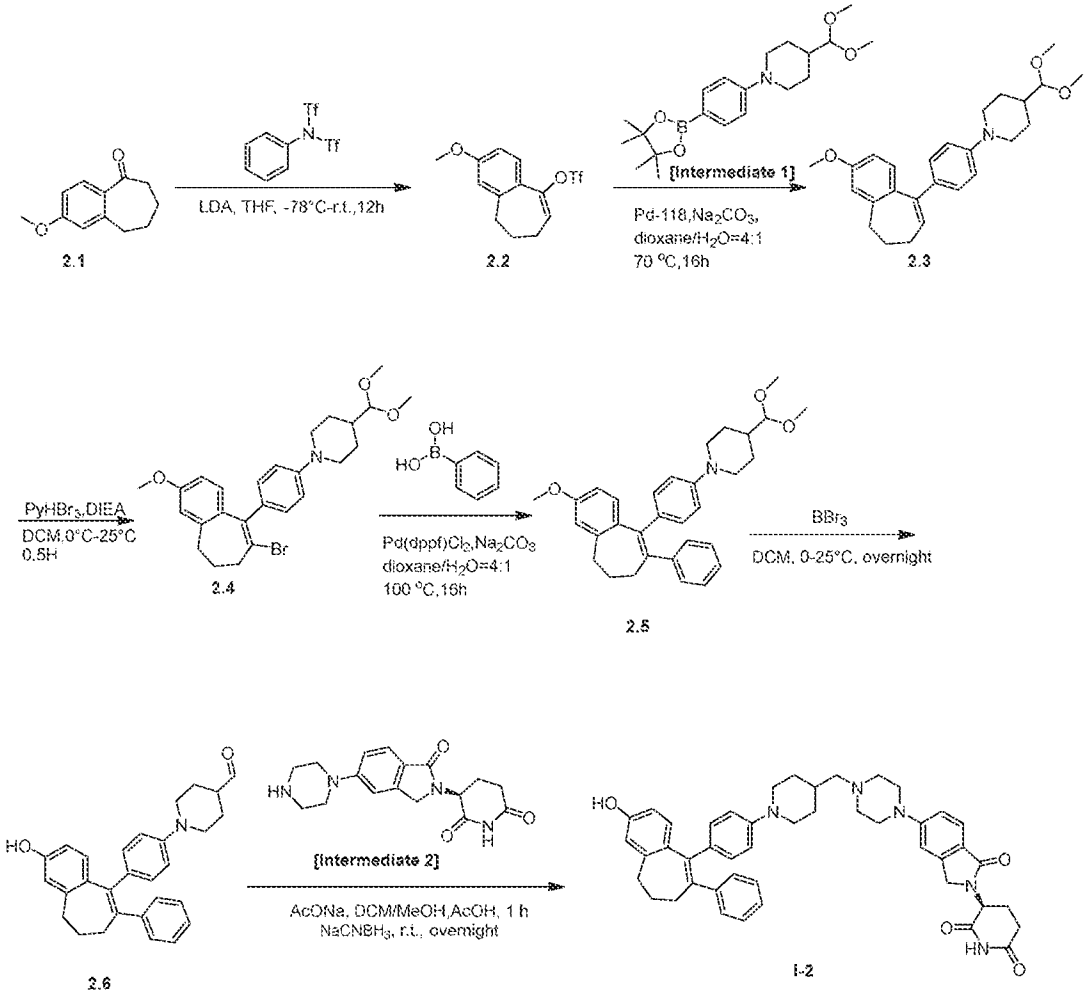
[0638] LC-MS (ESI^+) m/z: 764.4 $(M+H)^+$

[0639] HPLC: 99.818% purity at 220 nm.

[0640] SFC: ret. time:9.688 Area: 98.631%, method: AD-RH_10-80_B_08ML_20min.

[0641] ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.85 (br s, 1H), 10.96 (s, 1H), 8.14 (s, 0.132 H), 7.89 (d, *J*=1.7 Hz, 1H), 7.74 (dd, *J*=1.7, 8.1 Hz, 1H), 7.52 (d, *J*=8.7 Hz,1H), 7.25 - 7.11 (m, 5H), 7.11 - 7.04 (m, 2H), 6.89 (d, *J*=8.0 Hz, 1H), 6.66 (s, 4H), 5.05 (dd, *J*=4.9, 13.3 Hz, 1H), 4.39 - 4.28 (m, 1H), 4.26 - 4.16 (m, 1H),3.62 (br d, *J*=12.2 Hz, 2H), 3.29 (br s, 4H), 2.98 - 2.79 (m, 3H), 2.59 (br d, *J*=12.0 Hz, 6H), 2.44 - 2.35 (m, 2H), 2.24 (br d, *J*=7.0 Hz, 4H), 2.12 (br d, *J*=6.6Hz, 2H), 2.03 - 1.88 (m, 1H), 1.86 - 1.60 (m, 3H), 1.27 - 1.08 (m, 2H).

Example 2. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione , I-2



Synthesis of compound 2.2

[0642] A mixture of 2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one **2.1** (7 g, 1 Eq, 0.04 mol) in THF (100 mL) at -78 °C with N_2, then lithium diisopropylamide solution (6 g, 0.03 L, 2 molar, 1.5 Eq, 0.06 mol) was added to the mixture at -78 °C. Then 1,1,1-trifluoro–N-phenyl-N-

((trifluoromethyl)sulfonyl)methanesulfonamide (20 g, 1.5 Eq, 0.06 mol) in THF (50 mL) was added, the mixture was stirred for 3 hour at -78 °C and warmed to 20 °C for 9 hours under N_2 atmosphere.

[0643] TLC (petroleum ether: ethyl acetate=10:1, R_f =0.4) indicated a new spot formed. The mixture was quenched by the addition of 50 mL of saturated aqueous NH_4Cl. Then the mixture was treated with H_2O (100 mL), extracted with EtOAc (150 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a yellow oil. The yellow oil was purified by flash column (petroleum ether/ethyl acetate from 100/0 to 90/10) and the organic layer was concentrated in vacuo to give 3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl trifluoromethanesulfonate **2.2** (7.34 g, 20.7 mmol, 60 %, 90.723% Purity) as a gray oil.

Synthesis of compound 2.3

[0644] A mixture of 1,1'-bis(di-t-butylphosphino)ferrocene palladium dichloride (0.39 g, 0.1 Eq, 0.59 mmol), 3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl trifluoromethanesulfonate **2.2** (2.1 g, 1 Eq, 5.9 mmol), 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl) phenyl)piperidine **[Intermediate 1]** (3.1 g, 1.3 Eq, 7.5 mmol) and Na_2CO_3 (1.9 g, 3 Eq, 18 mmol) in dioxane (32 mL) and H_2O (8 mL) at r.t.. N_2 was bubbled into the mixture for 5 min. The reaction mixture was heated at 70 °C for 16 hour. Then the reaction was cooled to room temperature.

[0645] TLC (PE/EtOAc = 2/1, R_f = 0.4). The mixture was treated with H_2O (100 mL), extracted with EtOAc (100 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue.

[0646] The residue was subjected to column chromatography over silica gel (gradient elution:0~20% ethyl acetate in petroleum ether).The pure fractions were collected and concentrated to dryness in vacuo to give 4-(dimethoxymethyl)-1-(4-(3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine **2.3** (1.2 g, 2.9 mmol, 49 %, 98.887% Purity) as a white solid.

[0647] LC-MS (ESI^+) m/z: 408.2 $(M+H)^+$

Synthesis of compound 2.4

[0648] To a mixture of 4-(dimethoxymethyl)-1-(4-(3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine **2.3** (1.2 g, 1 Eq, 2.9 mmol) in DCM (15 mL) and DIEA (0.56 g, 0.76 mL, 1.5 Eq, 4.4 mmol), pyridinium bromide perbromide (0.93 g, 1 Eq, 2.9 mmol) were added at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. TLC (PE/EtOAc = 2/1, R_f = 0.3). The mixture was concentrated to dryness in vacuo to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution:0~50% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuo to give 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine **2.4** (1.3 g, 2.4 mmol, 84 % yield, 91.554% Purity) as a white solid.

[0649] LC-MS (ESI^+) m/z: 486.1 $(M+H)^+$

Synthesis of compound 2.5

[0650] A 40 mL thread vial was equipped with magnetic stirrer. 1,1'-bis(di-t-butylphosphino)ferrocene palladium dichloride (40.5 mg, 0.1 Eq, 62.1 µmol) was added to the mixture of 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine **2.4** (330 mg, 1 Eq, 621 µmol) phenylboronic acid (90.9 mg, 1.2 Eq, 745 µmol) and sodium carbonate (197 mg, 115 µL, 3 Eq, 1.86 mmol) in dioxane (8 mL) and H_2O (2 mL) at r.t.. N_2 was bubbled into the mixture for 5 min. The reaction mixture was heated at 80 °C for 12 hour. Then the reaction was cooled to room temperature.

[0651] TLC (PE/EtOAc = 5/1, R_f = 0.5). The mixture was filtered and the filter cake was washed with EtOAc (50 mL). The filtrate was treated with H_2O (50 mL), extracted with EtOAc (50 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue.

[0652] The residue was subjected to column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 80/20). The pure fractions were collected and concentrated to dryness in vacuo to give 4-(dimethoxymethyl)-1-(4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine **2.5** (300 mg, 528 µmol, 85.1 %yield, 85.179% Purity) as a yellow solid.

[0653] LC-MS (ESI^+) m/z: 484.2 $(M+H)^+$

Synthesis of compound 2.6

[0654] To a solution of 4-(dimethoxymethyl)-1-(4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine **2.5** (150 mg, 1 Eq, 264 µmol) in DCM (6 mL) at 0 °C was added BBr_3 (199 mg, 793 µL, 1 molar, 3 Eq, 793 µmol) with N_2. After addition, the mixture was stirred at 0 °C for 4 hour, and then the reaction was warmed to 25 °C and was stirred at this temperature for 12 hour. The reaction was filtered and concentrated to dryness in vacuo to give 1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde **2.6** (110 mg, 260 µmol, 98.3 %, 100% Purity) as a brown solid.

[0655] LC-MS (ESI^+) m/z: 442.3 $(M+H+18)^+$

Synthesis of compound I-2

[0656] A mixture of 1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde **2.6** (100.00 mg, 243.00 umol, 1.3 *eq*), (3S)-3-[5-[(3R)-3-methylpiperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione **[Intermediate 2]** (160 mg, 186.92 umol, 40% purity, 1 *eq*, p-TSA salt) and sodium acetate (58 mg, 5 Eq, 0.71 mmol) in DCM (3 mL) and MeOH (3 mL) at 20°C for 0.5 hr, then AcOH (22.45 mg, 373.84 umol, 21.38 uL, 2 *eq*) and $NaCNBH_3$ (23.49 mg, 373.84 umol, 2 *eq*) the mixture, and then the mixture was stirred at 20 °C for 16 hr . The yellow oil was purified by prep-HPLC (column: Xtimate C18 100*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 7%-47%, 12min). The pure fractions were collected and concentrated in vacuo to remove organic solvent. The aqueous phase was lyophilized to dryness to give the product of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **I-2** (13.9mg, 13% yield, 99.531%,purity).

[0657] LC-MS (ESI^+) m/z: 736.4 $(M+H)^+$

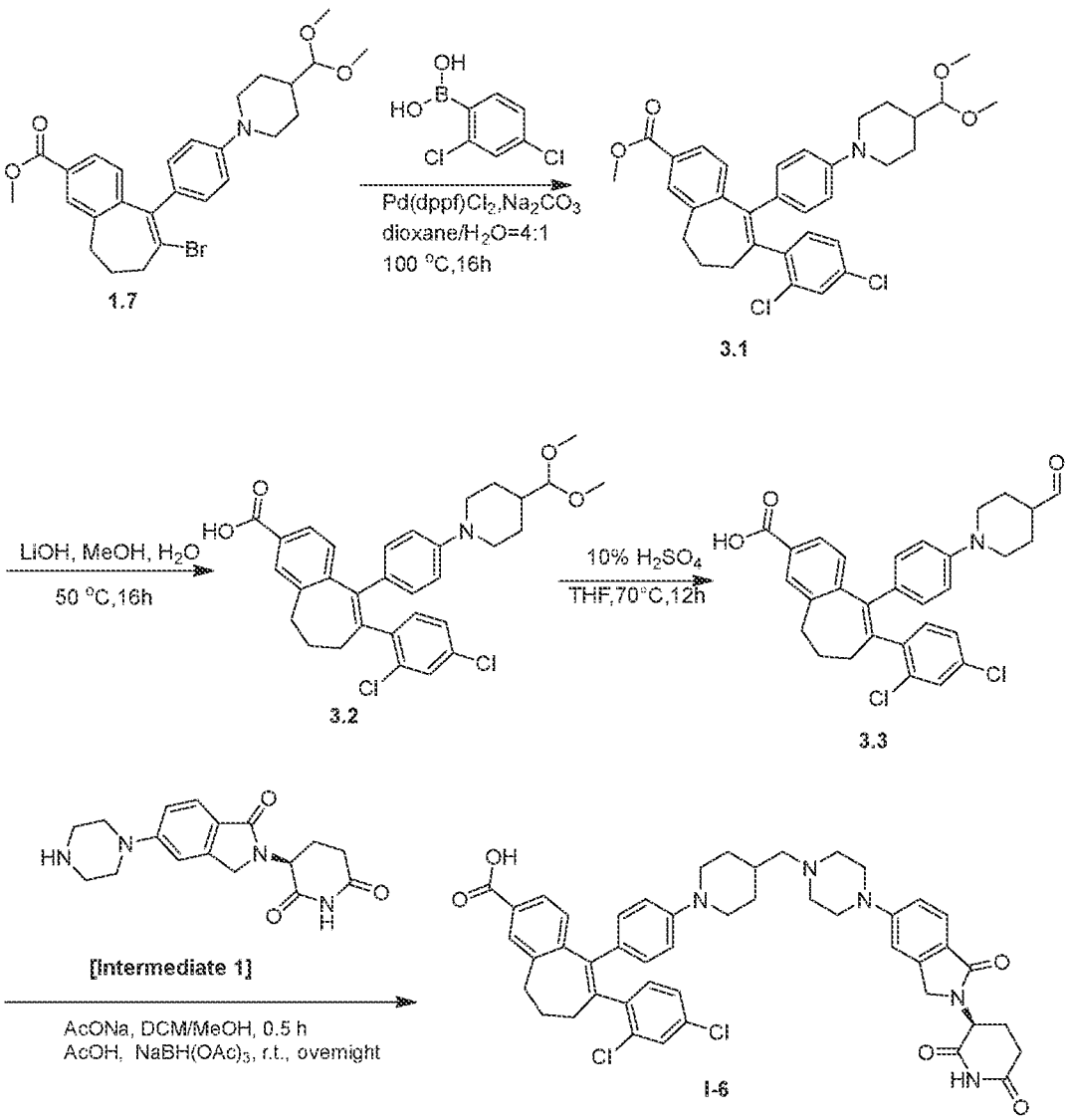
[0658] HPLC: 99.531% purity at 220 nm.

[0659] SFC: ret.time:8.088 Area: 90.00%, method: OJ_ETOH_DEA_50_25ML_10CM

[0660] ^1H NMR (400MHz, DMSO-d_6) δ = 10.96 (s, 1H), 9.38 (s, 1H), 8.14 (s, 1H), 7.53 (br d, *J*=8.3 Hz, 1H), 7.21 - 7.01 (m, 7H), 6.73 - 6.49 (m, 7H), 5.06 (br dd,*J*=4.9, 13.4 Hz, 1H), 4.37 - 4.18 (m, 3H), 3.61 (br d, *J*=11.7 Hz, 2H), 2.99 - 2.82 (m, 1H), 2.59 (br d, *J*=12.4 Hz, 10H), 2.42 - 2.35 (m, 3H), 2.28 - 2.22 (m,3H), 2.08 - 1.92 (m, 4H), 1.79 (br d, *J*=11.2 Hz, 2H), 1.73 - 1.63 (m, 1H), 1.27 - 1.12 (m, 2H).

Example 3. Synthesis of (S)-8-(2,4-dichlorophenyl)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-6

Synthetic scheme:



Synthesis of compound 3.1

[0661] A mixture of sodium carbonate (124 mg, 72.0 µL, 2 Eq, 1.17 mmol), methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate **1.7** (400 mg, 1 Eq, 583 µmol) , (2,4-dichlorophenyl)boronic acid (134 mg, 1.2 Eq, 700 µmol) , [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (476 mg, 1 Eq, 583 µmol) in dioxane (1 mL) and H_2O (0.1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. TLC

(petroleum ether: ethyl aceatte=5:1, R_f=0.5) showed one main new spot was observed. The reaction mixture was quenched by addition 1L H_2O at 20°C, and extracted with Etoac (1 L * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 60 mL/min). Methyl 8-(2,4-dichlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate **3.1** (200 mg, 89.925% purity, 53.1% yeild) was obtained was obtained as a white solid.

Synthesis of compound 3.2

[0662] To a solution of methyl 6-(2,4-dichlorophenyl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate **3.1** (300 mg, 516.76 umol, 1 *eq*) in MeOH (2 mL) was added lithium;hydroxide;hydrate (2 M, 2.58 mL, 10 *eq*). The mixture was stirred at 50 °C for 16 hr. The reaction mixture was added $NaHCO_3$ (2 M) 5 mL to make pH=7~8, and then extracted with EtOAc (5 mL * 3). The combined organic layers were washed with NaCl (5 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow oil. The combined organic layers was filtered and concentrated under reduced pressure to give 6-(2,4-dichlorophenyl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid **3.2** (280 mg, 354.07 umol, 68.52% yield, 71.638% purity) as a yellow oil.

[0663] LC-MS (ESI^+) m/z: 566.2 $(M+H)^+$.

Synthesis of compound 3.3

[0664] To a solution of 6-(2,4-dichlorophenyl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid **3.2** (200 mg, 353.04 umol, 1 eq) in THF (0.25 mL) was added H_2SO_4 (4.60 g, 4.69 mmol, 2.50 mL, 10% purity, 13.28 eq) at 0°C. The mixture was stirred at 70 °C for 12 hr. The reaction mixture was cooled to room temperature and diluted with water (2 mL). The solids were filtered out and to the filtrate was added saturated $NaHCO_3$ to adjust the pH to 7. The resulting mixture was extracted with ethyl acetate (20 mL x 2) and the organic layers combined. The organic was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. compound 6-(2,4-dichlorophenyl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid **3.3** (180 mg, 345.86 umol, 97.97% yield) was obtained as a yellow solid.

[0665] LC-MS (ESI^+) m/z: 537.9 $(M+H+18)^+$

Synthesis of compound I-6

[0666] To a solution of 8-(2,4-dichlorophenyl)-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid **3.3** (60 mg, 1 Eq, 92 μmol) and (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione **[Intermediate 1]** (37 mg, 1.1 Eq, 0.10 mmol, p-TSA salt) and sodium acetate (38 mg, 5 Eq, 0.46 mmol) in DCM (1 mL) and MeOH (1 mL) was stirred at 20°C for 30 mins, Then sodium triacetoxyborohydride (39 mg, 27 μL, 2 Eq, 0.18 mmol) and acetic acid (11 mg, 11 μL, 2 Eq, 0.18 mmol) was added. The mixture was stirred at 20°C for 16h.

[0667] The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ethergradient at 60 mL/min) to give (S)-8-(2,4-dichlorophenyl)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid **I-6** (12 mg, 16% yield) was obtained as a white solid.

[0668] LC-MS (ESI^+) m/z: 832.3$(M+H)^+$

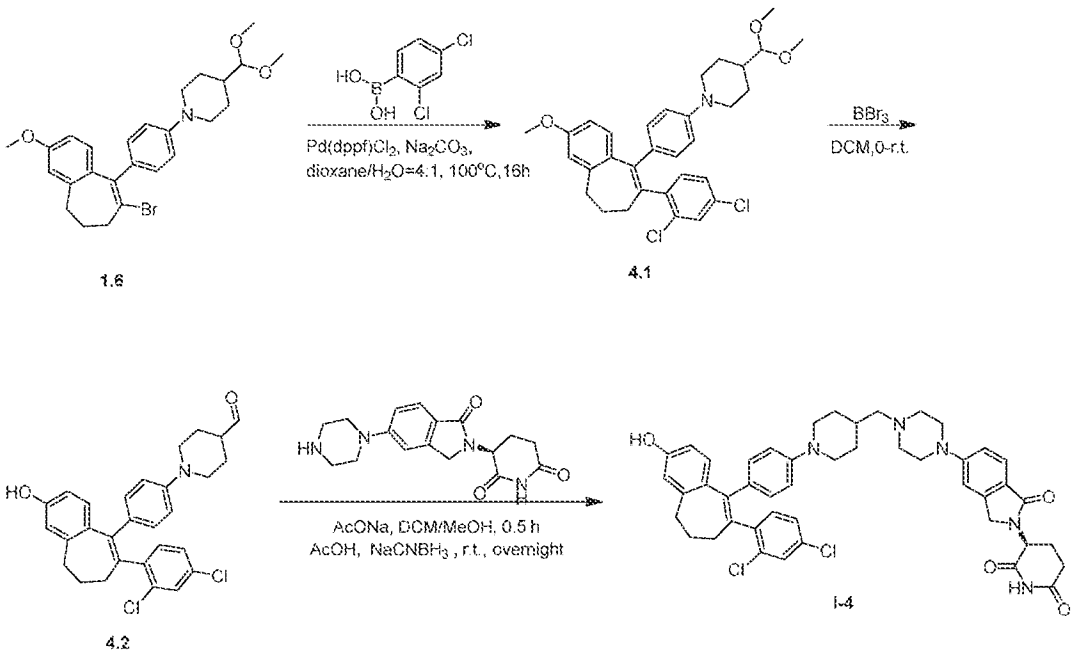
[0669] HPLC: 93.557% purity at 220 nm.

[0670] ^1H NMR (400MHz, DMSO-d_6) δ= 10.95 (s, 1H), 8.20 (s, 0.125H), 7.89 (d, J=1.4 Hz, 1H), 7.75 (dd, J=1.7, 8.0 Hz, 1H), 7.60 (d, J=2.0 Hz, 1H), 7.51 (d,J=8.6 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.20 (d, J=8.2 Hz, 1H), 7.07 - 7.02 (m, 2H), 6.89 (d, J=8.1 Hz, 1H), 6.71 - 6.62 (m, 4H), 5.04 (dd, J=5.0, 13.5 Hz, 1H),4.36 - 4.29 (m, 1H), 4.24 - 4.16 (m, 1H), 3.62 (br d, J=10.8 Hz, 2H), 3.28 (br s, 6H), 2.90 (br s, 3H), 2.62 - 2.53 (m, 6H), 2.38 (br d, J=4.4 Hz, 1H), 2.22 -2.09 (m, 6H), 2.00 - 1.90 (m, 1H), 1.77 (br d, J=11.9 Hz, 2H), 1.66 (br s, 1H), 1.14 (br d, J=10.6 Hz, 2H).

[0671] SFC: retention time, 3.990 min; Area, 96.85 %; method: OJ_ETOH_DEA_50_25ML_10CM.

Example 4. Synthesis of (S)-3-(5-(4-((1-(4-(8-(2,4-dichlorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-4

Synthetic scheme:



1.6 4.1 4.2 I-4

Synthesis of compound 4.1

[0672] 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine **[1.6]** (300 mg, 1 Eq, 617 μmol) was added to a mixture suspension of (2,4-dichlorophenyl)boronic acid (153 mg, 1.3 Eq, 802 μmol) , [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (50.4 mg, 0.1 Eq, 61.7 μmol) and sodium carbonate (196 mg, 114 μL, 3 Eq, 1.85 mmol) and in 1,4-dioxane (8 mL) and H_2O (2mL).The mixture was stirred at 100 °C for 16h. TLC (petroleum ether: ethyl aceatte=1:1,R_f=0.3) showed one main new spot was observed.The reaction was quenched with water (100 mL) and extracted with ethyl acetate(200 mL*2). The organic layer was washed with brine(50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give 1-(4-(8-(2,4-dichlorophenyl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine as black oil. The black oil was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 1-(4-(8-(2,4-dichlorophenyl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine **4.1** (300 mg ,88.0% yield) as a yellow solid.

[0673] LC-MS (ESI^+) m/z: 552.0 $(M+H)^+$

Synthesis of compound 4.2

[0674] To a solution of 1-(4-(8-(2,4-dichlorophenyl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine **4.1** (300 mg, 1 Eq, 543 µmol) in DCM (200 mL) at 0 °C was added tribromoborane (680 mg, 1.36 mL, 2 molar, 5 Eq, 2.71 mmol) with N_2. After addition, the mixture was stirred at this temperature for 4 hr, and then the reaction was warmed to 25 °C and was stirred at this temperature for 12 hour. The reaction was filtered and concentrated to dryness in vacuo to give 1-(4-(8-(2,4-dichlorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde **4.2** (150mg, 354 µmol, 56.1 %,yield) as a brown solid.

[0675] LC-MS (ESI^+) m/z: 510.2 $(M+H+18)^+$

Synthesis of compound I-4

[0676] A mixture of 1-(4-(8-(2,4-dichlorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde **4.2** (100.00 mg, 243.00 umol, 1.3 *eq*) , (3S)-3-[5-[(3R)-3-methylpiperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (160 mg, 186.92 umol, 40% purity, 1 *eq*, p-TSA salt) and sodium;acetate (76.67 mg, 934.60 umol, 5 *eq*) in DCM (3 mL) and MeOH (3 mL) at 20°C for 0.5 hr, then AcOH (22.45 mg, 373.84 umol, 21.38 uL, 2 *eq*) and $NaCNBH_3$ (23.49 mg, 373.84 umol, 2 *eq*) were added, and then the mixture was stirred at 25 °C for 16 hr . The reaction was concentrated to dryness in vacuo to give a yellow oil. The yellow oil was purified by prep-HPLC (Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B%: 30%-60%,7min).The pure fractions were collected and concentrated in vacuo to remove organic solvent. The aqueous phase was lyophilized to dryness to give the product of (S)-3-(5-(4-((1-(4-(8-(2,4-dichlorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione **I-4** (38.5 mg, 22.7% yield, 96.254%,purity)

[0677] LC-MS (ESI^+) m/z: 804.3 $(M+H)^+$

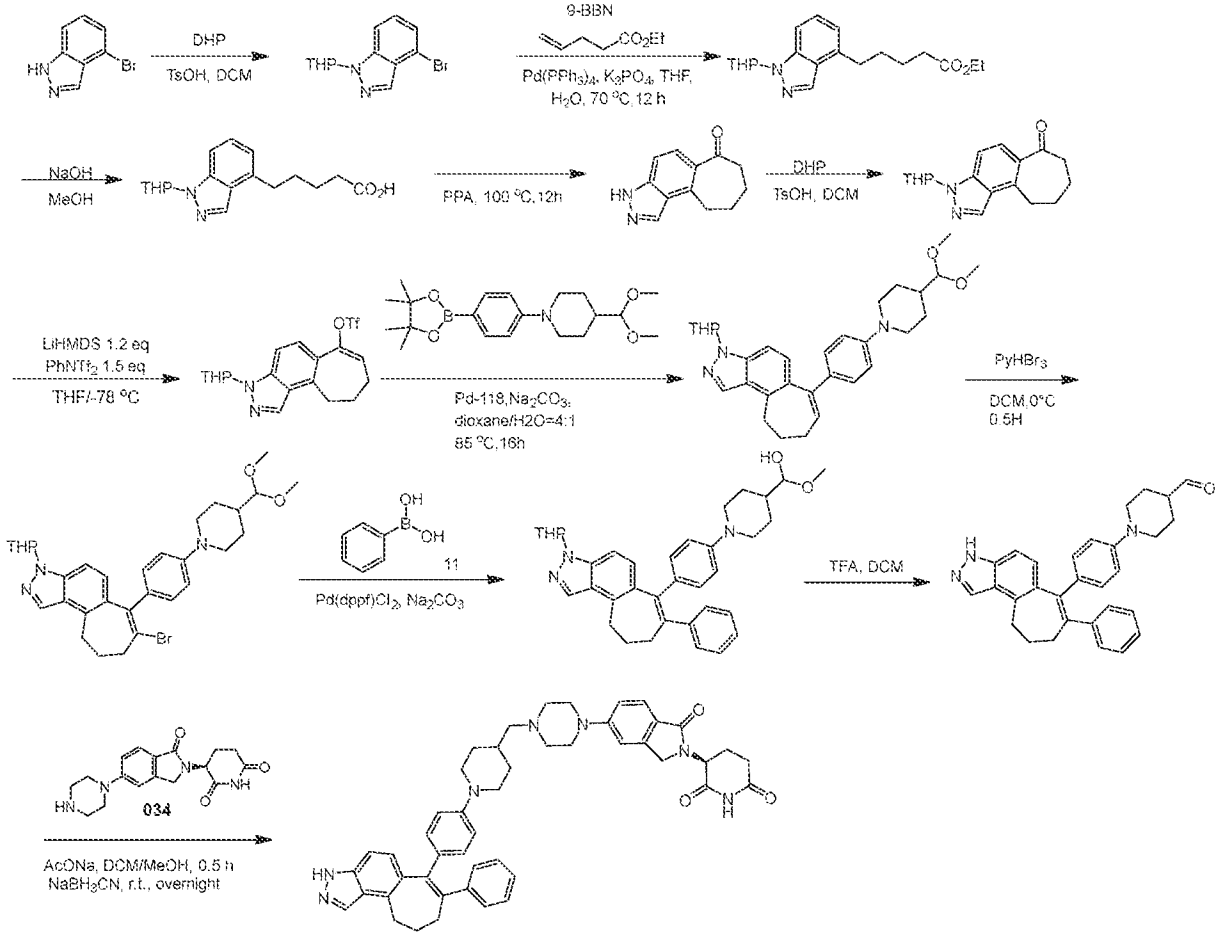
[0678] HPLC: 96.037% purity at 220 nm.

[0679] SFC: ret.time: 3.354 Area: 91.6%, method: ID_MeOH_DEA_MeCN_50_1ML_15MIN_10CM

[0680] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.01 - 10.97 (m, 1H), 9.49 - 9.46 (m, 1H), 8.20 - 8.16 (m, 1H), 7.61 - 7.53 (m, 2H), 7.30 - 7.26 (m, 1H), 7.11 (br s, 3H),6.78 - 6.60 (m, 8H), 5.12 - 5.06

(m, 1H), 4.41 - 4.35 (m, 1H), 4.29 - 4.23 (m, 1H), 3.69 - 3.64 (m, 2H), 2.98 - 2.91 (m, 1H), 2.82 - 2.59 (m, 9H), 2.47 - 2.34 (m,3H), 2.25 - 1.95 (m, 7H), 1.86 - 1.75 (m, 3H), 1.31 - 1.17 (m, 3H).

Example 5. Synthesis of (3S)-3-[1-oxo-5-[4-[[1-[4-(7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione, I-38



[0681] ***Step 1.*** To a solution of 4-bromo-1H-indazole (20 g, 101.51 mmol, 1 eq) and PPTS (5.8 g, 23.3 mmol, 0.23 eq) in DCM (250 mL) was added DHP (18.7 g, 223.3 mmol, 20.41 mL, 2.2 eq) under 0 °C. The mixture was stirred at 25 °C for 3 h. The residue was concentrated and purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 10/1, TLC: PE/EtOAc = 5/1, R_f = 0.83) to yield 4-bromo-1-tetrahydropyran-2-yl-indazole (18 g, 60.82 mmol, 59.9% yield, 95% purity) as a white solid. LC-MS (ESI^+) m/z 281.2, 283.2 $[M+H]^+$.

[0682] ***Step 2.*** To a mixture of ethyl pent-4-enoate (7.36 g, 57.44 mmol, 1.7 eq), 9-BBN (0.5 M, 114.89 mL, 1.7 eq) in THF (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 3 h under N_2 atmosphere. And then was added 4-bromo-1-

tetrahydropyran-2-yl-indazole (10 g, 33.80 mmol, 95% purity, 1 eq), $Pd(PPh_3)_4$ (1.95 g, 1.69 mmol, 0.05 eq), K_3PO_4 (21.52 g, 101.37 mmol, 3 eq), THF (15 mL) and H_2O (40 mL) in mixture solution. The mixture was stirred at 70 °C for 12 h. The reaction mixture was quenched by addition of water (150 mL), extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.48) to yield ethyl 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoate (11 g, 30.9 mmol, 91.6% yield, 93% purity) as yellow oil. LC-MS (ESI^+) m/z 331.2 $[M+H]^+$.

[0683] ***Step 3***. To a solution of ethyl 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoate (11 g, 30.96 mmol, 93% purity, 1 eq) in MeOH (90 mL), THF (30 mL) and H_2O (30 mL) was added NaOH (2.48 g, 61.9 mmol, 2 eq). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition of water (80 mL), adjust pH to 6 by HCl(1 M), extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoic acid (7.2 g, 23.57 mmol, 76.1% yield, 99% purity) as yellow oil which was used in the next step without further purification. LC-MS (ESI^+) m/z 303.3 $[M+H]^+$.

[0684] ***Step 4.*** A mixture of 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoic acid (7.2 g, 23.57 mmol, 99% purity, 1 eq) in PPA (30 g) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition of water (80 mL) under 0 °C, extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.46) to yield 7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (1.2 g, 5.51 mmol, 23.3% yield, 92.0% purity) as a yellow solid. LC-MS (ESI+) m/z 201.1 [M+H]+.

[0685] ***Step 5.*** To a solution of 7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (1.2 g, 5.51 mmol, 92% purity, 1 eq) and $TsOH.H_2O$ (20.98 mg, 110.27 μmol, 0.02 eq) in DCM (20 mL) was added 3,4-dihydro-2H-pyran (695.66 mg, 8.27 mmol, 756.15 μL, 1.5 eq) under 0 °C. The mixture was stirred at 25 °C for 12 h. The residue was concentrated and purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 10/1, TLC: PE/EtOAc = 5/1, R_f = 0.83) to yield 3-

tetrahydropyran-2-yl-7,8,9,10-tetrahydrocyclohepta[e]indazol-6-one (1.7 g, 5.26 mmol, 95.42% yield, 88% purity) as yellow oil. LC-MS (ESI+) m/z 285.3 [M+H]+.

[0686] ***Step 6.*** To a solution of 3-tetrahydropyran-2-yl-7,8,9,10-tetrahydrocyclohepta[e]indazol-6-one (1 g, 3.09 mmol, 88% purity, 1 eq) in THF (30 mL) was added LiHMDS (1 M, 7.74 mL, 2.5 eq) under -78 °C. After stirred 3 h was added 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.66 g, 4.64 mmol, 1.5 eq) The mixture was stirred at -78 °C for 9 h. The reaction mixture was quenched by added to addition of saturation solution of NH_4Cl (50 mL) under 0 °C, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.65) to yield (3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl) trifluoromethanesulfonate (1.7 g, 2.9 mmol, 94.9% yield, 72% purity) as colourless oil. LC-MS (ESI+) m/z 417.2 [M+H]+.

[0687] ***Step 7.*** To a solution of (3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl) trifluoromethanesulfonate (1.7 g, 2.94 mmol, 72% purity, 1 eq) and 4-(dimethoxymethyl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (1.59 g, 3.53 mmol, 80% purity, 1.2 eq) in dioxane (24 mL) and H_2O (6 mL) was added ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (191.5 mg, 293.9 μmol, 0.1 eq) and Na_2CO_3 (623.08 mg, 5.88 mmol, 2 eq). The mixture was stirred at 90 °C for 12 h. The reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.53) to yield 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (1.5 g, 2.8 mmol, 97.6% yield, 96% purity) as a yellow solid. LC-MS (ESI+) m/z 502.3 [M+H]+.

[0688] ***Step 8.*** To a solution of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (1.4 g, 2.68 mmol, 96% purity, 1 eq) in DCM (20 mL) was added TEA (406.65 mg, 4.02 mmol, 559.35 μL, 1.5 eq) and BLAH;pyridin-1-ium (856.83 mg, 2.68 mmol, 1 eq). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of water (50 mL), extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 5/1, TLC: PE/EtOAc = 5/1, R_f = 0.60) to yield 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (900 mg, 1.32 mmol, 49.18% yield, 85% purity) as a yellow solid. LC-MS (ESI+) m/z 580.3, 582.3 [M+H]+.

[0689] ***Step 9.*** To a solution of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (400 mg, 585.65 μmol, 85% purity, 1 eq) and phenylboronic acid (85.69 mg, 702.78 μmol, 1.2 eq) in dioxane (8 mL) and H_2O (2 mL) was added $Pd(dppf)Cl_2$ (42.85 mg, 58.56 μmol, 0.1 eq) and Na_2CO_3 (124.14 mg, 1.17 mmol, 2 eq). The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.73) to yield 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-7-phenyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (320 mg, 515.1 μmol, 87.9% yield, 93% purity) as a yellow solid. LC-MS (ESI+) m/z 578.4 [M+H]+.

[0690] ***Step 10.*** To a solution of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-7-phenyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (170 mg, 273.65 umol, 93% purity, 1 eq) in DCM (4 mL) was added TFA (1.22 g, 10.68 mmol, 790.50 μL, 39.0 eq) .The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition of saturation solution ($NaHCO_3$ 10 mL), extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-[4-(7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (150 mg, crude) as a yellow solid which was used in the next step without further purification. LC-MS (ESI+) m/z 448.3 [M+H]+.

[0691] ***Step 11.*** To a solution of 1-[4-(7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (150 mg, 335.14 μmol, N/A purity, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (167.76 mg, 335.14 μmol, 1 eq, TsOH) in DCM (6 mL) and MeOH (6 mL), after stirred 1 h was added sodium;triacetoxyboranuide (284.12 mg, 1.34 mmol, 4 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to yield a residue. The residue was purified by

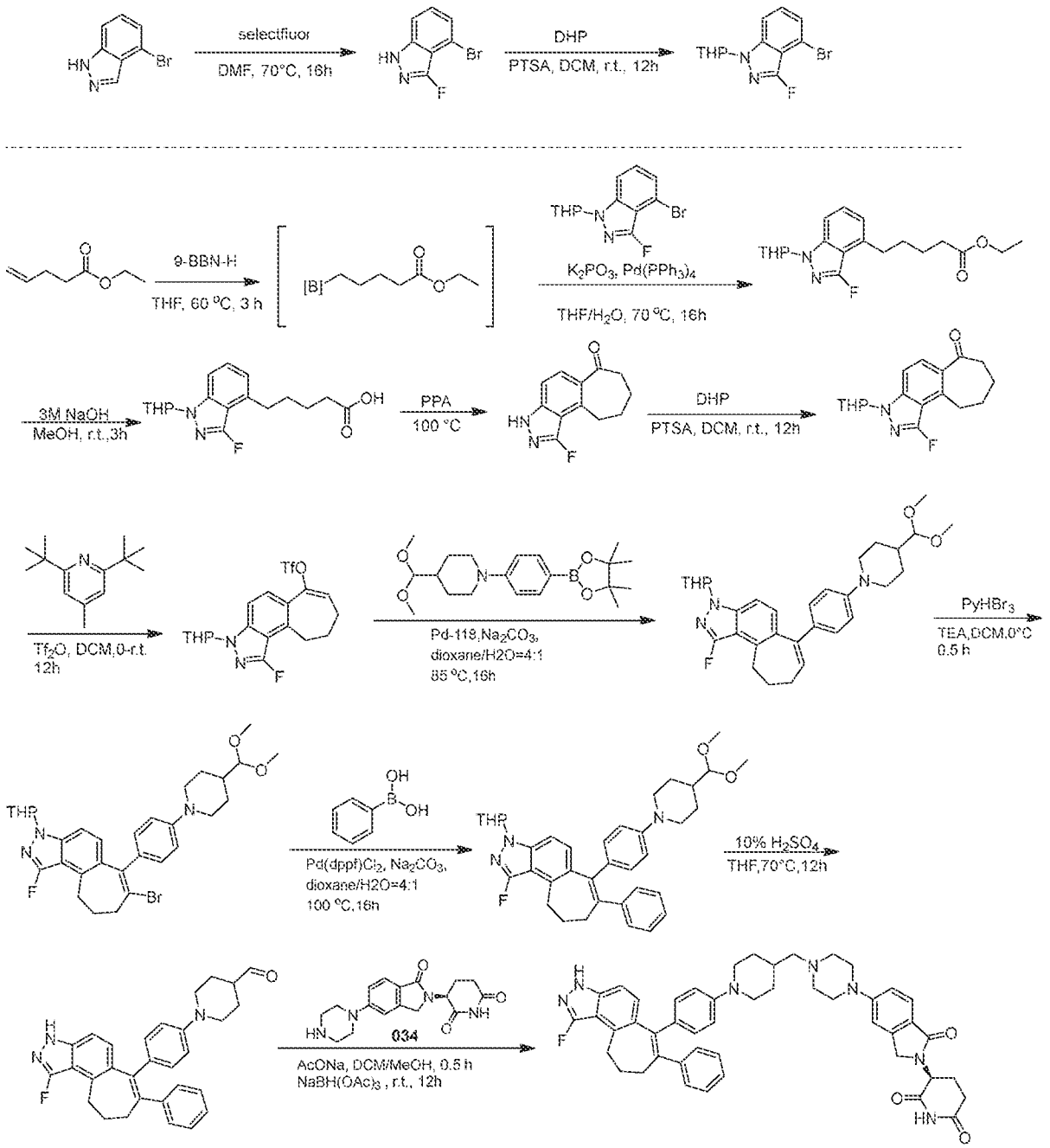
preparative HPLC (column: Boston Green ODS 150 * 30 mm * 5um; mobile phase: [water (FA) - ACN]; B%: 17%-47%,12min), followed by lyophilization to yield (3S)-3-[1-oxo-5-[4-[[1-[4-(7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione (81.4 mg, 103.73 μmol, 30.9% yield, 97.5% purity, 0.112HCOOH) was obtained as a white solid. LC-MS (ESI^+) m/z 760.3 $[M+H]^+$.

[0692] LCMS: calc. for C47H49N7O3: 759.4, found: $[M+H]^+$ 760.3.

[0693] HPLC: 97.50% purity at 220 nm.

[0694] ^1H NMR (400MHz, CD_3OD) δ = 8.19 (s, 1H), 8.07 (s, 1H), 7.73 - 7.69 (m, 1H), 7.27 (d, J=8.7 Hz, 1H), 7.22 - 7.15 (m, 6H), 7.11 (br d, J=7.2 Hz, 1H), 6.86 (d, J=8.7 Hz, 1H), 6.82 - 6.77 (m, 2H), 6.77 - 6.72 (m, 2H), 5.12 (dd, J=5.1, 13.3 Hz, 1H), 4.49 - 4.38 (m, 2H), 3.67 (br d, J=12.5 Hz, 2H), 3.58 - 3.47 (m, 2H), 3.29 - 3.08 (m, 6H), 2.94 - 2.84 (m, 1H), 2.83 - 2.69 (m, 3H), 2.52 - 2.31 (m, 6H), 2.20 - 2.00 (m, 2H), 1.91 (br d, J=13.5 Hz, 2H), 1.61 (br s, 1H), 1.54 - 1.42 (m, 2H), 1.29 (br s, 2H)

Example 6. Synthesis of (3S)-3-[5-[4-[[1-[4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-39



[0695] ***Step 1.*** A mixture of 4-bromo-1H-indazole (50 g, 253.77 mmol, 1 eq) and selectfluor (98.89 g, 279.14 mmol, 1.1 eq) was added in DMF (300 mL), and then the mixture was stirred at 70 °C for 12 hr. The residue was diluted with ethyl acetate (1 L) and extracted with solvent ethyl acetate (300 mL * 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (column: YMC Triart C18 250*80mm*7um; mobile phase: [water (FA)-ACN]; B%: 30%-85%, 30min). Compound 4-

bromo-3-fluoro-1H-indazole (20 g, 98.67 mmol, 38.88% yield, 53.0% purity) was obtained as a white solid. LC-MS (ESI+) m/z: 217.0 $(M+H)^+$

[0696] ***Step 2.*** A mixture of 4-methylbenzenesulfonic acid (1.73 g, 10.05 mmol, 0.3 eq), 4-bromo-3-fluoro-1H-indazole (7.2 g, 33.48 mmol, 1 eq), DHP (2.82 g, 33.48 mmol, 3.06 mL, 1 eq) was degassed in DCM (50 mL) and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 hr under N_2 atmosphere. The residue was diluted with DCM (200 mL) and extracted with solvent DCM (100 mL * 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=0% to 30%). Compound 4-bromo-3-fluoro-1-tetrahydropyran-2-yl-indazole (8.2 g, 27.41 mmol, 81.86% yield) was obtained as a white solid.

[0697] ***Step 3.*** A mixture of ethyl-4-pentenoate (5.83 g, 6 mL, 1.7 Eq, 45.5 mmol) , 9-Borabicyclo[3.3.1]nonane solution (5.55 g, 90.9 mL, 0.5 molar, 1.7 Eq, 45.5 mmol) in THF (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 3 h under N_2 atmosphere. And then was added 4-bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (8.00 g, 1 Eq, 26.7 mmol), Potassium phosphate, tribasic (17.0 g, 6.64 mL, 3 Eq, 80.2 mmol), Tetrakis(triphenylphosphine)palladium(o) (1.55 g, 0.05 Eq, 1.34 mmol) ,THF (20 mL) and H_2O (50 mL) in mixture solution. The mixture was stirred at 70 °C for 16 hour . The reaction mixture was quenched by addition of water (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0% to 50%). Compound ethyl 5-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)pentanoate (7 g, 0.02 mol, 80 %) was obtained as yellow oil. LC-MS (ESI+) m/z: 349.18 (M+H) +.

[0698] ***Step 4.*** A mixture of ethyl 5-(3-fluoro-1-tetrahydropyran-2-yl-indazol-4-yl)pentanoate (7 g, 20.09 mmol, 1 eq) and NaOH (3 M, 26.79 mL, 4 eq) was degassed in MeOH (50 mL), and then the mixture was stirred at 25 °C for 3 hr. The residue was quenched with 30 mL 2N HCl, diluted with H_2O (250 mL) and extracted with solvent ethyl acetate (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product 5-(3-fluoro-1-tetrahydropyran-2-yl-indazol-4-yl)pentanoic acid (4.46 g, 13.92 mmol, 69.29% yield) was used

into the next step without further purification. Compound 5-(3-fluoro-1-tetrahydropyran-2-yl-indazol-4-yl)pentanoic acid (4.46 g, 13.92 mmol, 69.29% yield) was obtained as a yellow solid.

[0699] ***Step 5.*** A mixture of 5-(3-fluoro-1-tetrahydropyran-2-yl-indazol-4-yl)pentanoic acid (4.46 g, 13.92 mmol, 1 eq), PPA (15 mL)in was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The residue was quenched with Saturated $NaHCO_3$ 80 ml and diluted with H_2O (250 mL) and extracted with solvent ethyl acetate (200 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 1-fluoro-7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (3 g, 13.74 mmol, 75% yield) was obtained as a white solid. LC-MS (ESI^+) m/z:219.09 $(M+H)^+$

[0700] ***Step 6.*** A mixture of 4-methylbenzenesulfonic acid (833.6 mg, 4.84 mmol, 0.3 eq) , 4-bromo-3-fluoro-1H-indazole (3.47 g, 16.14 mmol, 1 eq), DHP (2.72 g, 32.28 mmol, 2.95 mL, 2 eq), was degassed in DCM (15 mL) and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The residue was diluted with H_2O (100 mL) and extracted with solvent DCM (100 mL* 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=0% to 30%). Compound 4-bromo-3-fluoro-1-tetrahydropyran-2-yl-indazole (3.87 g, 12.94 mmol, 80.17% yield) was obtained as a white solid.

[0701] ***Step 7.*** To a solution of 2,6-ditert-butyl-4-methyl-pyridine (3.06 g, 14.88 mmol, 3 eq) was added 1-fluoro-3-tetrahydropyran-2-yl-7,8,9,10-tetrahydrocyclohepta[e]indazol-6-one (1.5 g, 4.96 mmol, 1 eq) in DCM (15 mL) at 0°C, after addition, the mixture was stirred at this remperture of 0.5h and then Tf_2O (2.10 g, 7.44 mmol, 1.23 mL, 1.5 eq) was added dropwise at 0°C, the resulting was stirred at 25°C for 12h. The residue was diluted with H_2O (100 mL) and extracted with DCM (100 mL ×2). The combined organic layers were washed with brine (100 mL), The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=0% to 30%). Compound (1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl) trifluoromethanesulfonate (1.1 g, 2.53 mmol, 51.04% yield) was obtained as a yellow solid. LC-MS (ESI+) m/z: 435.1 (M+H)+.

[0702] ***Step 8.*** A mixture of (1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl) trifluoromethanesulfonate (1.1 g, 2.53 mmol, 1 eq), 4-

(dimethoxymethyl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (914.84 mg, 2.53 mmol, 1 eq), Na_2CO_3 (805.16 mg, 7.60 mmol, 3 eq), Pd-118 (165.04 mg, 253.22 umol, 0.1 eq) in dioxane (20 mL) and H_2O (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 12 hr under N_2 atmosphere. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL ×2). The combined organic layers were washed with brine (100 mL), The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0% to 20%). Compound 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (960 mg, 1.85 mmol, 72.96% yield) was obtained as a red oil. LC-MS (ESI+) m/z: 520.2 $(M+H)^+$.

[0703] ***Step 9.*** A mixture of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (810 mg, 1.56 mmol, 1 eq), TEA (236.59 mg, 2.34 mmol, 325.44 uL, 1.5 eq), Py·HBr_3(498.52 mg, 1.56 mmol, 1 eq) in DCM (10 mL) was stirred at 0 °C for 2 hr. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL ×2). The combined organic layers were washed with brine (100 mL), The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0% to 20%). Compound 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (860 mg, 1.44 mmol, 92.18% yield) was obtained as a red oil. LC-MS (ESI+) m/z: 600.0 $(M+H)^+$.

[0704] ***Step 10.*** A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (400 mg, 668.29 umol, 1 eq), phenylboronic acid (81.48 mg, 668.29 umol, 1 eq), Pd(dppf)Cl_2(43.56 mg, 66.83 umol, 0.1 eq), Na_2CO_3 (212.49 mg, 2.00 mmol, 3 eq) in dioxane (8 mL) and H_2O(2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 16 h under N_2 atmosphere. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL ×2). The combined organic layers were washed with brine (100 mL). The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=0% to 20%). Compound 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-7-phenyl-3-

tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (350 mg, 587.50 umol, 87.91% yield) was obtained as a red oil. LC-MS (ESI+) m/z: 596.2 $(M+H)^+$.

[0705] ***Step 11.*** A mixture of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-7-phenyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (250 mg, 419.64 umol, 1 eq) in H_2SO_4 (10 mL, 10% purity) and THF (10 mL) , and then the mixture was stirred at 70 °C for 5 h. The residue was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL ×2). The combined organic layers were washed with brine (50 mL), The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. Compound 1-[4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (160 mg, 343.67 umol, 81.90% yield) was obtained as a red oil. LC-MS (ESI+) m/z: 484.1 $(M+H_2O)^+$.

[0706] ***Step 12.*** To a solution of 1-[4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (154.04 mg, 330.87 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (165.62 mg, 330.87 umol, 1 eq, p-TSA salt) in DCM (2 mL), MeOH (2 mL) was added AcONa (81.43 mg, 992.61 umol, 3 eq) was stirred at 20 °C for 30 mins, Then Acetic acid (91.36 mg, 330.87 umol, 87.01 uL, 1 eq) and $NaBH(OAc)_3$ (140.25 mg, 661.74 umol, 2 eq) was added .The mixture was stirred at 25 °C for 12 h. The resulting solution was extracted with DCM (50 mL ×1). The combined organic layers were washed with brine (100 mL), The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN];B%:32%-62%,7min). Compound (3S)-3-[5-[4-[[1-[4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (9.5 mg, 12.21 umol, 3.69% yield) was obtained as a yellow solid.

[0707] LCMS: calc. for $C_{47}H_{48}FN_7O_3$: 778.2, found: $[M+H]^+$ 779.2.

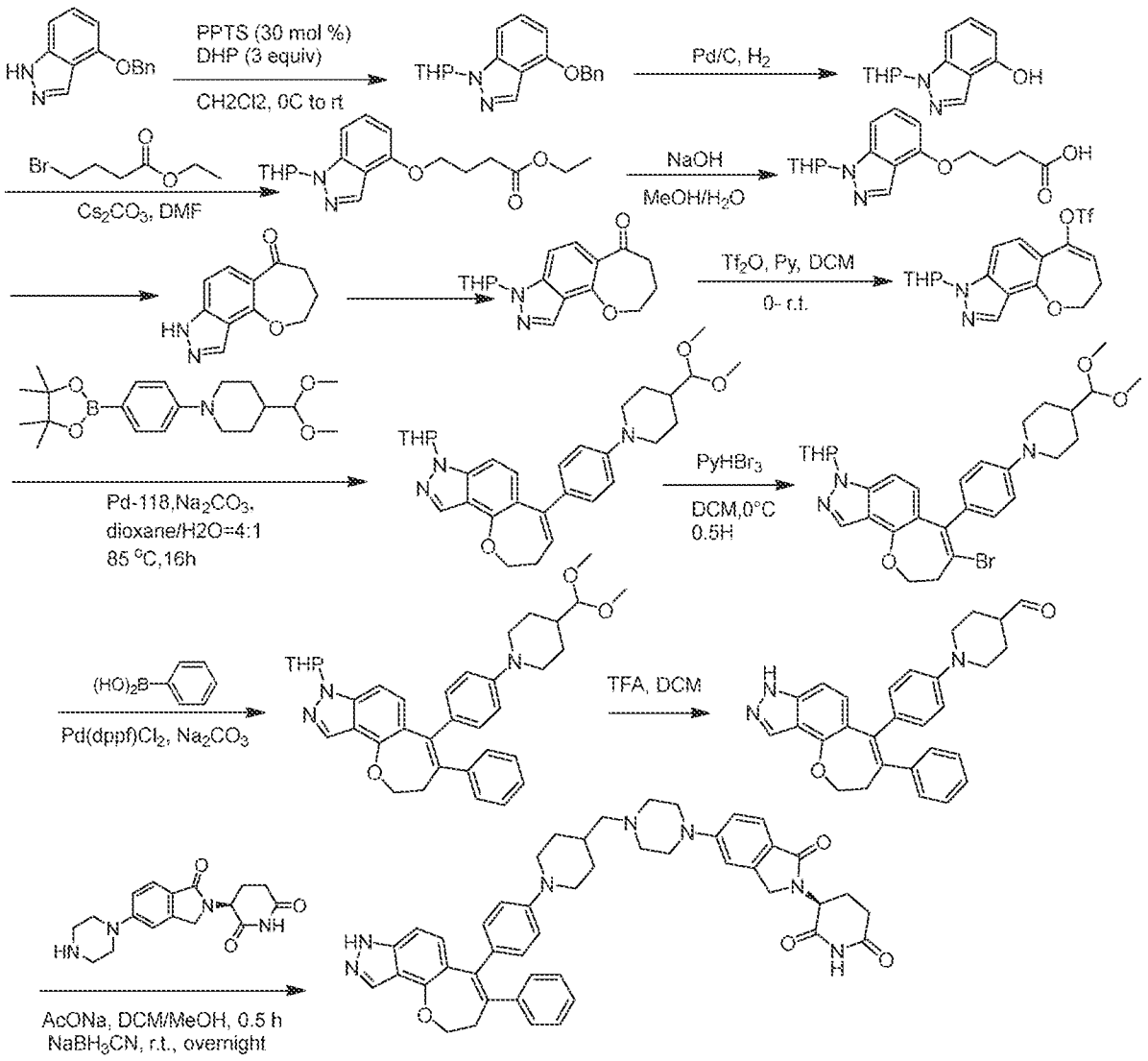
[0708] HPLC: 98.377% purity at 220 nm.

[0709] ^1H NMR 1H NMR (400 MHz, DMSO-d_6) δ = 12.66 - 12.39 (m, 1H), 11.03 - 10.82 (m, 1H), 8.37 - 8.31 (m, 0.467H), 7.55 - 7.48 (m, 1H), 7.24 - 7.17 (m, 5H), 7.15 -7.09 (m, 1H), 7.07 - 7.03 (m, 2H), 6.84 - 6.79 (m, 1H), 6.71 - 6.62 (m, 4H), 5.15 - 4.92 (m, 1H), 4.36 - 4.27 (m, 1H), 4.25 - 4.15 (m, 1H), 3.64 - 3.58 (m, 2H),3.28 (br s, 5H), 3.10 - 3.02 (m, 2H), 2.94 - 2.83 (m, 1H),

2.63 - 2.53 (m, 4H), 2.35 - 2.30 (m, 1H), 2.28 - 2.16 (m, 6H), 2.00 - 1.93 (m,1H), 1.82 - 1.73 (m,2H), 1.70 - 1.60 (m, 1H), 1.31 - 1.10 (m, 3H)

[0710] SFC: retention time, 2.878 min; Area, 95.463%; method: IE_MeOH_DEA_MeCN_50_1ML_15MIN_5CM.lcm.

Example 7. Synthesis of (S)-3-(1-oxo-5-(4-((1-(4-(4-phenyl-3,8-dihydro-2H-oxepino[2,3-e]indazol-5-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, I-40



[0711] ***Step 1.*** To a mixture of 4-bromo-1H-indazole (10 g, 1 Eq, 51 mmol) and 3,4-dihydro-2H-pyran (6.4 g, 6.956 mL, 1.5 Eq, 76 mmol),QA-5220 (2.6 g, 0.2 Eq, 10 mmol), REACTANTin DCM (200 mL).The mixture was stirred at 25 °C for 8h. TLC (ethyl acetate: petroleum ether=1:3iodide fuming) showed that the new spot was observed .The mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product. The aqueous

phase was extracted with DCM (200 mL) (200mL*2). The combined organic phase was washed with brine (200mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography(Petroleum/ether/Ethylacetate=10/1)to afford 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (10.8 g, 29 mmol, 58 %, 76% Purity) as yellow liquid.LC-MS (ESI^+) m/z: 283.1$(M+H)^+$.

[0712] ***Step 2.*** To a mixture of 4-(benzyloxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (15.00 g, 1 Eq, 48.64 mmol) in EtOH (100 mL) was dd Pd/C (5.176 g, 10% Wt, 0.1 Eq, 4.864 mmol) in one portion at 25°C. The mixture was sittred a 25 °C under 15 PSI for 16h. LCMS（TLC） showed the reaction was completed. The mixture was filtered through celite plate, and the filtrate was concentrated in reduced pressure to give the product.ethyl)piperidine as white solid LC-MS (ESI+) m/z: 219.3 (M+H)+.

[0713] ***Step 3.*** To a mixture of 1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-ol (10.6 g, 1 Eq, 48.6 mmol)Cesium carbonate (47.5 g, 11.7 mL, 3 Eq, 146 mmol) and ETHYL-4-BROMOTBUTYRATE (14.2 g, 10.4 mL, 1.5 Eq, 72.8 mmol) in HCN (50 mL) .The mixture was stirred at 25 °C for 4h. LCMS（TLC） showed the reaction was completed. The mixture was concentrated in reduced pressure at 25°C. The aqueous phase was extracted with ethyl acetate (100 mL*2). The combined organic phase was washed with brine (100 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1) to afford ethyl 4-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)butanoate (13.9 g, 37.5 mmol, 77.1 %, 89.56% Purity)as white solid.

[0714] ***Step 4.*** To a mixture ofethyl 4-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)butanoate (13.00 g, 1 Eq, 39.11 mmol) and NaOH (6.3 g, 4 Eq, 156.4 mmol) in CH3OH (60 mL)H2O (20 L)was added {reagent.1}.The mixture was stirred for 4 hours. HPLC（TLC） showed the reaction was completed. The mixture concentrated in reduced pressure at 25 °C. Adjust PH to 3 with hydrochloric acid. The aqueous phase was extracted with ethyl acetate (10mL*2). The combined organic phase was washed with brine (10mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1) to afford 4-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)butanoic acid (10.5 g, 33 mmol, 85 %, 96% Purity) as yellow oil

[0715] ***Step 5.*** 4-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)butanoic acid (10.5 g, 1 Eq, 34.5 mmol) was added ppp (20 mL) in one portion at 25°C under N2.The mixture heated to 100°C and stirred for 4 hours. HPLC（TLC）showed the reaction was completed. The mixture was cooled to 25°C and concentrated in reduced pressure at 25 °C. The aqueous phase was extracted with ethyl acetate (100 mL*2). The combined organic phase was washed with brine (50mL*20), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1) to afford 3,4-dihydro-2H-oxepino[2,3-e]indazol-5(8H)-one (2.45 g, 9.6 mmol, 28 %, 79% Purity) as yellow solid.

[0716] ***Step 6.*** To a mixture of 3,4-dihydro-2H-oxepino[2,3-e]indazol-5(8H)-one (500 mg, 1 Eq, 2.47 mmol)Dihydropyran (624 mg, 675 µL, 3 Eq, 7.42 mmol) andp-Toluenesulfonic acid (42.6 mg, 38.3 µL, 0.1 Eq, 247 µmol) in DCM (5 mL) .The mixture was stirred at 25 °C for 2h. HPLC（TLC）showed the reaction was completed. The aqueous phase was extracted with ethyl acetate (50mL*2). The combined organic phase was washed with brine (50*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1) to afford 8-(tetrahydro-2H-pyran-2-yl)-3,4-dihydro-2H-oxepino[2,3-e]indazol-5(8H)-one (367 mg, 1.2 mmol, 49 %, 95% Purity) as yellow solid.

[0717] ***Step 7.*** To a mixture of 3,4-dihydro-2H-oxepino[2,3-e]indazol-5(8H)-one (1.90 g, 1 Eq, 9.40 mmol),p-Toluenesulfonic acid (162 mg, 146 µL, 0.1 eq, 940 µmol) and Dihydropyran (2.37 g, 2.56 mL, 3 Eq, 28.2 mmol) in DCM (5 mL) .The mixture was stirred at 25 °C for 2h. TLC showed the reaction was completed. The aqueous phase was extracted with ethyl acetate (100 mL*2). The combined organic phase was washed with brine (50mL*2), dried with anhydrous Na2SO4, filtered and concentrated in va cuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1) to afford 8-(tetrahydro-2H-pyran-2-yl)-3,4-dihydro-2H-oxepino[2,3-e]indazol-5(8H)-one (1.225 g, 3.7 mmol, 39 %, 86% Purity) as yellow solid

[0718] ***Step 8.*** To a mixture of 8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazol-5-yl trifluoromethanesulfonate (600 mg, 1 eq., 1.43 mmol),4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (777 mg, 1.5 Eq, 2.15 mmol),Na2CO3 (456 mg, 3 Eq, 4.30 mmol) and 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (93.5 mg, 0.1 Eq, 143 µmol) in dioxane (8 mL)and h2o (2 mL) was added

{reagent.1} in one portion at 25°C under N2.The mixture heated to 90°C and stirred for 8 hours. HPLC（TLC）showed the reaction was completed. The mixture was cooled to 25 °C and concentrated in reduced pressure at X25°C. The aqueous phase was extracted with ethyl acetate (100 mL*1). The combined organic phase was washed with brine(50mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. Theresidue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=4/1) to afford 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazole (270 mg, 536 μmol, 37.4 %) as yellow solid

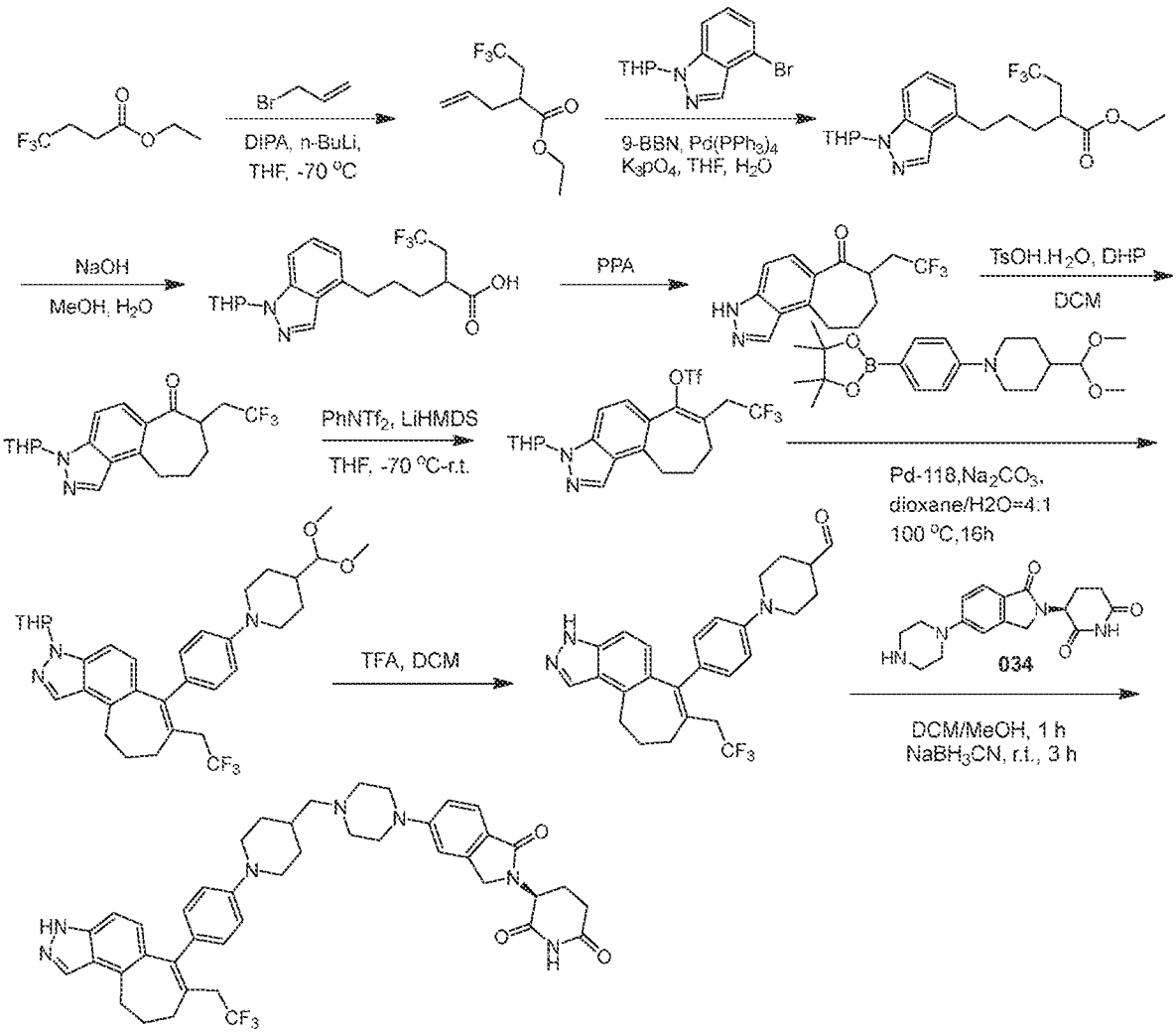
[0719] ***Step 9.*** To a solution of 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazole (520 mg, 1 Eq, 1.03 mmol),triethylamine (209 mg, 288 μL, 2 Eq, 2.06 mmol) in DCM (10 mL) was added {reagent.1} .The mixture was stirred at 0°C for 1 hour. Than add triethylamine (209 mg, 288 μL, 2 Eq, 2.06 mmol)to the mixture and stirred for 0.5 hour .LC-MS showed Reactant 1 was consumed completely and one main peak with desired MS was detectedThe reaction mixture was quenched by addition Na2CO3 50 mL at 25 °C, and then diluted with whate 50 mL and extracted with Ethyl acetate 50 mL (50mL * 2). The combined organic layers were washed with brine 50 mL (50mL * 1), dried over [Drying agent], filtered and concentrated under reduced pressure to give 4-bromo-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazole (475 mg, 673 μmol, 65.2 %, 82.5% Purity) was obtained as a white solid.

[0720] ***Step 10.*** A mixture of 4-bromo-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazole, phenylboronic acid , PdCl2(dppf) , Na2CO3 in Dioxane was degassed and purged with N2 for 3 times, and then the mixture was stirred at 90°C for 8 hours under N2 atmosphere. LC-MS showed 0% of Reactant 1 was remained. Only one new peaks were shown on LC-MS and 89% of desired compound was detected. The reaction mixture was partitioned between brine 100 mL and Ethyl acetate 100 mL. The organic phase was separated, washed with whate 50 mL (50 mL *2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1) to give 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-4-phenyl-8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazolewas obtained as a yellow solid

[0721] *Step 11.* To a solution of 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-4-phenyl-8-(tetrahydro-2H-pyran-2-yl)-3,8-dihydro-2H-oxepino[2,3-e]indazole in TFAand DCM .The mixture was stirred at 25°C for 2 hours. LC-MS showed 0% of Reactant 1 was remained. Several new peaks were shown on LC-MS and 86.15% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent and used for next step directly.

[0722] *Step 12.* To a solution of 1-(4-(4-phenyl-3,8-dihydro-2H-oxepino[2,3-e]indazol-5-yl)phenyl)piperidine-4-carbaldehyde (60.00 mg, 1.00 Eq, 133.5 µmol)in DCE (3 mL) was added (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (90.00 mg, 1.348 Eq, 179.9 µmol)and Sodium triacetoxyborohydride (56.57 mg, 39.6 µL, 2.00 Eq, 266.9 µmol). The mixture was adjusted to pH 5-6 with 4-methylmorfolin (40.50 mg, 44 µL, 3.00 Eq, 400.4 µmol).The mixture was stirred at 25 °C for 8 hour . LCMS showed the reaction was completed. The mixture was concentrated and then water (30 mL) was added. The mixture was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na2SO4, filtered and concentrated. The residue was purified by HPLC (Column Welch Xtimate C18 150*25mm*5um Condition water(NH4HCO3)-ACN Begin B 31 End B 51 Gradient Time(min) 11 100%B Hold Time(min) 2 FlowRate(ml/min) 25) to give (S)-3-(1-oxo-5-(4-((1-(4-(4-phenyl-3,8-dihydro-2H-oxepino[2,3-e]indazol-5-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (25.2 mg, 31.4 µmol, 23.5 %, 94.86% Purity) as a white solid

Example 8. Synthesis of (3S)-3-[1-oxo-5-[4-[[1-[4-[7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione, I-41



[0723] ***Step 1.*** To a solution of DIPA (7.73 g, 76.41 mmol, 10.80 mL) in THF (100 mL) was added n-BuLi (2.5 M, 28.21 mL) dropwise at 0 °C under N_2 atmosphere and stirred at 0 °C for 0.5 h. Then the mixture was cooled to -70 °C and ethyl 4,4,4-trifluorobutanoate (10 g, 58.78 mmol) in THF (100 mL) was added dropwise at -70 °C and stirred at -70 °C for 0.5 h. 3-Bromoprop-1-ene (8.53 g, 70.53 mmol) in THF (10 mL) was added dropwise at -70 °C and stirred at -70 °C for 3h. The reaction was quenched with sat.aq. NH_4Cl (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 8%) to give the product of ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (7.7 g, 56.1% yield) as yellow liquid.

[0724] ***Step 2.*** To a solution of ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (7.7 g, 36.63 mmol) in THF (40 mL) was added 9-BBN (0.5 M, 80.59 mL) under N_2 atmosphere and stirred at 60 °C for 3 h. After addition, the mixture was cooled to 25 °C, then H_2O (20 mL), 4-bromo-1-tetrahydropyran-2-yl-indazole (10.30 g, 36.63 mmol), $Pd(PPh_3)_4$ (4.23 g, 3.66 mmol) and K_3PO_4 (11.66 g, 54.95 mmol) was added and stirred at 70 °C for 16 h. The reaction was quenched with sat.aq. NH_4Cl (100 mL) and extracted with EtOAc (80mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 10%) to give the product of ethyl 5-(1-tetrahydropyran-2-ylindazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoate (7.1 g, 42.3% yield) as yellow oil. LC-MS (ESI^+) m/z: 413.4 $(M+H)^+$.

[0725] ***Step 3.*** To a solution of ethyl 5-(1-tetrahydropyran-2-ylindazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoate (7.1 g, 15.49 mmol) in MeOH (80 mL) and H_2O (20 mL) was added NaOH (1.55 g, 38.73 mmol). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue which was diluted with water (100 mL) and extracted with DCM (80 mL x 2). The aqueous phase was adjust pH to 2 with 2 M HCl, and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the product of 5-(1-tetrahydropyran-2-ylindazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoic acid (6.1 g, 97.3% yield) as a yellow solid. LC-MS (ESI^+) m/z: 385.2 $(M+H)^+$.

[0726] ***Step 4.*** A solution of 5-(1-tetrahydropyran-2-ylindazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoic acid (6.1 g, 15.08 mmol) in PPA (60 mL) was stirred at 110 °C for 16 h. The reaction mixture was diluted with water (1000 mL) and extracted with EtOAc (300 mL x 3). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 10%) to give the product of 7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (3 g, 69.8% yield) as yellow gum. LC-MS (ESI^+) m/z: 283.1 $(M+H)^+$.

[0727] ***Step 5.*** To a solution of 7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (3 g, 10.52 mmol) in DCM (30 mL) was added DHP (1.33 g, 15.77 mmol, 1.44 mL) and TsOH H_2O (1.00 mg, 5.26 μmol). The mixture was stirred at 25 °C for 16 h. The solvent was removed to yield a residue. The residue was purified by flash silica gel

chromatography (ethyl acetate in petroleum ether= 0% to 10%) to give the product of 3-tetrahydropyran-2-yl-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6-one (3.5 g, 88.9% yield) as yellow gum. LC-MS (ESI^+) m/z: 367.2 $(M+H)^+$.

[0728] ***Step 6.*** To a solution of 3-tetrahydropyran-2-yl-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6-one (1.5 g, 4.01 mmol) in THF (20 mL) was added LiHMDS (1 M, 6.02 mL) at -70 °C under N_2 atmosphere and stirred at -70 °C for 0.5 h. After addition, 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (2.15 g, 6.02 mmol) in THF (5 mL) was added dropwise at -70 °C and stirred at 25 °C for 16 h. The reaction mixture was quenched by addition sat.aq. NH_4Cl (30 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 8%) to give the product of [3-tetrahydropyran-2-yl-7-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl] trifluoromethanesulfonate (800 mg, 32.0% yield) as a yellow solid. LC-MS (ESI^+) m/z: 499.2 $(M+H)^+$.

[0729] ***Step 7.*** A mixture of [3-tetrahydropyran-2-yl-7-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl] trifluoromethanesulfonate (800 mg, 1.28 mmol), 4-(dimethoxymethyl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (603.06 mg, 1.67 mmol), Na_2CO_3 (340.23 mg, 3.21 mmol), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (83.68 mg, 128.40 μmol) in dioxane (4 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The reaction mixture was quenched by water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 15%) to give the product of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-7-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-cyclohepta[e]indazole (700 mg, 89.6% yield) as a yellow solid. LC-MS (ESI^+) m/z: 584.4 $(M+H)^+$.

[0730] ***Step 8.*** To a solution of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-7-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-cyclohepta[e]indazole (300 mg, 493.42 μmol) in DCM (3 mL) was added TFA (1.11 g, 9.72 mmol, 720.00 μL). The mixture was stirred at 25 °C for 16 h. The solvent was removed to yield a residue which was added H_2O (3

mL) and ACN(5 mL), followed by lyophilization to give the product of 1-[4-[7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (240 mg, crude) as a yellow solid. LC-MS (ESI^+) m/z: 454.2 $(M+H)^+$.

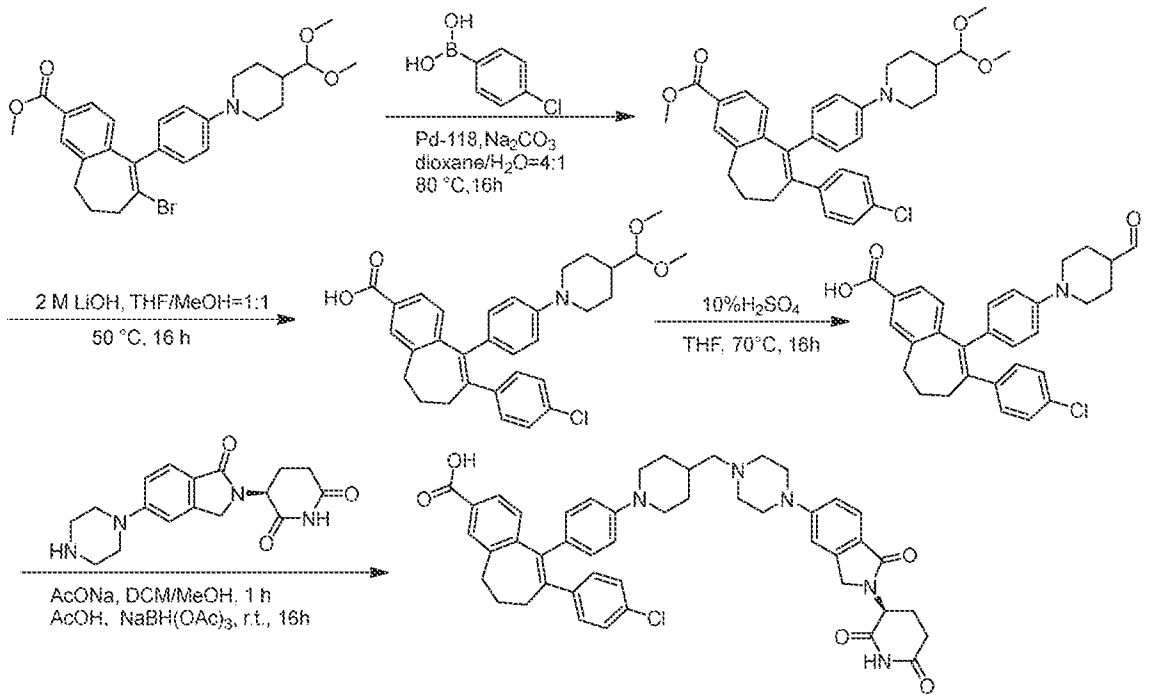
[0731] ***Step 9.*** To a solution of 1-[4-[7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (240 mg, 529.22 μmol) in MeOH (5 mL) and DCM (5 mL) was added (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (201.34 mg, 529.22 μmol, TSOH) and stirred at 25 °C for 1 h. Then $NaBH_3CN$ (166.29 mg, 2.65 mmol) was added and stirred at 25 °C for 3 h. The solvent was removed to yield a residue. The residue was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 22%-52%,12min), followed by lyophilization to yield (3S)-3-[1-oxo-5-[4-[[1-[4-[7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione (54.9 mg, 13.2% yield, 0.25FA) as a white solid. LC-MS (ESI^+) m/z: 766.5 $(M+H)^+$.

[0732] LCMS: calc. for $C_{43}H_{46}F_3N_7O_3$: 765.3, found: $[M+H]^+$ 766.5.

[0733] HPLC: 99.45% purity at 254 nm.

[0734] ^{1}HNMR (500MHz, MeOD-d4): δ 8.31 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.16 - 7.08 (m, 2H), 7.00 (s, 4H), 6.82 (d, J = 8.7 Hz, 1H), 5.11 (dd, J = 5.2, 13.3 Hz, 1H), 4.47 - 4.36 (m, 2H), 3.75 (d, J = 12.2 Hz, 2H), 3.46 (s, 4H), 3.20 (q, J = 11.1 Hz, 2H), 3.09 (t, J = 7.0 Hz, 2H), 2.98 - 2.82 (m, 5H), 2.81 - 2.71 (m, 3H), 2.59 (br s, 2H), 2.52 - 2.37 (m, 3H), 2.21 - 2.11 (m, 3H), 1.94 (d, J = 14.0 Hz, 3H), 1.50 - 1.36 (m, 2H)

Example 9. Synthesis of 6-(4-chlorophenyl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-44



[0735] ***Step 1.*** A mixture of Methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (400 mg, 1 Eq, 778 μmol) , 4-ChlorobenzeneboronicAcid (122 mg, 1 Eq, 778 μmol) , Sodium carbonate (247 mg, 3 Eq, 2.33 mmol) ,1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (50.7 mg, 0.1 Eq, 77.8 μmol) in 1,4-Dioxane (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hour under N_2 atmosphere. LCMS showed 60% desired MS was detected. Then the reaction was cooled to room temperature. The mixture was treated with H_2O (50 mL), extracted with EtOAc (50 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~20% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuo to give methyl 8-(4-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (410 mg, 751 μmol, 96.6 %)as a yellow solid. LC-MS (ESI^+) m/z: 546.1 $(M+H)^+$

[0736] ***Step 2.*** To a solution of methyl 8-(4-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (320 mg, 1 Eq, 586 μmol) in THF

(2 mL) and MeOH (2 mL) was added lithium hydroxide (140 mg, 2.93 mL, 2 molar, 10 Eq, 5.86 mmol) .The mixture was stirred at 50 °C for 16 hour . TLC (petroleum ether/ethyl acetate=1:1, Rf=0.3) showed new spot was formed. The mixture was adjusted to pH=~4 with 1N HCl. 50 mL H_2O was added, and the mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 8-(4-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (300 mg, 564 µmol, 96.2 %) as yellow oil. LC-MS (ESI^+) m/z: 532.2 $(M+H)^+$.

[0737] ***Step 3.*** To a solution of 8-(4-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (190 mg, 1 Eq, 357 µmol) in 10% H_2SO_4 (10 mL)and THF (10 mL).The mixture was stirred at 70 °C for 3 hour . TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4, UV) showed one main new spot was observed. The solvent was removed under vaccum. The aqueous solution was added $NaHCO_3$ to adjust pH=6. The reaction mixture was quenched by addition H_2O 50 mL at 25°C, and then diluted with H_2O 50 mL and extracted with Ethyl acetate 50 mL (50 mL * 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give 8-(4-chlorophenyl)-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (150 mg, 309 µmol, 86.4 %) as yellow oil. LC-MS (ESI+) m/z: 486.18 (M+H)+

[0738] ***Step 4.*** A mixture of 6-(4-chlorophenyl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (150 mg, 308.64 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (101.35 mg, 308.64 umol, 1 eq) and sodium; acetate (75.96 mg, 925.93 umol, 3 eq) and acetic acid (55.60 mg, 925.93 umol, 52.96 uL, 3 eq) in DCM (4 mL) and MeOH (4 mL) at 25 °C for 1 hour, then $NaBH(OAc)_3$(130.83 mg, 617.28 umol, 2 eq) was added to the mixture and was stirred at 25 °C for 16 hour. The reaction was treated with H_2O (20 mL), extracted with EtOAc (30 mL*3). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep. HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%:32%-62%,7min). The aqueous phase was lyophilized to dryness to give 6-(4-chlorophenyl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (52.9 mg, 66.26 umol, 21.47% yield) as a yellow solid.

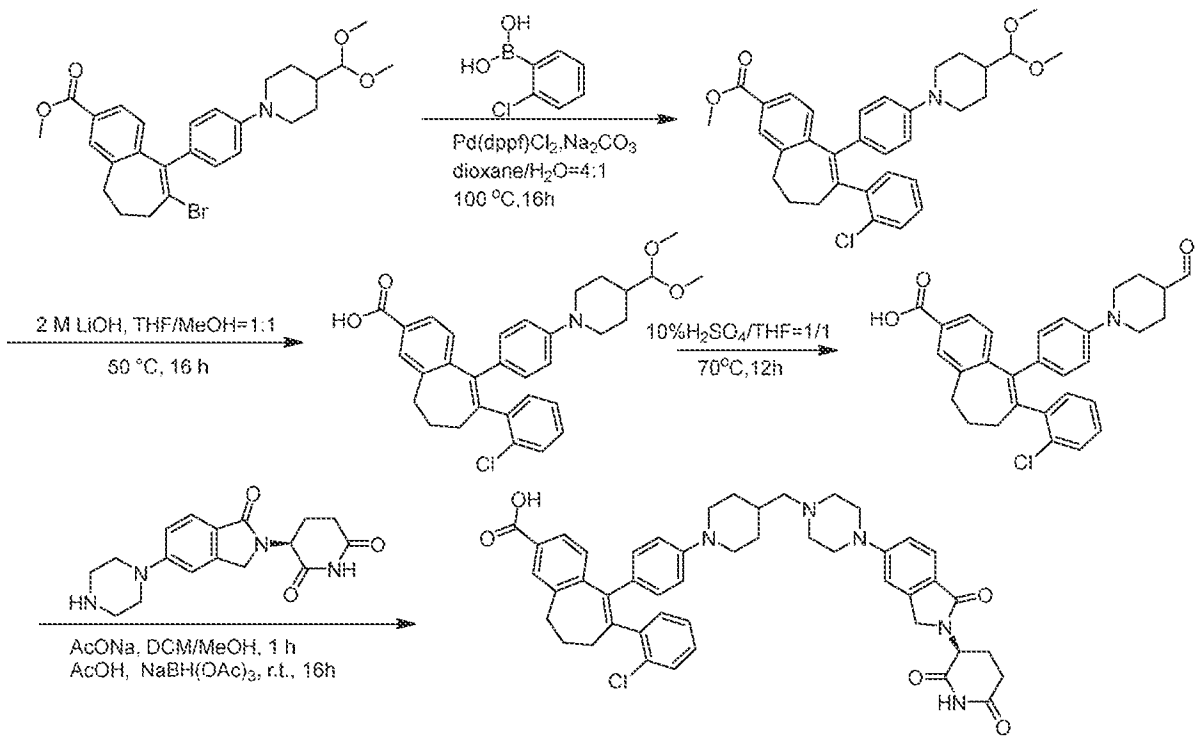
[0739] LC-MS (ESI+) m/z: 798.2 (M+H)+

[0740] HPLC: 98.735%, purity at 220 nm.

[0741] SFC: retention time, 2.610 min; Area, 99.404%; method: IE_MeOH_DEA_MeCN_50_1ML_15MIN_5CM.lcm

[0742] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 - 10.91 (m, 1H), 8.25 - 8.17 (m, 0.205H), 7.95 - 7.84 (m, 1H), 7.79 - 7.67 (m, 1H), 7.57 - 7.46 (m, 1H), 7.33 - 7.24 (m, 2H), 7.22 - 7.13 (m, 2H), 7.11 - 7.00 (m, 2H), 6.94 - 6.83 (m, 1H), 6.75 - 6.56 (m, 4H), 5.12 - 4.97 (m, 1H), 4.40 - 4.28 (m, 1H), 4.25 - 4.12 (m, 1H), 3.72 - 3.52 (m, 3H), 3.35 (br s, 5H), 2.95 - 2.77 (m, 3H), 2.65 - 2.53 (m, 5H), 2.41 - 2.32 (m, 1H), 2.29 - 2.19 (m, 4H), 2.14 - 2.05 (m, 2H), 2.01 - 1.89 (m, 1H), 1.84 - 1.74 (m, 2H), 1.72 - 1.60 (m, 1H), 1.27 - 1.08 (m, 2H).

Example 10. Synthesis of (S)-8-(2-chlorophenyl)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-43



[0743] ***Step 1.*** A mixture of methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (400 mg, 1 Eq, 778 µmol) ,2-ChlorophenylboronicAcid (122 mg, 1 Eq, 778 µmol) , Sodium carbonate (247 mg, 144 µL, 3 Eq, 2.33 mmol) ,1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (50.7 mg, 0.1 Eq, 77.8 µmol) in 1,4-Dioxane (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. TLC(petroleum

ether/ethyl acetate=5/1,Rf=0.4) The reaction mixture was quenched by addition H_2O 50 mL at 20°C, and then diluted with H_2O 50 mL and extracted with Ethyl acetate (50 mL * 2). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 50~50% Ethylacetate/Petroleum ethergradient @ 30 mL/min) and the organic layer was concentrated in vacuo to give methyl 8-(2-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (340 mg, 535 µmol, 68.8 %, 85.859% Purity)as a yellow solid.

[0744] LC-MS (ESI^+) m/z: 546.1 $(M+H)^+$.

[0745] ***Step 2.*** To a solution of methyl 8-(2-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (340 mg, 1 Eq, 623 µmol) in THF (3 mL) and MeOH (3 mL) was added lithium hydroxide (149 mg, 3.11 mL, 2 M, 10 Eq, 6.23 mmol) .The mixture was stirred at 50 °C for 16 hour . The reaction mixture was concentrated under reduced pressure to give 8-(2-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (240 mg, 451 µmol, 72.4 %) as a white solid.LC-MS (ESI+) m/z: 532.1 (M+H) +.

[0746] ***Step 3.*** A solution of 8-(2-chlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (240 mg, 1 Eq, 451 µmol) in 10% H_2SO_4 (7 mL) and THF (7 mL) was stirred at 70 °C for 12 hour to give a yellow suspension. The solvent was removed under vaccum. The aqueous solution was added $NaHCO_3$ to adjust pH=6. The reaction mixture was quenched by addition H_2O 50 mL at 25°C, and then diluted with H_2O 50 mL and extracted with Ethyl acetate 50 mL (50 mL * 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give 8-(2-chlorophenyl)-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (200 mg, 312 µmol, 69.1 %, 75.79% Purity) as a yellow oil.

[0747] LC-MS (ESI^+) m/z: 486.18 $(M+H)^+$.

[0748] ***Step 4.*** To a solution of 8-(2-chlorophenyl)-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (200 mg, 1 Eq, 412 µmol), (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, TsOH salt(206 mg, 1 Eq, 412 µmol) in DCM (3 mL), MeOH (3 mL) was added Sodium acetate (101 mg, 3 Eq, 1.23 mmol) was stirred at r.t. for 60 mins, Then Sodium triacetoxyborohydride (174 mg, 2 Eq, 823

μmol) and Acetic acid (74.1 mg, 71.0 μL, 3 Eq, 1.23 mmol) was added .The mixture was stirred at r.t. for 16 hour. The reaction was treated with H_2O (20 mL), extracted with EtOAc (20 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 29%-59%, 7min) to give (S)-8-(2-chlorophenyl)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (48.7 mg, 60.7 μmol, 14.8 %, 99.53% Purity) was obtained as a white solid.

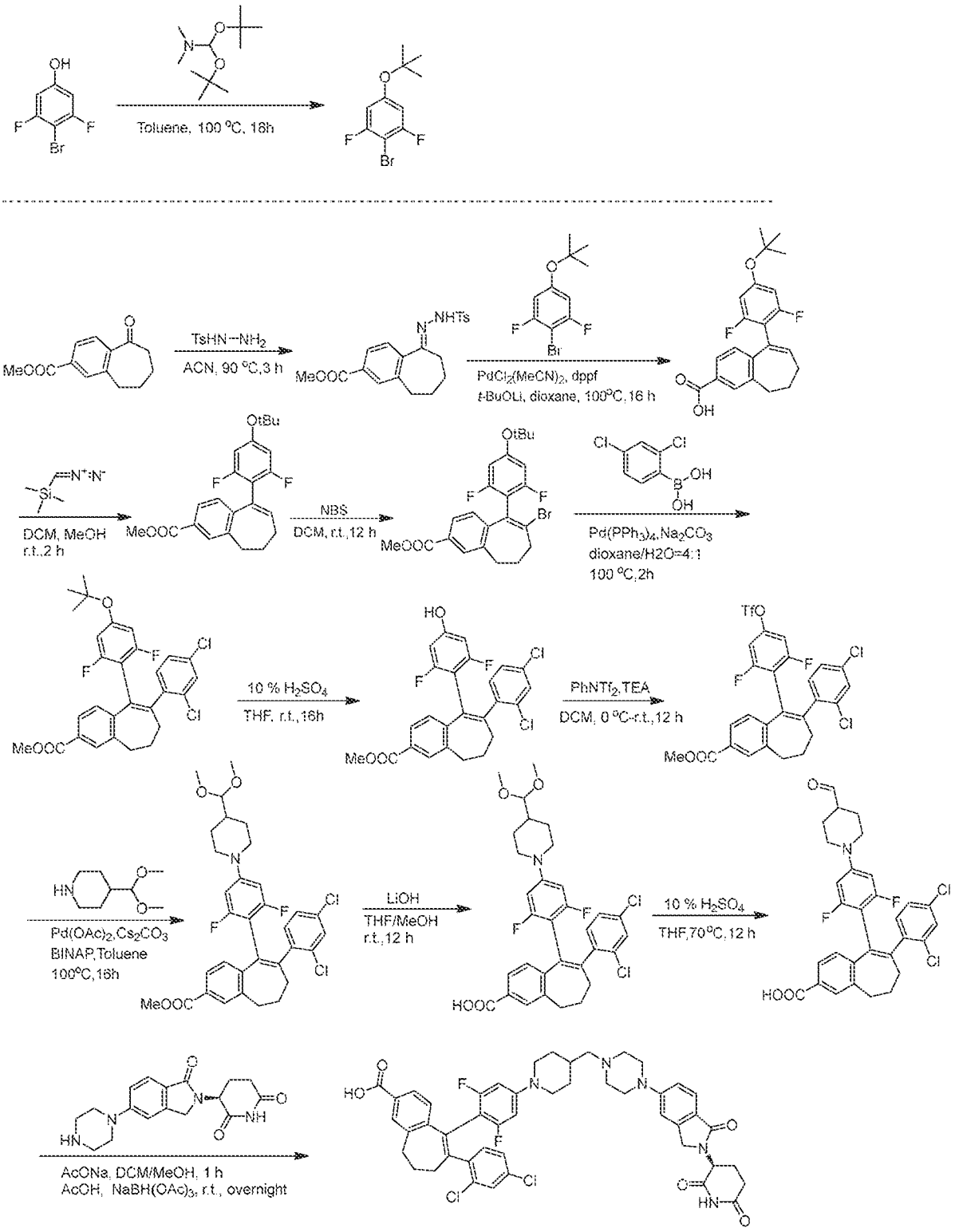
[0749] LCMS: calc. for $C_{47}H_{48}ClO_5N_5$: 797.33, found: $[M+H]^+$ 798.1.

[0750] HPLC: 99.530% purity at 220 nm.

[0751] ^1H NMR (400 MHz, DMSO-d_6) δ= 11.01 - 10.91 (m, 1H), 8.23 - 8.19 (m, 0.132H), 7.94 - 7.87 (m, 1H), 7.79 - 7.72 (m, 1H), 7.58 - 7.49 (m, 1H), 7.46 - 7.39 (m, 1H), 7.26 - 7.15 (m, 3H), 7.10 - 7.01 (m, 2H), 6.94 - 6.86 (m, 1H), 6.70 - 6.60 (m, 4H), 5.11 - 4.99 (m, 1H), 4.39 - 4.28 (m, 1H), 4.26 - 4.16 (m, 1H), 3.67 - 3.56 (m, 2H), 3.42 (br s, 6H), 2.98 - 2.84 (m, 3H), 2.71 - 2.58 (m, 2H), 2.71 - 2.55 (m, 4H), 2.43 - 2.27 (m, 2H), 2.24 - 2.09 (m, 6H), 2.04 - 1.91 (m, 1H), 1.83 - 1.72 (m, 2H), 1.71 - 1.60 (m, 1H), 1.23 - 1.05 (m, 2H)

[0752] SFC: retention time, 2.750 min; Area, 99.868 %; method: IF_MeOH_DEA_MeCN_50_1ML_15MIN_10CM

Example 11. Synthesis of (S)-8-(2,4-dichlorophenyl)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-46



[0753] *Step 1.* To a mixture of 4-bromo-3,5-difluorophenol (3 g, 1 Eq, 0.01 mol) and 1,1-Ditert-butoxy-N,N-dimethyl-methanamine (30 g, 3 mL, 10 Eq, 0.1 mol) in Toluene (60 mL) , then the mixture was stirred at 100 °C for 18 hour. TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.5, UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 2-bromo-5-(tert-butoxy)-1,3-difluorobenzene (2.87 g, 10.8 mmol, 80 %) as a yellow oil. LC-MS (ESI^+) m/z: 265.10 $(M+H)^+$

[0754] *Step 2.* To a mixture of methyl 5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (4 g, 1 Eq, 0.02 mol) and 4-Methylbenzenesulfonic acid hydrazide (4 g, 1.2 Eq, 0.02 mol) in Acetonitrile (80 mL) , then the mixture was stirred at 90 °C for 3 hour. TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc).The desired fractions were collected, and concentrated to dryness in vacuo to give methyl (E)-5-(2-tosylhydrazineylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (7.4 g, 18 mmol, 100 %, 95.379% purity) as a white solid. LCMS showed 95.379% desired MS. LC-MS (ESI^+) m/z: 387.0 $(M+H)^+$.

[0755] *Step 3.* A mixture of methyl (E)-5-(2-tosylhydrazineylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (4.18 g, 1 Eq, 10.8 mmol) , 2-bromo-5-(tert-butoxy)-1,3-difluorobenzene (2.87 g, 1 Eq, 10.8 mmol) , $PdCl_2(MeCN)_2$ (281 mg, 0.1 Eq, 1.08 mmol), dppf (1.20 g, 0.2 Eq, 2.16 mmol) and lithium 2-methylpropan-2-olate (2.60 g, 3 Eq, 32.4 mmol) in 1,4-Dioxane (100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate = 5:1, Rf = 0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 9-(4-(tert-butoxy)-

2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (1.5 g, 2.2 mmol, 21 %, 55.317% purity) as a white solid. LC-MS (ESI^+) m/z: 373.0 $(M+H)^+$.

[0756] ***Step 4.*** To a mixture of (Trimethylsilyl)diazomethane solution (1.58 g, 6.93 mL, 2 molar, 3 Eq, 13.9 mmol) in DCM (15 mL) and MeOH (15 mL), and 9-(4-(tert-butoxy)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (1.72 g, 1 Eq, 4.62 mmol) was added at 25 °C. Then the mixture was stirred at 25 °C for 2 hour. TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with DCM (100 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give methyl 9-(4-(tert-butoxy)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (1.8 g, 4.7 mmol, 100 %) as a white solid. LC-MS (ESI^+) m/z: 387.0 $(M+H)^+$.

[0757] ***Step 5.*** To a mixture of methyl 9-(4-(tert-butoxy)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (650 mg, 1 Eq, 1.68 mmol) and 1-bromopyrrolidine-2,5-dione (329 mg, 1.1 Eq, 1.85 mmol) in DCM (12 mL) at 0 °C for 1 hour , then the mixture was stirred at 25 °C for 12 hour. LCMS showed 100% desired MS was detected. TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with DCM (100 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give methyl 8-bromo-9-(4-(tert-butoxy)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (640 mg, 1.38 mmol, 81.8 %, 100% purity)as a yellow solid. LC-MS (ESI^+) m/z: 464.9 $(M+H)^+$.

[0758] ***Step 6.*** To a solution of (2,4-dichlorophenyl)boronic acid (375 mg, 1.5 Eq, 1.97 mmol) and methyl 8-bromo-9-(4-(tert-butoxy)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (610 mg, 1 Eq, 1.31 mmol) in Dioxane (10 mL)and Water (2.0 mL) was added Na_2CO_3 (417 mg, 3 Eq, 3.93 mmol) and $Pd(PPh_3)_4$ (151 mg, 0.1 Eq, 131 µmol) at 25 °C. The mixture was stirre at 80 °C for 2 hour under N_2. TLC (petroleum ether: ethyl acetate = 5:1, Rf = 0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (100 mL*2). The organic layer was washed with brine (100

mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give methyl 9-(4-(tert-butoxy)-2,6-difluorophenyl)-8-(2,4-dichlorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (600 mg, 890 µmol, 67.9 %, 78.846% Purity) as a white solid. LCMS showed 78.846% desired MS. LC-MS (ESI^+) m/z: 530.9 $(M+H)^+$.

[0759] ***Step 7.*** To a solution of methyl 9-(4-(tert-butoxy)-2,6-difluorophenyl)-8-(2,4-dichlorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (550 mg, 1 Eq, 1.03 mmol) in 10%H_2SO_4 (6 mL) and THF (6 mL) was stirred at 70 °C for 16 hour . TLC (petroleum ether: ethyl acetate = 3:1, R_f = 0.4 UV) showed one main new spot was observed. The reaction was adjust to pH=8 with aq.$NaHCO_3$ (30 mL).Then the mixture was added water(30 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give methyl 8-(2,4-dichlorophenyl)-9-(2,6-difluoro-4-hydroxyphenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (430 mg, 681 µmol, 65.8 %, 75.289% purity) as a yellow solid. LC-MS (ESI^+) m/z: 475.1 $(M+H)^+$.

[0760] ***Step 8.*** To a solution of methyl 8-(2,4-dichlorophenyl)-9-(2,6-difluoro-4-hydroxyphenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (430 mg, 1 Eq, 905 µmol) and TEA (915 mg, 1.26 mL, 10 Eq, 9.05 mmol) in DCM (30 mL) was added Phenyl triflimide (970 mg, 3 Eq, 2.71 mmol) in DCM (30 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 12 hour. TLC (Petroleum ether/EtOAc = 3/1) showed the starting material was remained and new spots were observed. The mixture was quenched by H_2O (50 mL) at 0 °C. Then the mixture was warmed to room temperature, and extracted with DCM 60 mL (20 mL * 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Petroleum ether/EtOAc = 0~50%) to give methyl 8-(2,4-dichlorophenyl)-9-(2,6-difluoro-4-(((trifluoromethyl)sulfonyl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (590 mg, 638 µmol, 70.5 %, 65.670% Purity) as a colorless oil. LC-MS (ESI^+) m/z: 607.0 $(M+H)^+$.

[0761] ***Step 9.*** A mixture of methyl 8-(2,4-dichlorophenyl)-9-(2,6-difluoro-4-(((trifluoromethyl)sulfonyl)oxy)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (580 mg, 1 Eq, 955 µmol) , 4-(dimethoxymethyl)piperidine (182 mg, 192 µL, 1.2 Eq, 1.15 mmol),

$Pd(OAc)_2$ (10.7 mg, 0.05 Eq, 47.7 μmol), Cs_2CO_3 (622 mg, 2 Eq, 1.91 mmol), BINAP (59.5 mg, 0.1 Eq, 95.5 μmol) in Toluene (14 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate = 5:1, R_f = 0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (100 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white soild. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give methyl 8-(2,4-dichlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (310 mg, 431 μmol, 45.2 %, 85.754% purity) as a white solid. LCMS showed 85.754% desired MS. LC-MS (ESI^+) m/z: 616.3 $(M+H)^+$.

[0762] ***Step 10.*** To a solution of methyl 8-(2,4-dichlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (260 mg, 1 Eq, 422 μmol) in THF (7 mL) and MeOH (7 mL) was added lithium hydroxide (40.4 mg, 2 M, 4 Eq, 1.69 mmol). The mixture was stirred at 25 °C for 16 hour. TLC (petroleum ether: ethyl acetate = 3:1, R_f=0.3 UV) showed one main new spot was observed. Then the mixture was added 2 mL 1M HCl and water (50 mL) and extracted with ethyl acetate (2×50 mL).The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 8-(2,4-dichlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (260 mg, 327 μmol, 77.5 %, 75.733% purity) as a yellow solid. LC-MS (ESI^+) m/z: 602.2 $(M+H)^+$.

[0763] ***Step 11.*** To a solution of 8-(2,4-dichlorophenyl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (260 mg, 1 Eq, 432 μmol) in 10%H_2SO_4 (4 mL) and THF (4 mL) was stirred at 70 °C for 3 hour. TLC (petroleum ether: ethyl acetate = 1:1, R_f = 0.4 UV). The reaction was adjust to pH=8 with aq.$NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 8-(2,4-dichlorophenyl)-9-(2,6-difluoro-4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (260 mg, 324 μmol, 75.1 %, 69.317% purity) as a yellow solid. LC-MS (ESI^+) m/z: 556.2 $(M+H)^+$.

[0764] *Step 12.* To a solution of 8-(2,4-dichlorophenyl)-9-(2,6-difluoro-4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (130 mg, 1 Eq, 234 µmol), (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, TsOH salt (117 mg, 1 Eq, 234 µmol) in DCM (4 mL) and MeOH (4 mL) was added Sodium acetate (57.5 mg, 3 Eq, 701 µmol) was stirred at 25 °C for 60 mins, Then Sodium triacetoxyborohydride (99.0 mg, 2 Eq, 467 µmol) and acetic acid (42.1 mg, 40.3 µL, 3 Eq, 701 µmol) was added .The mixture was stirred at 25 °C for 16 hour. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 31%-51%,7min) to give (S)-8-(2,4-dichlorophenyl)-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)-2,6-difluorophenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (55.8 mg, 64.2 mmol, 27.5 %, 100% purity) was obtained as a white solid. LC-MS (ESI^+) m/z: 866.3 $(M+H)^+$.

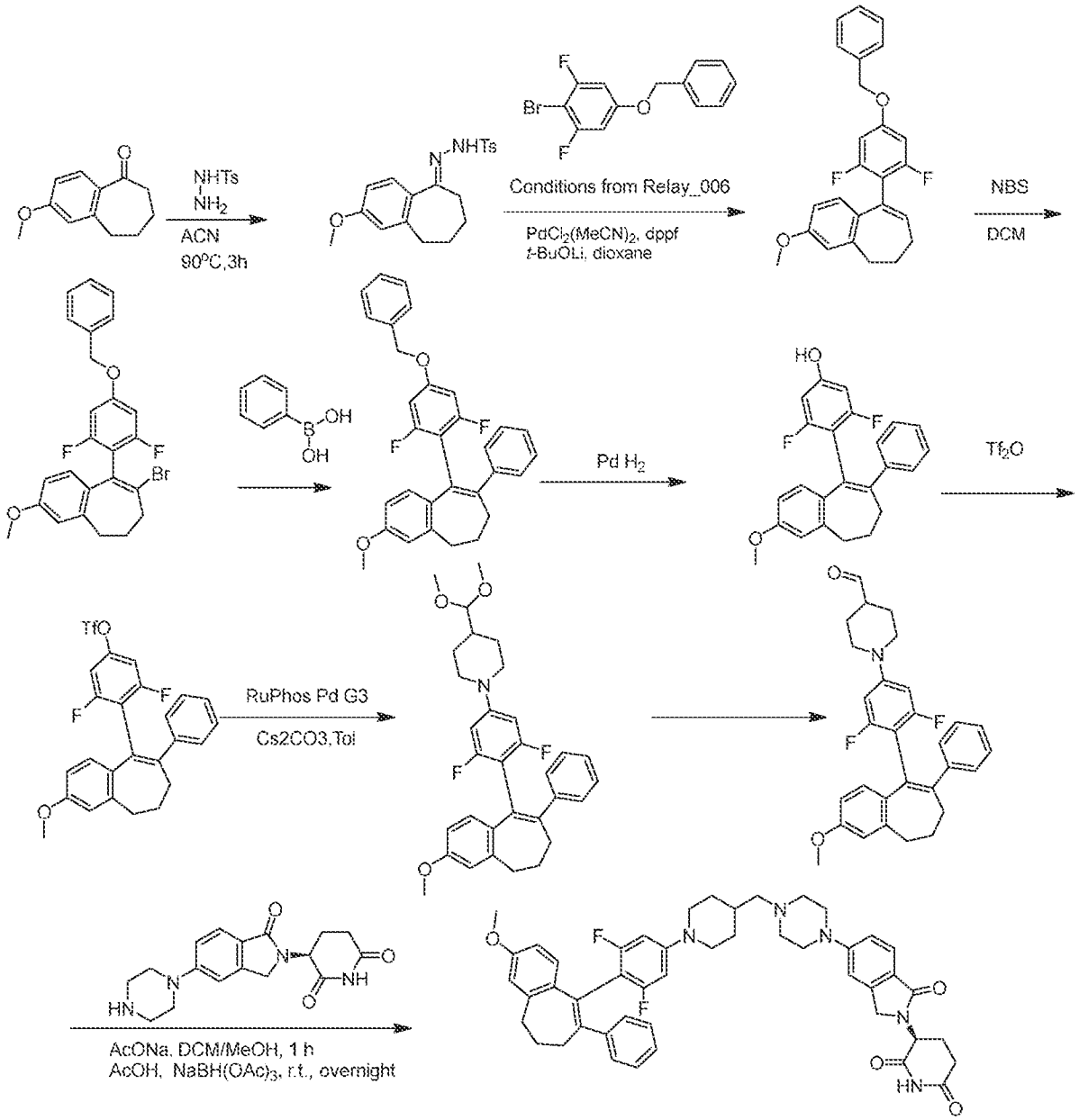
[0765] LCMS: calc. for $C_{47}H_{45}Cl_2F_2N_5O_5$: 868.80, found: [M+H]+ 868.3.

[0766] HPLC: 100.00% purity at 220 nm.

[0767] 1H NMR (400 MHz, DMSO-d_6) δ = 10.95 (s, 1H), 8.15 - 8.14 (m, 0.117H), 7.90 (d, J = 1.5 Hz, 1H), 7.77 (dd, J = 1.7, 8.0 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.33 (dd, J = 2.1, 8.3 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.10 - 7.03 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 6.43 (s, 1H), 5.05 (dd, J = 5.1, 13.3 Hz, 1H), 4.33 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.0 Hz, 1H), 3.69 (br d, J = 11.8 Hz, 2H), 3.30 - 3.21 (m, 6H), 2.98 - 2.85 (m, 3H), 2.73 - 2.54 (m, 4H), 2.41 - 2.28 (m, 2H), 2.27 - 2.11 (m, 6H), 1.96 (br s, 1H), 1.75 (br d, J = 11.4 Hz, 3H), 1.10 (br d, J = 11.6 Hz, 2H)

[0768] SFC: retention time, 1.579 min; Area, 100.000%; method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

Example 12. Synthesis of (S)-3-(5-(4-((1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-47



[0769] ***Step 1.*** To a mixture of 2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2.00 g, 1 Eq, 10.5 mmol) and 4-methylbenzenesulfonohydrazide (2.00 g, 1.02 Eq, 10.7 mmol) in EtOH (50 mL) .The mixture was stirred 75 °C for 3h. TLC showed the reaction was completed. The mixture was cooled to 25 °C and concentrated in reduced pressure. The aqueous phase was extracted with ethyl acetate (200 mL*2). The combined organic phase was washed with brine (100 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200

mesh silica gel, Petroleum ether/Ethyl acetate=3/1) to afford (E)-N'-(2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ylidene)-4-methylbenzenesulfonohydrazide (3.5 g, 8.3 mmol, 79 %, 85.25% Purity) as yellow solid.

[0770] ***Step 2.*** To a mixture of (E)-N'-(2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ylidene) -4-methylbenzenesulfonohydrazide (3.00 g, 1.2 Eq, 8.37 mmol) and 5-(benzyloxy)-2-bromo-1,3-difluorobenzene (2.09 g, 1 Eq, 6.97 mmol),Lithium 2-methyl-2-propanolate (1.68 g, 1.95 mL, 3 Eq, 20.9 mmol),Reactant IV (1.02 g, 0.2 Eq, 1.39 mmol) in Dioxane (100 mL) was added ,reagent in one portion at 25°C and degrssed 3 times under N2.The mixture was stirred at 75 °C for 8 hours. HPLC（TLC）showed the reaction was completed. The mixture was cooled to 20 °C and concentrated in reduced pressure at 20 °C. The residue was poured into ice-water (200 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (200 mL*2). The combined organic phase was washed with brine (50 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5/1) to afford 9-(4-(benzyloxy)-2,6-difluorophenyl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulene (1.05 g, 2.60 mmol, 37.3 %, 97.263% Purity)as yellow solid.

[0771] ***Step 3.*** To a mixture of 9-(4-(benzyloxy)-2,6-difluorophenyl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulene (500 mg, 1 Eq, 1.27 mmol) and NBS (227 mg, 1 Eq, 1.27 mmol) in DCM (20 mL) .The mixture was stirred at 25 °C for 1 hour. HPLC（TLC）showed the reaction was completed. The mixture was cooled to 20 °C and concentrated in reduced pressure at 20 °C. The residue was poured into ice-water (200 mL) and stirred for 50 min. The aqueous phase was extracted with ethyl acetate (200 mL*2). The combined organic phase was washed with brine (50 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5/1) to afford 9-(4-(benzyloxy)-2,6-difluorophenyl)-8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulene (550 mg, 1.12 mmol, 87.9 %, 95.99% Purity) as yellow solid.

[0772] ***Step 4.*** To a mixture of 9-(4-(benzyloxy)-2,6-difluorophenyl)-8-bromo-3-methoxy-6,7-dihydro -5H-benzo[7]annulene (500 mg, 1 Eq, 1.06 mmol) and phenylboronic acid (155 mg, 1.2 Eq, 1.27 mmol),PdCl2(dppf) (77.6 mg, 0.1 Eq, 106 μmol),K2CO3 (440 mg, 3 Eq, 3.18 mmol) in Dioxane (30 mL)and h2o (0.2 mL)was added reagent in one portion at 25°C and degressed 3 times under N2 .The mixture was stirred at 25 °C for 5 min, then heated to 85°C and stirred for 8

hours. HPLC（TLC）showed the reaction was completed. The mixture was cooled to 20 °C and concentrated in reduced pressure at 35°C. The residue was poured into ice-water (100 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (100 mL*2). The combined organic phase was washed with brine (50mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5/1) to afford (9-(4-(benzyloxy)-2,6-difluorophenyl)-3- methoxy-6,7-dihydro-5H-benzo[7]annulen-8-yl)argon (428 mg, 0.91 mmol, 86 %, 92% Purity) as yellow solid

[0773] ***Step 5.*** To a mixture of 9-(4-(benzyloxy)-2,6-difluorophenyl)-3-methoxy-8-phenyl-6,7 -dihydro-5H-benzo[7]annulene (1.00 g, 1 Eq, 2.13 mmol),Pd/C (114 mg, 0.5 Eq, 1.07 mmol) in MeOH (100 mL) was added {reagent.1} in one portion at 25°C under H2.The mixture was stirred at 25 °C for 1 hours. HPLC（TLC）showed the reaction was completed. The reaction solution was filtered with diatomaceous earth The mixture concentrated in reduced pressure at 25°C to afford 4-(8-argio-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3,5- difluorophenol (687 mg, 1.77 mmol, 83.0 %, 87.98% Purity)as yellow solid

[0774] ***Step 6.*** To a mixture of 9-(4-(benzyloxy)-2,6-difluorophenyl)-3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulene (700 mg, 1 Eq, 1.49 mmol),DIEA (579 mg, 781 µL, 3 Eq, 4.48 mmol) and Trifluoromethanesulfonic Anhydride (506 mg, 301 µL, 1.2 Eq, 1.79 mmol) in DCM (20 mL) was added {reagent.1} in one portion at 0°C .The mixture was stirred at 0 °C for 1 hours. TLC showed the reaction was completed. The mixture was concentrated in reduced pressure at 30 °C. The residue was poured into water (50 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (50mL*2). The combined organic phase was washed with brine (20 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=10/1) to afford 4-(8-argio-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl) -3,5-difluorophenyl trifluoromethanesulfonate (690 g, 1.07 mol, 71900 %, 73.65% Purity) as yellow oil

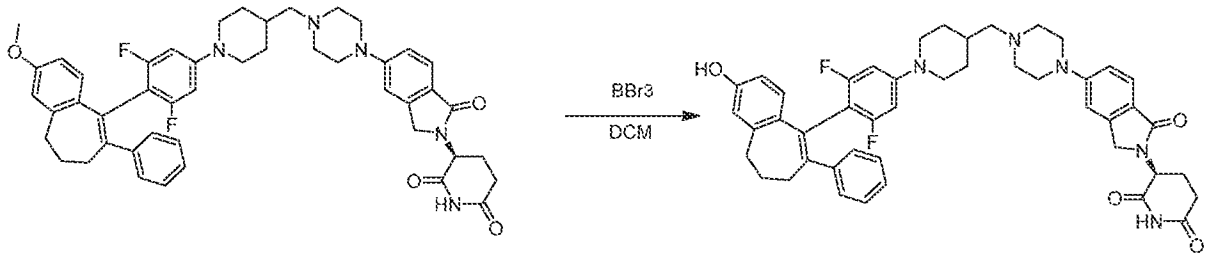
[0775] ***Step 7.*** To a mixture of 3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenyl trifluoromethanesulfonate (600.00 mg, 1 Eq, 1.1754 mmol),4-(dimethoxymethyl)piperidine (224.58 mg, 1.2 Eq, 1.4104 mmol),Cs2CO3 (1.1489 g, 3 Eq, 3.5261 mmol) and (2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (196.61 mg, 0.2 Eq, 235.07 µmol) in Dioxane (25

mL) was added reagent in one portion at 25°C and dugressed 3 times under N2 .The mixture was stirred at 25 °C for 1 min, then heated to 90 °C and stirred for 8 hours. TLC showed the reaction was completed. The mixture was cooled to 20 °C and concentrated in reduced pressure at 25 °C. The residue was poured into water (100 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (50 mL*2). The combined organic phase was washed with brine (20 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=10/1) to afford 1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (428 mg, 532 µmol, 45.2 %, 64.550% Purity)as yellow oil.

[0776] ***Step 8.*** To a mixture of 1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen -9-yl)phenyl)-4-(dimethoxymethyl)piperidine (300 mg, 1 Eq, 577 µmol) and Trifluoroacetic acid (329 mg, 220 µL, 5 Eq, 2.89 mmol) in DCM (15 mL) .The mixture was stirred at 25 °C for 2 hours. TLC showed the reaction was completed. The mixture concentrated in reduced pressure at 25 °C. The residue was poured into water (50mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (50 mL*2). The combined organic phase was washed with brine (20mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=10/1) to afford 1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenyl)piperidine-4-carbaldehyde (295 mg, 302 µmol, 52.3 %, 48.507% Purity) as yellow oil.

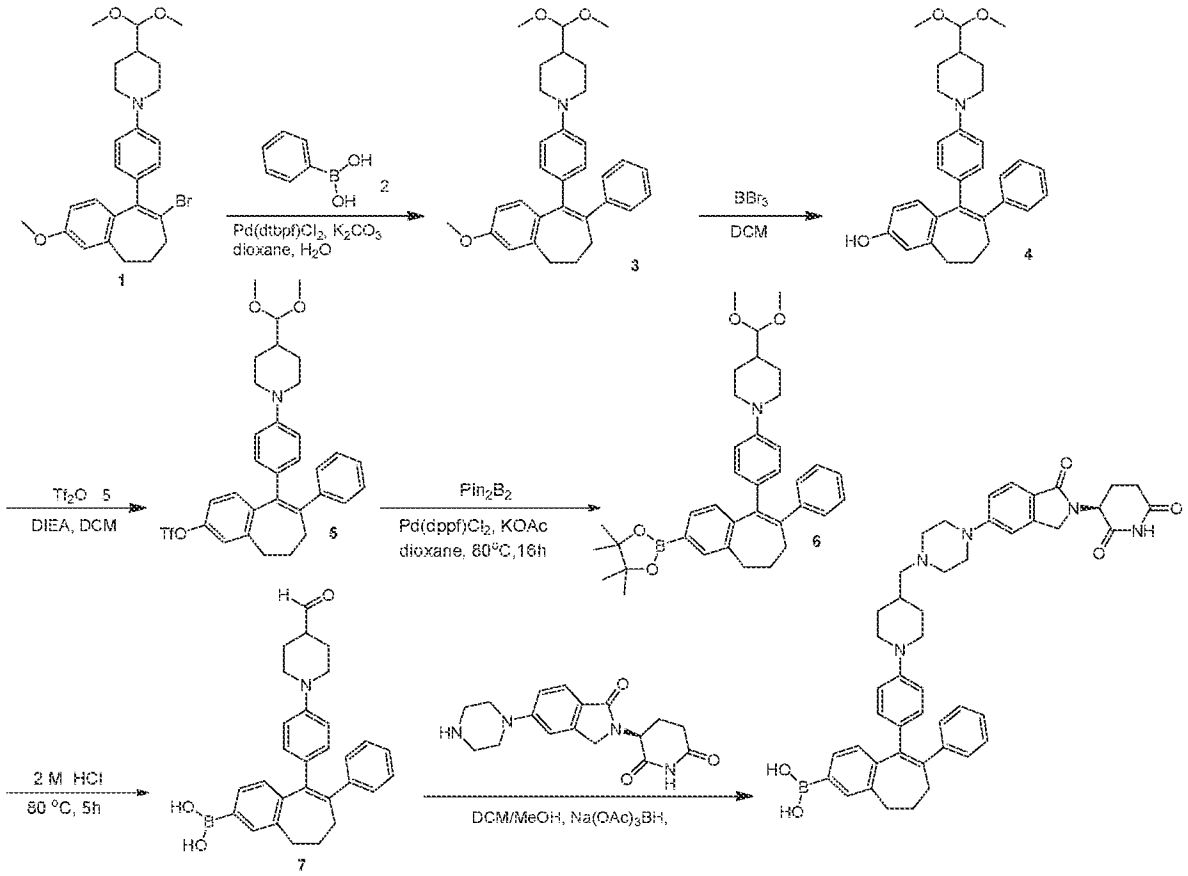
[0777] ***Step 9.*** To a mixture of 1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenyl)piperidine-4-carbaldehyde (100 mg, 1 Eq, 211 µmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (83.2 mg, 1.2 Eq, 253 µmol) in DCM (20 mL),Adjust the PH to about 6 with 4-methylmorfolin (64.1 mg, 70 µL, 3 Eq, 633 µmol).The mixture was stirred at 25°C for 10 min, then add Sodium triacetoxyborohydride (134 mg, 93.9 µL, 3 Eq, 633 µmol) and stirred for 3 hours. TLCshowed the reaction was completed. The mixture was reduced pressure at 25°C. The residue was further purification by pre-HPLC to give (S)-3-(5-(4-((1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (28.5 mg, 36.3 µmol, 17.2 %, 100% Purity) The white solid was re-crystallized from water, dried by lyophilization to give a white solid.

Example 13. Synthesis of (S)-3-(5-(4-((1-(3,5- difluoro-4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-48



[0778] To a mixture of (S)-3-(5-(4-((1-(3,5-difluoro-4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (40.00 mg, 1 Eq, 50.89 μmol) in DCM (5 mL) was added tribromoborane (63.75 mg, 5 Eq, 254.5 μmol) in one portion at 0°C .The mixture was stirred at 0 °C for 2 hours. TLC showed the reaction was completed. The mixture was poured into ice-MeOH (w/w = 1/1) (50 mL) and stirred for 10 min. The mixture was cooled to 25 °C and concentrated in reduced pressure at 25 °C The aqueous phase was extracted with ethyl acetate (50 mL*2). The residue was further purification by pre-HPLC to give (S)-3-(5-(4-((1-(3,5- difluoro-4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (19.5 mg, 25.3 μmol, 49.6 %, 100% Purity)

Example 14. Synthesis of (S)-(9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-3-yl)boronic acid, I-45



[0779] ***Step 1.*** To a mixture of compound 1(2.00 g, 4.11 mmol, 1.0 eq.), compound 2 (602 mg, 4.93 mmol, 1.2 eq.), K_2CO_3 (1.70 g, 12.3 mmol, 3.0 eq.) in Dioxane (20 mL) was added $Pd(dbpf)Cl_2$ (451 mg, 617 μmol, 0.15 eq.) in one portion at 25 °C under N_2. The mixture was stirred and heated to 85 °C and stirred for 6 hours. LCMS showed the reaction was completed. The mixture was cooled to 20 °C and concentrated in reduced pressure at 35 °C. The residue was poured into water (200 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (100mL x 2). The combined organic phase was washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=10/1) to afford compound 3 (1.85 g, 3.48 mmol, 84.5 % yield) as a yellow solid. LC-MS (ESI+) m/z: 484.3(M+H) +.

[0780] ***Step 2.*** To a mixture of compound 3 (1.89 g, 3.91 mmol, 1.0 eq.) in DCM (10 mL) was added tribromoborane (1.47 g, 565 μL, 5.86 mmol, 1.5 eq.) in one portion at 0 °C. The mixture

was stirred at 0 °C for 1 hours. LCMS showed the reaction was completed. The mixture was poured into MeOH and DCM (200 mL, 1:1) and stirred for 30 min. The aqueous phase was extracted with ethyl acetate (100 mL x 2). The combined organic phase was washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5/1) to afford compound 4 (1.59 g, 3.38 mmol, 86.5 % yield) as a yellow solid. LC-MS (ESI+) m/z: 470.3(M+H) +.

[0781] ***Step 3.*** To a mixture of compound 4 (820 mg, 1.75 mmol, 1.0 eq.) and DIPEA (677 mg, 5.24 mmol, 3.0 eq.) in DCM (20 mL) was added compound 5 (739 mg, 2.62 mmol, 1.5 eq.) in one portion at 0 °C. The mixture was stirred at 0 °C for 2 hours. TLC showed the reaction was completed. The mixture concentrated in reduced pressure at 20 °C. The residue was poured into water (100 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (100 mL x 2). The combined organic phase was washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=10/1) to afford compound 6 (735 mg, 1.05 mmol, 60.2 %, 86.065% Purity) as yellow solid. LC-MS (ESI+) m/z: 602.2(M+H)+.

[0782] ***Step 4.*** To a mixture compound 6 (100 mg, 166 µmol, 1.0 eq.), Bis(pinacolato)diborane (50.6 mg, 199 µmol, 1.2 eq.),Potassium acetate (48.9 mg, 499 µmol, 3.0 eq.) and in Dioxane (10 mL) was added $PdCl_2$(dppf) (18.2 mg, 24.9 µmol, 0.15 eq.) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 5 min, then heated to 90 °C and stirred for 6 hours. LCMS was showed the reaction was completed. The mixture was filter solid and concentrated in reduced pressure at 25 °C. The residue was poured into ice-water (50 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (50 mL x 2). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=X/1, N/1) to afford compound 7 (95 mg, 0.13 mmol, 79 %, 80.601% Purity) as a yellow solid. LC-MS (ESI+) m/z: 580.3 (M+H)+

[0783] ***Step 5.*** To a mixture of compound 7 (260 mg, 449 µmol, 1.0 eq.)in H_2O (5 mL)was added HCl (81.8 mg, 2.24 mmol, 5.0 eq.) in one portion at 20 °C. The mixture heated to 70 °C and stirred for 5 hours. TLC showed the reaction was completed. The mixture was cooled to 20

°C and concentrated in reduced pressure at 25 °C to afford compound 8 (192 mg, 323 µmol, 72.1 %, 76.033% Purity) as yellow solid. LC-MS (ESI+) m/z: 452.24(M+H)+

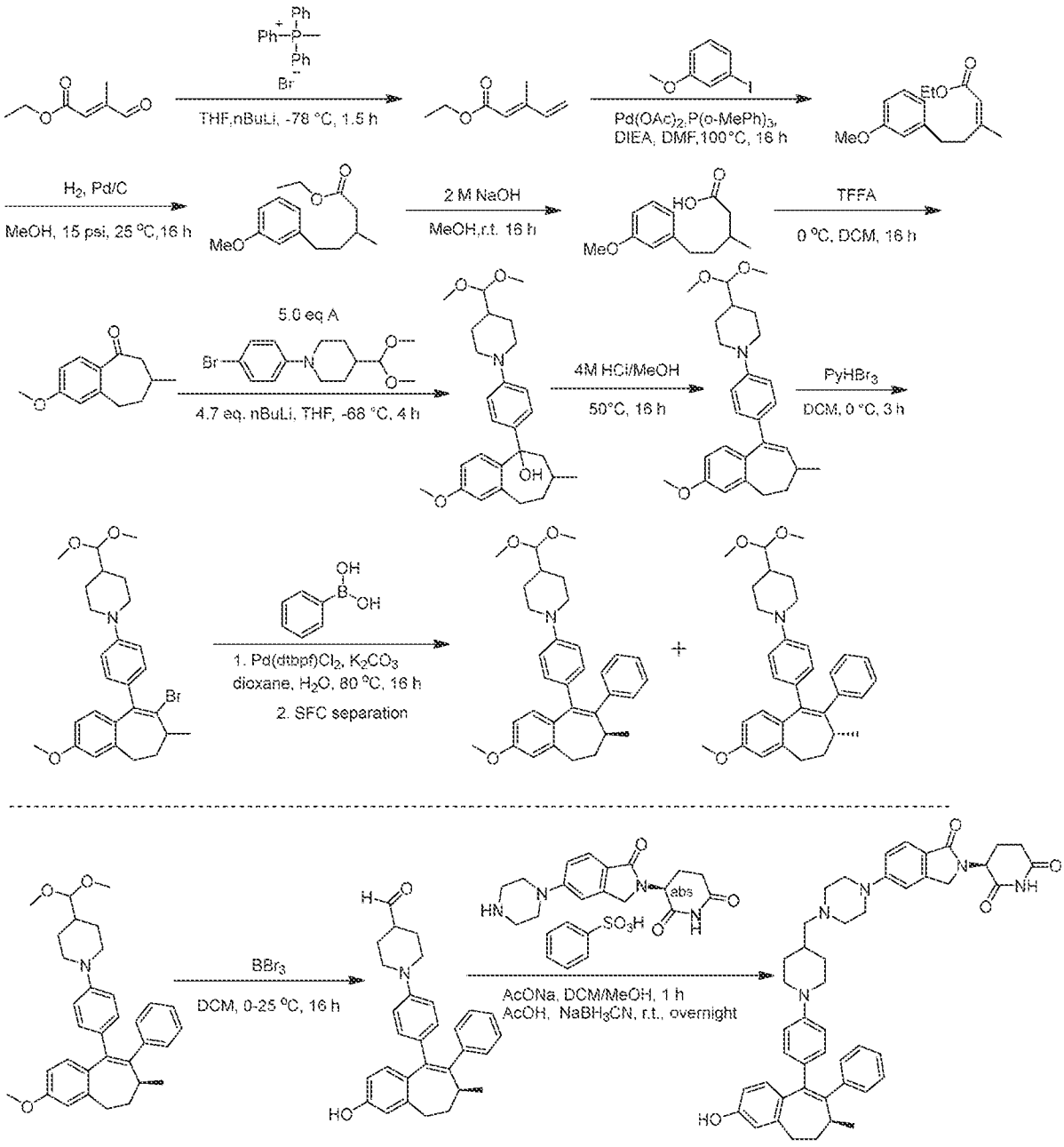
[0784] ***Step 6.*** To a mixture of compound 8 (100 mg, 222 µmol, 1.0 eq.) in DCM (10 mL)/MeOH (3 mL) was added compound 9 (146 mg, 445 µmol, 2.0 eq.) in one portion at 25 °C. The mixture was stirred at 25 °C for 5 min and add 4-methylmorfolin (67.5 mg, 667 µmol, 3.0 eq.) to adjuset PH to about 6, then add Sodium triacetoxyborohydride (94.3 mg, 445 µmol, 2.0 eq.) and stirred for 2 hours. TLC showed the reaction was completed. The mixture was pre-purified by column chromatography followed by prep. HPLC purification or re-crystallization to afford the pure compound (S)-(9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-3-yl)boronic acid (38 mg, 48 µmol, 21 %, 95.593% Purity) as a white solid

[0785] LCMS: calc. for $C_{46}H_{50}BN_5O_5$: 763.75, found: $[M+H]^+$ 764.3.

[0786] HPLC: 99.37% purity at 220 nm.

[0787] 1H NMR (500 MHz, METHANOL-d_4) δ ppm 8.38 - 8.51 (m, 1 H) 7.53 - 7.71 (m, 2 H) 7.14 - 7.21 (m, 4 H) 7.08 - 7.13 (m, 3H) 6.79 - 6.85 (m, 1 H) 6.70 - 6.78 (m, 4 H) 5.09 - 5.15 (m, 1 H) 4.36 - 4.48 (m, 2 H) 3.58 - 3.66 (m, 2 H) 3.38 - 3.47 (m, 4 H)2.87 - 2.97 (m, 1 H) 2.79 - 2.87 (m, 3 H) 2.72 - 2.78 (m, 4 H) 2.60 - 2.70 (m, 2 H) 2.42 - 2.53 (m, 3 H) 2.36 (br t, J=6.94 Hz, 2H) 2.11 - 2.21 (m, 3 H) 1.90 (br d, J=11.90 Hz, 2 H) 1.74 - 1.84 (m, 1 H) 1.29 - 1.42 (m, 2 H)

Example 15. Synthesis of (S)-3-(5-(4-((1-(4-((*R)-3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-120



[0788] ***Step 1***. To a solution of MethyltriphenylphosphoniumBromide (24 g, 1.08 Eq, 67 mmol) in THF (100 mL), The resultant mixture was sparged with N_2 for three times and was subsequently cooled to -78 °C, n-Butyllithium, 2.5M in hexane (4.4 g, 27 mL, 2.5 M, 1.1 Eq, 68 mmol) was added to the reaction over 30 min. After addition, the mixture was stirred at -78 °C for 1 hour, and then ethyl (E)-3-methyl-4-oxobut-2-enoate (8.8 g, 1 Eq, 62 mmol) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 0.5 hour. Then the mixture

was cooled to room temperature. The reaction was quenched with NH_4Cl (100 mL), the mixture was treated with H_2O (100 mL), extracted with DCM (200 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a yellow oil. The yellow oil was purified by flash column (petroleum ether/ethyl acetate from 100/0 to 85/15) and the organic layer was concentrated in vacuo to give ethyl (E)-3-methylpenta-2,4-dienoate (1.6 g, 11 mmol, 18 % yield) as a yellow oil.

[0789] ^1H NMR (400 MHz, $CDCl_3$) δ = 6.42 - 6.25 (m, 1H), 5.79 - 5.64 (m, 1H), 5.60 - 5.45 (m, 1H), 5.38 - 5.23 (m, 1H), 4.19 - 4.00 (m, 2H), 2.27 - 2.11 (m, 3H), 1.25 - 1.19 (m, 3H)

[0790] ***Step 2.*** To a solution of 3-Iodophenyl methyl ether (3.2 g, 1.7 mL, 1.2 Eq, 14 mmol) in DMF (15 mL), then added Phosphine,tris(2-methylphenyl)- (0.35 g, 0.1 Eq, 1.1 mmol), Palladium diacetate (26 mg, 0.01 Eq, 0.11 mmol), Diisopropylethylamine (3.5 g, 4.7 mL, 2.4 Eq, 27 mmol) and ethyl 3-methylpenta-2,4-dienoate (1.6 g, 1 Eq, 11 mmol). The resulting mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. Then the reaction was cooled to room temperature. The mixture was treated with H_2O (100 mL), extracted with EtOAc (100 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~10% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuo togive ethyl (2E,4E)-5-(3-methoxyphenyl)-3-methylpenta-2,4-dienoate (1 g, 3 mmol, 30 %, 75% purity) as a yellow oil. LC-MS (ESI+) m/z: 247.1 (M+H)+.

[0791] ***Step 3.*** A mixture of ethyl 5-(3-methoxyphenyl)-3-methylpenta-2,4-dienoate (50 mg, 1 Eq, 0.15 mmol), Pd/C (50 mg, 10% Wt, 0.31 Eq, 47 µmol), H_2 (0.31 mg, 1 Eq, 0.15 mmol) in MeOH (2 mL). The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 psi) at 25 °C for 16 hour. Then the reaction was cooled to room temperature. The mixture was filtered and concentrated to dryness in vacuo to give ethyl 5-(3-methoxyphenyl)-3-methylpentanoate (35 mg, 0.13 mmol, 83 %, 90% purity) as a yellow oil. LC-MS (ESI^+) m/z: 250.8 $(M+H)^+$.

[0792] ***Step 4.*** A 100 mL thread vial equipped with magnetic stirrer, sodium hydroxide (451 mg, 5.63 mL, 2 molar, 5 Eq, 11.3 mmol) was added to the solution of ethyl 5-(3-methoxyphenyl)-3-methylpentanoate (600 mg, 1 Eq, 2.25 mmol) in MeOH (10 mL). The mixture was stirred at 25 °C for 16 hour. Then the reaction was cooled to room temperature. The reaction was treated with 1M HCl (100 mL), extracted with EtOAc (100 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 5-(3-methoxyphenyl)-3-

methylpentanoic acid (500 mg, 2.25 mmol, 99.8 %) as a yellow oil. LC-MS (ESI^+) m/z: 223.1 $(M+H)^+$.

[0793] ***Step 5.*** A 40 mL thread vial was equipped with magnetic stirrer. Trifluoroaceticanhydride (5.2 g, 3.5 mL, 5 Eq, 25 mmol) was added to the solution of 5-(3-methoxyphenyl)-3-methylpentanoic acid (1.1 g, 1 Eq, 4.9 mmol) in DCM (12 mL). The mixture was stirred at 0 °C for 16 hour. The reaction was treated with H_2O (50 mL), extracted with DCM (50 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a yellow oil. The reaction was purified by flash column (petroleum ether/ethyl acetate from 100/0 to 90/10) and the organic layer was concentrated in vacuo to give 3-methoxy-7-methyl-6,7-dihydro-5H-benzo[7]annulen-9-ol (1 g, 5 mmol, 100%, 98.83% purity) as a yellow oil. LC-MS (ESI^+) m/z: 205.1 $(M+H)^+$.

[0794] ***Step 6.*** To a mixture of 1-(4-bromophenyl)-4-(dimethoxymethyl)piperidine (3.80 g, 5 Eq, 12.1 mmol) in THF (30 mL) at r.t. and the mixture was degassed and purged with N_2 for 10 minutes. Then the mixture was stirred until it reached -78 °C. n-Butyllithium, 2.5M in hexane (728 mg, 4.55 mL, 2.5 M, 4.7 Eq, 11.4 mmol) was added to the mixture and stirred at -78 °C for 1 hour, then 2-methoxy-7-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (500 mg, 1 Eq, 2.42 mmol) was added to the mixture at -78 °C and stirred at -78 °C for 3 hour. The reaction was quenched with NH_4Cl (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a blue oil. The blue oil was subjected to column chromatography over silica gel (gradient elution: 0 - 70% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-2-methoxy-7-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (850 mg, 1.81 mmol, 74.7%, 93.5% purity) as a yellow oil. LC-MS (ESI^+) m/z: 422.2 $(M+H)^+$.

[0795] ***Step 7.*** To a mixture of 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-2-methoxy-7-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (30 mg, 1 Eq, 64 µmol) in hydrogen chloride in methanol solution (0.8 g, 1 mL, 4 M, 4 mmol) at r.t. Then the mixture was stirred at 50 °C for 16 hour. The mixture was treated with H_2O (20 mL), extracted with EtOAc (30 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 4-(dimethoxymethyl)-1-(4-(3-methoxy-7-methyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (28 mg, 66 µmol, 100 %) as a yellow oil. LC-MS (ESI^+) m/z: 422.1 $(M+H)^+$.

[0796] ***Step 8.*** To a solution of 4-(dimethoxymethyl)-1-(4-(3-methoxy-7-methyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (700 mg, 1 Eq, 1.66 mmol), DIEA (322 mg, 434 µL, 1.5 Eq, 2.49 mmol) in DCM (8 mL), Pyridinium bromide perbromide (531 mg, 1 Eq, 1.66 mmol) was added to the reaction under ice bath. The mixture was stirred at 0 °C for 3 hour. Then the reaction was cooled to room temperature. TLC (PE/EtOAc=5/1, R_f=0.3) showed a new spot was formed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (100 mL).

[0797] The organic layer was washed with brine (50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 - 30% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 1-(4-(8-bromo-3-methoxy-7-methyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (600 mg, 1.06 mmol, 64.1%, 88.712% purity) as a yellow oil. LC-MS (ESI^+) m/z: 501.9 $(M+H)^+$.

[0798] ***Step 9.*** To a solution of 1-(4-(8-bromo-3-methoxy-7-methyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (600 mg, 1 Eq, 1.06 mmol), phenylboronic acid (195 mg, 1.5 Eq, 1.60 mmol), K_2CO_3 (441 mg, 3 Eq, 3.19 mmol) in dioxane (10 mL), H_2O (2.5 mL). 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (69.3 mg, 0.1 Eq, 106 µmol) was added to the reaction. Then the resultant mixture was stirred for 16 hour at 80 °C under N_2. TLC (petroleum ether/ethyl acetate=5/1, R_f=0.3) showed three spots was formed. The mixture was treated with H_2O (100 mL), extracted with EtOAc (100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give the compound as a yellow oil. The reaction was purified by flash column (petroleum ether/ethyl acetate from 100/0 to 70/30) and the organic layer was concentrated in vacuo to give a yellow solid. The yellow solid was subjected by SFC: Column: DAICEL CHIRALPAK IG (250 mm *30 mm, 10 um); Mobile phase: A: Supercritical CO_2, B: MeOH (0.1% NH3 H2O), A:B = 45:45 at 80 mL/min. The aqueous phase was lyophilized to dryness to give (*R)-4-(dimethoxymethyl)-1-(4-(3-methoxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (140 mg, 281 µmol, 26.5 %, 100% purity) and (*S)-4-(dimethoxymethyl)-1-(4-(3-methoxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (120 mg, 238 µmol, 22.4 %, 98.658% purity) as a yellow solid. LC-MS (ESI^+) m/z: 498.2 $(M+H)^+$.

[0799] ***Step 10.*** To a solution of (*R)-4-(dimethoxymethyl)-1-(4-(3-methoxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (140 mg, 1 Eq, 281 µmol) in

DCM (2 mL) at 0 °C was added tribromoborane (211 mg, 844 µL, 1 M, 3 Eq, 844 µmol) with N_2. After addition, the mixture was stirred at 0 °C for 4 hour, and then the reaction was warmed to 25 °C and was stirred at this temperature for 12 hour. The reaction mixture was quenched with saturated $NaHCO_3$ 10 mL and stirred for 10 min at 0°C. Then the mixture was dissolved in water (30 mL) and extracted by ethyl acetate (40 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give the compound (*R)-1-(4-(3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (135 mg, 267 µmol, 94.8 %, 86.408% purity) as a yellow solid. LC-MS (ESI+) m/z: 438.2 (M+H)+

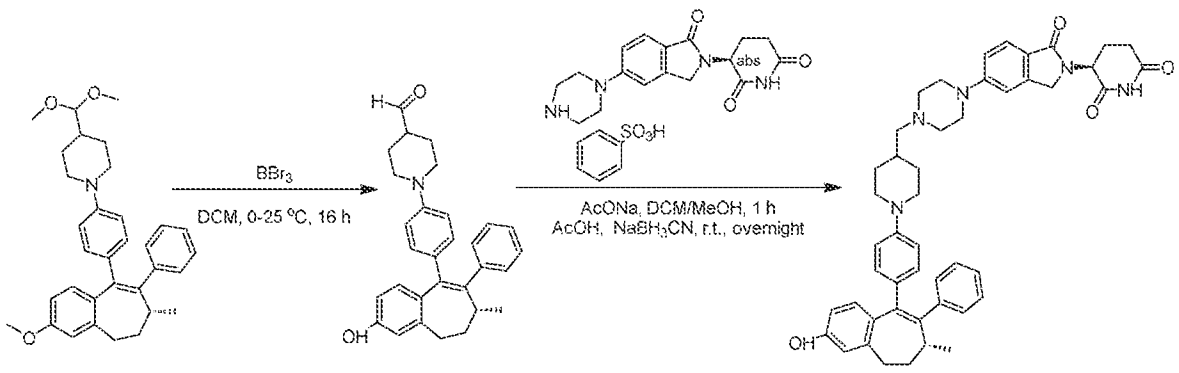
[0800] ***Step 11.*** A mixture of (*R)-1-(4-(3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (135 mg, 86.408% Wt, 1 Eq, 267 µmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione benzenesulfonate (169 mg, 1.3 Eq, 347 µmol) and sodium acetate (109 mg, 5 Eq, 1.33 mmol) and acetic acid (48.0 mg, 46.0 µL, 3 Eq, 800 µmol) in DCM (2 mL) and MeOH (2 mL) at 25 °C for 1 hour, then sodium triacetoxyborohydride (113 mg, 2 Eq, 533 µmol) was added to the mixture and stirred at 25 °C for 16 hour. The reaction was treated with H_2O (50 mL), extracted with EtOAc (50 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150*30 mm*5 um mobile phase: [water (FA)-ACN]; B%: 15%-55%, 8 min). The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-((*R)-3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (59.8 mg, 79.7 µmol, 29.9 %, 100% purity) as a pink solid. LC-MS (ESI+) m/z: 750.2 (M+H)+

[0801] HPLC: 100%, purity at 220 nm.

[0802] SFC: retention time, 2.885 min; Area, 90.200%; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[0803] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.96 (s, 1H), 9.63 - 9.10 (m, 1H), 8.18 (s, 0.428H), 7.52 (d, J = 8.7 Hz, 1H), 7.24 - 7.15 (m, 2H), 7.14 - 7.02 (m, 5H), 6.73 - 6.66 (m, 3H), 6.62 - 6.52 (m, 4H), 5.05 (dd, J = 5.0, 13.4 Hz, 1H), 4.37 - 4.29 (m, 1H), 4.24 - 4.17 (m, 1H), 3.60 - 3.50 (m, 4H), 3.30 - 3.18 (m, 8H), 2.95 - 2.85 (m, 2H), 2.65 - 2.54 (m, 3H), 2.40 - 2.29 (m, 1H), 2.19 (br d, J = 6.9 Hz, 2H), 2.15 - 2.05 (m, 1H), 2.01 - 1.92 (m, 1H), 1.91 - 1.81 (m, 1H), 1.76 (br d, J = 11.1 Hz, 2H), 1.70 - 1.57 (m, 1H), 1.20 - 1.06 (m, 2H), 0.71 (d, J = 6.9 Hz, 3H).

Example 16. Synthesis of (S)-3-(5-(4-((1-(4-((S)-3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-121



[0804] ***Step 1.*** To a solution of (*S)-4-(dimethoxymethyl)-1-(4-(3-methoxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (120 mg, 1 Eq, 238 µmol) in DCM (2 mL) at 0 °C was added tribromoborane (179 mg, 714 µL, 1 M, 3 Eq, 714 µmol) with N_2. After addition, the mixture was stirred at 0 °C for 4 hour, and then the reaction was warmed to 25 °C and stirred at this temperature for 12 hour. The reaction mixture was quenched with saturated $NaHCO_3$ 10 mL and stirred for 10 min at 0°C. Then the mixture was dissolved in water (30 mL) and extracted by ethyl acetate (40 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give the compound (*S)-1-(4-(3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (115 mg, 209 µmol, 87.7 %, 79.386% purity) as a yellow solid. LC-MS (ESI+) m/z: 438.1 (M+H)+

[0805] ***Step 2.*** A mixture of (*S)-1-(4-(3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (115 mg, 1 Eq, 209 µmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione benzenesulfonate (132 mg, 1.3 Eq, 271 µmol) and sodium acetate (85.6 mg, 5 Eq, 1.04 mmol) and Acetic acid (37.6 mg, 36.0 µL, 3 Eq, 626 µmol) in DCM (2 mL) and MeOH (2 mL) at 25 °C for 1 hour, then sodium triacetoxyborohydride (88.4 mg, 2 Eq, 417 µmol) was added to the mixture and was stirred at 25 °C for 16 hour. The reaction was treated with H_2O (50 mL), extracted with EtOAc (50 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150*30 mm*5 um mobile phase: [water (FA)-ACN]; B%: 15%-55%, 8 min). The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-((S)-3-hydroxy-7-methyl-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-

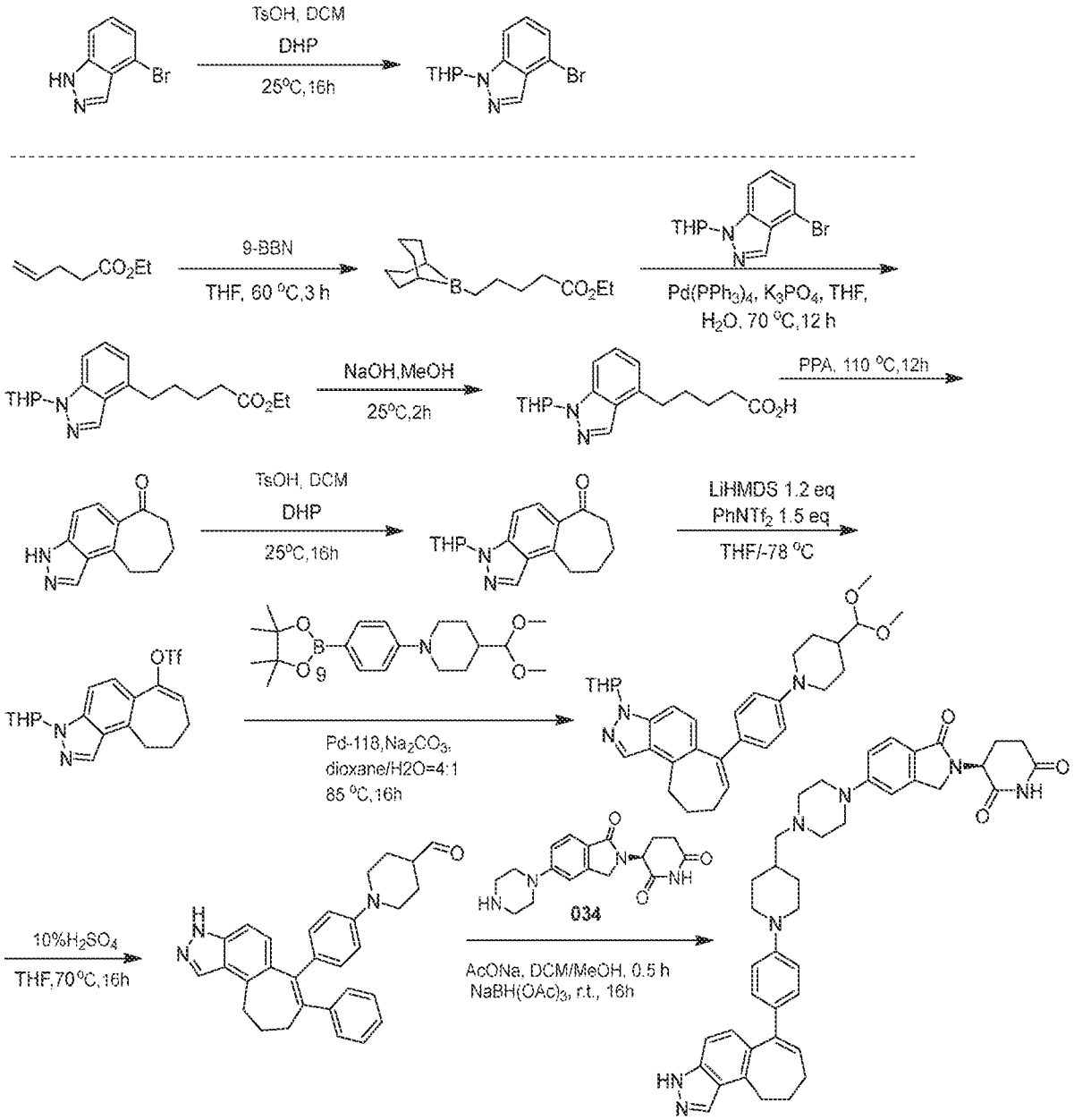
oxoisoindolin-2-yl)piperidine-2,6-dione (43.9 mg, 58.5 μmol, 28.1 %, 100% purity) as a white solid. LC-MS (ESI+) m/z: 750.2 $(M+H)^+$

[0806] HPLC: 100%, purity at 220 nm.

[0807] SFC: retention time, 3.053 min; Area, 91.827%; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[0808] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.96 (s, 1H), 8.16 (s, 0.690 H), 7.52 (d, J = 8.7 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.15 - 7.02 (m, 5H), 6.74 - 6.66 (m, 3H), 6.62 - 6.52 (m, 4H), 5.05 (dd, J = 5.0, 13.2 Hz, 1H), 4.38 - 4.28 (m, 1H), 4.26 - 4.15 (m, 1H), 3.31 - 3.09 (m, 11H), 2.99 - 2.81 (m, 3H), 2.64 - 2.53 (m, 3H), 2.40 - 2.31 (m, 1H), 2.19 (br d, J = 7.0 Hz, 2H), 2.15 - 2.03 (m, 1H), 2.01 - 1.92 (m, 1H), 1.85 (br d, J = 8.0 Hz, 1H), 1.80 - 1.70 (m, 2H), 1.69 - 1.56 (m, 1H), 1.23 - 1.04 (m, 2H), 0.70 (br d, J = 6.8 Hz, 3H).

Example 17. Synthesis of (3S)-3-[1-oxo-5-[4-[[1-[4-(3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione, I-50



[0809] ***Step 1.*** A mixture of 4-bromo-2H-indazole (50 g, 253.77 mmol, 1 eq) , 4-methylbenzenesulfonic acid (13.11 g, 76.13 mmol, 0.3 eq) , 3,4-dihydro-2H-pyran (25.62 g, 304.52 mmol, 27.84 mL, 1.2 eq) in DCM (500 mL) was added 3,4-dihydro-2H-pyran (25.62 g, 304.52 mmol, 27.84 mL, 1.2 eq) , and the the mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 16 h under N_2 atmosphere. LCMS showed desired 60% MS. The reaction mixture was diluted with 200 mL H_2O and extracted with EA

(150 mL * 2). The combined organic layers were washed with brine (100 mL * 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3/1). Compound 4-bromo-1-tetrahydropyran-2-yl-indazole (51 g, 181.40 mmol, 71.48% yield) was obtained as a white solid. LC-MS (ESI^+) m/z: 197.1 $(M+H)^+$.

[0810] ***Step 2.*** A mixture of ethyl4-pentenoate (6.000 g, 7 mL, 1.316 Eq, 46.81 mmol) , 9-Borabicyclo[3.3.1]nonane Solution (7.378 g, 120.9 mL, 0.5 M, 1.7 Eq, 60.47 mmol) in THF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 3 h under N_2 atmosphere. And then was added 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (10.00 g, 1 Eq, 35.57 mmol), Tetrakis(triphenylphosphine)palladium(0) (2.055 g, 0.05 Eq, 1.778 mmol), K_3PO_4 (22.65 g, 8.834 mL, 3 Eq, 106.7 mmol), THF (50 mL) and H_2O (250 mL) in mixture solution. The mixture was stirred at 70 °C for 16 hour. TLC (petroleum ether: ethyl acetate=5:1, R_f =0.4 UV) showed one main new spot was observed. The reaction mixture was quenched by addition of water (150 mL), extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 3/1) to yield a product. Compound ethyl 5-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)pentanoate (5.5 g, 16 mmol, 44 % yield) was obtained as yellow oil.

[0811] ***Step 3.*** To a solution of ethyl 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoate (11.2 g, 33.90 mmol, 1 eq) in MeOH (50 mL) was added NaOH (3 M, 45.19 mL, 4 eq) .The mixture was stirred at 25 °C for 2 hr . LC-MS showed 96% desired mass. The reaction mixture was diluted with H_2O 150 mL and extracted with EtOAc (100 mL * 2). The combined organic layers were washed with brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoic acid (9.4 g, 31.09 mmol, 91.72% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 303.1 (M+H) +.

[0812] ***Step 4.*** To a solution of 5-(1-tetrahydropyran-2-ylindazol-4-yl)pentanoic acid (8.4 g, 27.78 mmol, 1 eq) in PPA (40 mL) was stirred at 110 °C for 12 hr. LCMS showed 40% desired MS. The reaction was adjust to pH=~7 with $NaHCO_3$, Then the residue was diluted with 200 mL H_2O and extracted with ethyl acetate (300 mL * 2). The combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3/1). Compound 7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (5.5 g, 27.47 mmol, 98.87% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 200.9 (M+H) +

[0813] ***Step 5.*** A mixture of 7,8,9,10-tetrahydro-3H-cyclohepta[e]indazol-6-one (4.7 g, 23.47 mmol, 1 eq) , 4-methylbenzenesulfonic acid (1.21 g, 7.04 mmol, 0.3 eq) , 3,4-dihydro-2H-pyran (2.37 g, 28.17 mmol, 2.58 mL, 1.2 eq) in DCM (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. LCMS showed desired 66% MS. The reaction mixture was quenched by addition 20 mL saturated $NaHCO_3$ aqueous solution at 25°C, and then diluted with H_2O 30 mL and extracted with Ethyl acetate 40 mL (20 mL * 2). The combined organic layers were washed with brine 30 mL (15 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give Compound 1-[5-[(1R,2R)-6-hydroxy-2-phenyl-tetralin-1-yl]-2-pyridyl]piperidine-4-carbaldehyde (1.62 g, 5.7 mmol, 24.27% yield) as a white solid. LC-MS (ESI+) m/z: 285.2 $(M+H)^+$

[0814] ***Step 6.*** To a solution of 3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (1.600 g, 1 Eq, 5.627 mmol) in THF (30 mL) was added LiHMDS (1.130 g, 6.752 mL, 1 molar, 1.2 Eq, 6.752 mmol) under -78 °C after stirred 30 min added Phenyl triflimide (3.015 g, 1.5 Eq, 8.440 mmol) in THF (30 mL) . The mixture was stirred at -78 °C for 3 hr. TLC (PE/EtOAc = 10/1, R_f = 0.68) indicated the starting material was consumed completely and one new spot formed.

[0815] The reaction mixture was quenched by addition of saturated solution of NH_4Cl (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 1/0, TLC: PE/EtOAc = 10/1, R_f = 0.6) to yield a product. Compound 3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yltrifluoromethanesulfonate (1.4 g, 3.4 mmol, 60 %) was obtained as a yellow oil.

[0816] ***Step 7.*** A mixture of (3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl) trifluoromethanesulfonate (1.2 g, 2.88 mmol, 1 eq) , 4-(dimethoxymethyl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (832.90 mg, 2.31 mmol, 0.8 eq) , Na_2CO_3 (916.30 mg, 8.65 mmol, 3 eq) , ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (187.82 mg, 288.17 umol, 0.1 eq) and in dioxane (4 mL) and H_2O (1 mL) was degassed and

purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 16 hr under N_2 atmosphere. TLC (Petroleum ether/Ethyl acetate=5/1) showed new spot was formed. The reaction mixture was diluted with H_2O 40 mL and extracted with EtOAc (30 mL * 2). The combined organic layers were washed with brine 30 mL (15 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1 to 3/1) .Compound 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (480 mg, 956.83 umol, 33.20% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 502.4 $(M+H)^+$

[0817] ***Step 8.*** To a solution of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (120 mg, 239.21 umol, 1 eq) in THF (4 mL) was added H_2SO_4 (4 mL) .The mixture was stirred at 70 °C for 16 h. TLC (Petroleum ether/Ethyl acetate=5/1) showed new spot was formed. The reaction mixture was quenched by addition Saturated $NaHCO_3$ aqueous solution 10 mL at 25°C, and then diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 2). The combined organic layers were washed with brine 20 mL (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound 1-[4-(3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (85 mg, 228.82 umol, 95.66% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 447.2 $(M+H)^+$

[0818] ***Step 9.*** To a solution of 1-[4-(3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (85 mg, 228.82 umol, 1 eq) and (S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione $PhSO_3H$ salt (75.14 mg, 228.82 umol, 1 eq) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (56.31 mg, 686.45 umol, 3 eq) .The mixture was stirred at 25 °C for 0.5 h .Then the mixture was added $NaBH(OAc)_3$ (96.99 mg, 457.64 umol, 2 eq). The mixture was stirred at 25 °C for 16 h. LC-MS showed 68% desired mass. The reaction mixture was diluted with 20 mL H_2O and extracted with EtOAc (15 mL * 2). The combined organic layers were washed with brine (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B%: 14%-34%,7min) to give (3S)-3-[1-oxo-5-[4-[[1-[4-(3,8,9,10-tetrahydrocyclohepta[e]indazol-6-

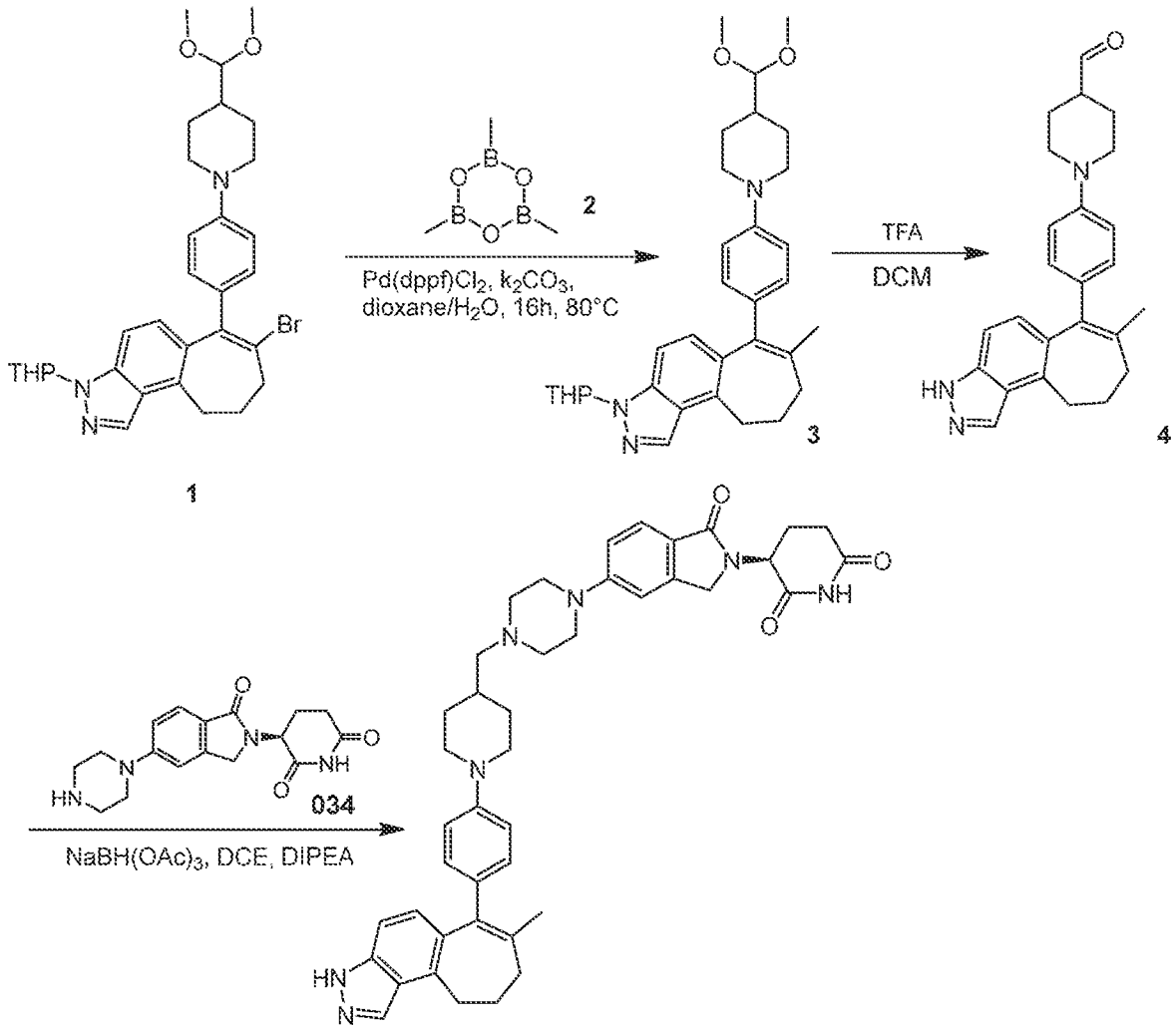
yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]isoindolin-2-yl]piperidine-2,6-dione (25 mg, 36.56 umol, 15.98% yield) as a white solid. LC-MS (ESI$^+$) m/z: 684.2 $(M+H)^+$.

[0819] HPLC: 95.276%, purity at 220 nm.

[0820] SFC: Rt: 4.401 min; Area, 95.264%; method: ID_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

[0821] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 - 13.11 (m, 1 H) 10.93 - 10.99 (m, 1 H) 8.23 (s, 1 H) 8.15 (s, 0.264 H) 7.53 (d, J=8.70 Hz, 1 H) 7.33 (d, J=8.58 Hz, 1 H) 7.06 (d, J=8.70 Hz, 4 H) 6.89 (t, J=8.82 Hz, 3 H) 6.33 - 6.43 (m, 1 H) 5.00 - 5.10 (m, 1 H) 4.17 - 4.38 (m, 2 H) 3.71 (br d, J=12.04 Hz, 2 H) 3.30 (br s, 8 H) 2.84 - 2.97 (m, 3 H) 2.56 - 2.72 (m, 4 H) 2.31 - 2.42 (m, 1 H) 2.20 - 2.29 (m, 4 H) 1.93 - 2.01 (m, 1 H) 1.77 - 1.91 (m, 4 H) 1.16 - 1.28 (m, 2 H)

Example 18. Synthesis of (S)-3-(5-(4-((1-(4-(7-methyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-52



[0822] ***Step 1.*** A mixture of compound 1 (100 mg, 172.25 umol, 1.0 eq.), compound 2 (43.25 mg, 172.25 umol, 48.16 uL, 1.0eq.), $Pd(dppf)Cl_2$ (12.60 mg, 17.22 umol, 0.1eq.), K_2CO_3 (47.61 mg, 344.50 umol, 2.0eq.) in dioxane (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hr under N_2 atmosphere. The mixture was concentrated in reduced pressure. The residue was poured into water (15 mL). The aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (15 mL), dried with Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate= 3/1) to afford compound 3. Compound 3 (80 mg, 155.13 μmol, 90.06% yield) was obtained as oil.

[0823] LC-MS (ESI+) m/z: 516.4 ($M+H^+$).

[0824] Step 2. To a solution of compound 3 (80 mg, 155.13 μmol, 1.0 eq) in DCM (4 mL) was added TFA (17.69 mg, 155.13 μmol, 11.49 μL, 1.0 eq). The mixture was stirred at 25 °C for 3 hr. The mixture was concentrated to give compound 4 (50 mg, 129.70 μmol, 83.61% yield) was obtained as oil.

[0825] LC-MS (ESI^+) m/z: 404.3 ($M+H^+$).

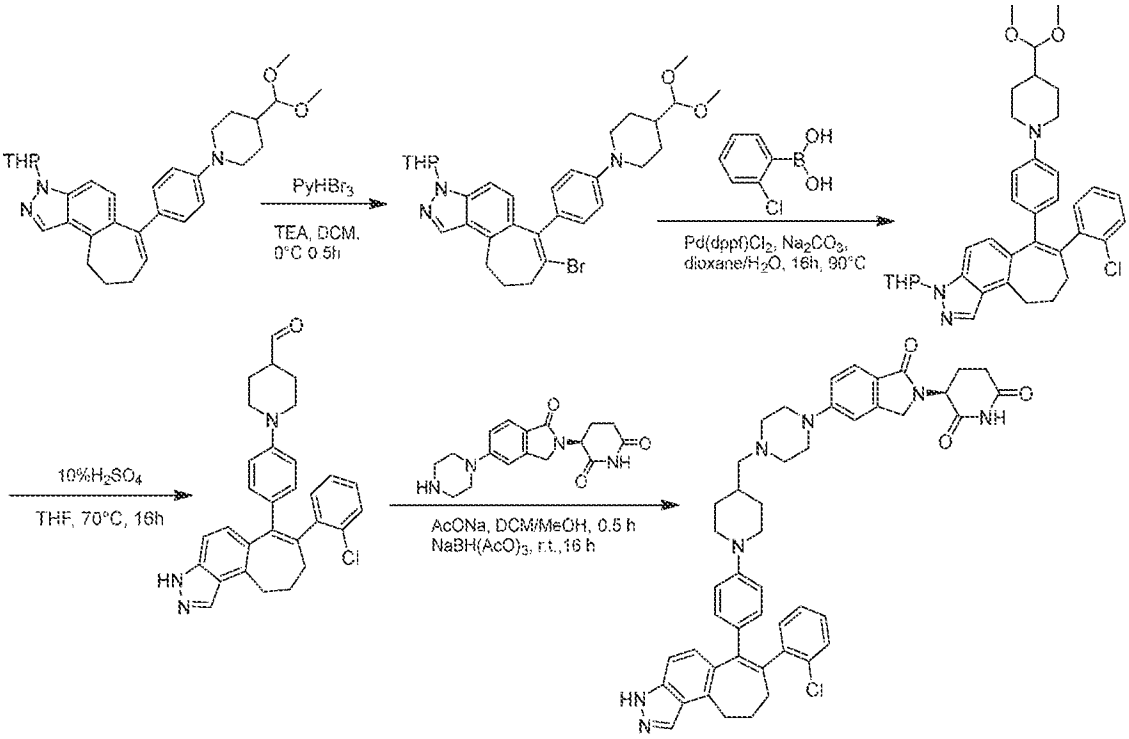
[0826] ***Step 3.*** To a solution of compound 4 (60 mg, 155.64 umol, 1.0 eq) and compound 034 (51.11 mg, 155.64 umol, 1.0 eq) in MeOH (2 mL) and DCM (2 mL) was added $C_6H_{10}BO_6Na$ (65.97 mg, 311.28 umol, 2.0 eq) and NMM (1.57 mg, 15.56 umol, 1.71 uL, 0.1 eq). The mixture was stirred at 25 °C for 5 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 10%-40%, 12min) to give (S)-3-(5-(4-((1-(4-(7-methyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (20 mg, 28.66 μmol, 18.41% yield) as a white solid. LCMS (ESI^+) m/z: 698.5 $[M+H]^+$.

[0827] LCMS: calc. for C42H47N7O3: 697.88, found: $[M+H]^+$ 698.5.

[0828] HPLC: 98.9% purity at 220 nm.

[0829] ^1H NMR (400 MHz, METHANOL-d4) δ = 8.44 - 8.33 (m, 1H), 8.10 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.22 - 7.16 (m, 1H), 7.11 - 7.06 (m, 2H), 6.98 - 6.91 (m, 4H), 6.76 (d, J = 8.7 Hz, 1H), 5.08 (dd, J = 5.1, 13.2 Hz, 1H), 4.45 - 4.31 (m, 2H), 3.73 - 3.66 (m, 2H), 3.41 (br s, 4H), 3.14 - 2.98 (m, 2H), 2.93 - 2.84 (m, 1H), 2.79 - 2.65 (m, 7H), 2.50 - 2.39 (m, 3H), 2.37 - 2.31 (m, 2H), 2.16 - 2.09 (m, 1H), 2.01 - 1.89 (m, 7H), 1.83 - 1.73 (m, 1H), 1.44 - 1.33 (m, 2H)

Example 19. Synthesis of (3S)-3-[5-[4-[[1-[4-[7-(2-chlorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-53



[0830] ***Step 1.*** A mixture of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole(400 mg, 797.36 umol, 1 eq) , $Py{\cdot}HBr_3$(306.01 mg, 956.83 umol, 1.2 eq), N,N-diethylethanamine(121.03 mg, 1.20 mmol, 166.47 uL, 1.5 eq) in DCM(4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 0.5 hr under N_2 atmosphere. TLC (petroleum ether/ethyl acetate=10:1, R_f=0.4) showed new spot was formed. The reaction mixture was diluted with H_2O 20 mL and extracted with DCM (15 mL* 2). The combined organic layers were washed with brine (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~50% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuo to give compound 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (270 mg, 465.07 umol, 58.33% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 580.3 $(M+H)^+$

[0831] ***Step 2.*** A mixture of (2-chlorophenyl)boronic acid (87.27 mg, 558.09 umol, 1.2 eq) , 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-

cyclohepta[e]indazole (270 mg, 465.07 umol, 1 eq), $Pd(dppf)Cl_2$ (37.98 mg, 46.51 umol, 0.1 eq), Na_2CO_3 (147.88 mg, 1.40 mmol, 3 eq) in dioxane (4 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 16 hr under N_2 atmosphere. TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The reaction mixture was diluted with 20 mL H_2O and extracted with ethyl acetate (15 mL * 2). The combined organic layers were washed with brine (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3/1). Compound 7-(2-chlorophenyl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (200 mg, 326.69 umol, 70.25% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 612.2 $(M+H)^+$.

[0832] ***Step 3.*** To a solution of 7-(2-chlorophenyl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (200 mg, 326.69 umol, 1 eq) in THF (4 mL) was added 10% H_2SO_4 (4 mL) .The mixture was stirred at 70 °C for 16 hr. TLC (petroleum ether/ethyl acetate=5:1, Rf =0.4) showed new spot was formed. The reaction mixture was quenched by addition saturated $NaHCO_3$ aqueous solution (20 mL) at 25°C, and then extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with brine (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound 1-[4-[7-(2-chlorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (110 mg, 228.21 umol, 69.85% yield) was obtained as a yellow solid. LC-MS (ESI+) m/z: 482.2 $(M+H)^+$.

[0833] ***Step 4.*** To a solution of 1-[4-[7-(2-chlorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (110 mg, 228.21 umol, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione $PhSO_3H$ salt (74.94 mg, 228.21 umol, 1 eq) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (56.16 mg, 684.63 umol, 3 eq) .The mixture was stirred at 25 °C for 0.5 hr .Then the mixture was added $NaBH(AcO)_3$ (96.73 mg, 456.42 umol, 2 eq) and AcOH (189.04 mg, 684.63 umol, 180.03 uL, 3 eq). The mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with 30 mL H_2O and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with brine (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18

150*30mm*5um;mobile phase: [water(FA)-ACN];B%: 24%-54%,7min) to give (3S)-3-[5-[4-[[1-[4-[7-(2-chlorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (90 mg, 113.30 μmol, 49.65% yield) was obtained as a white solid.

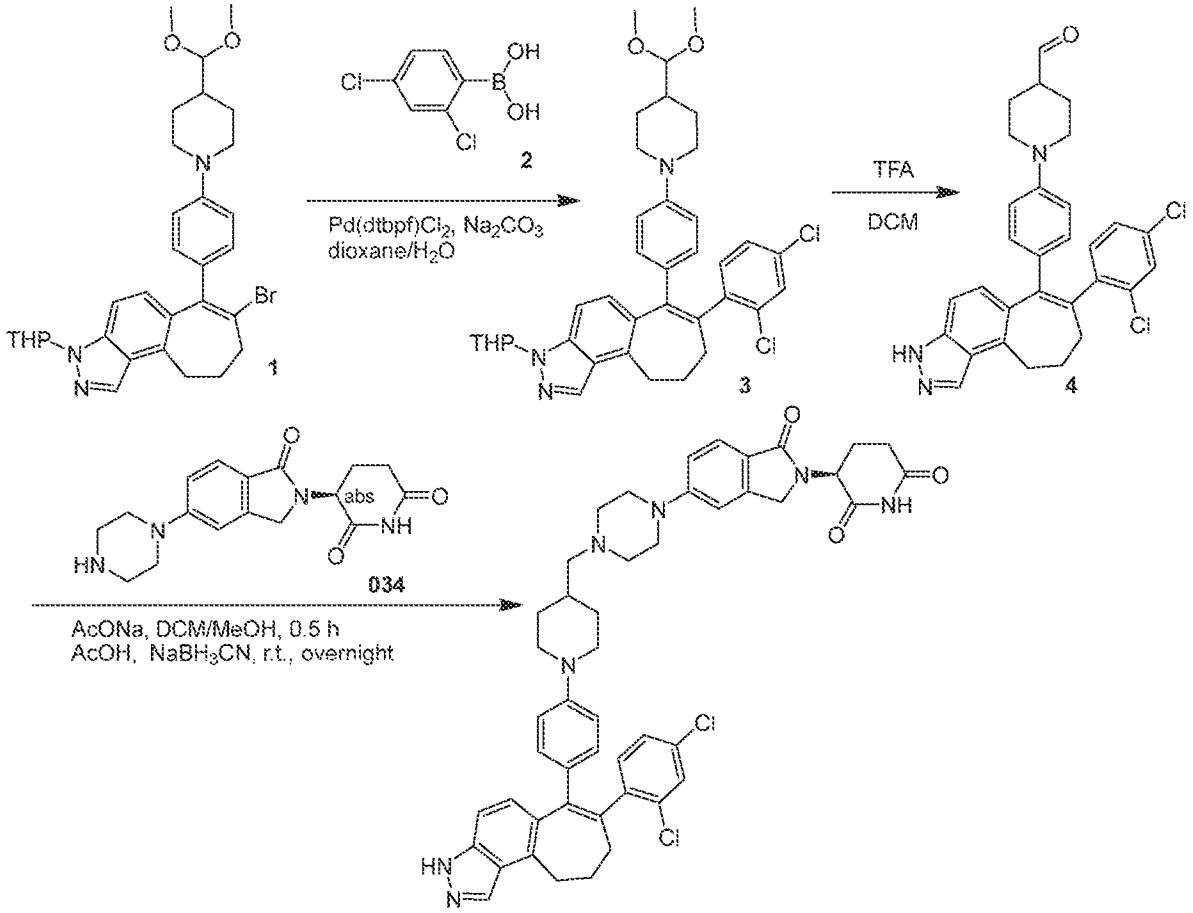
[0834] LC-MS (ESI^+) m/z: 794.2 $(M+H)^+$.

[0835] HPLC: 99.272%, purity at 220 nm.

[0836] SFC: Rt: 4.374 min; Area, 96.519%; method: ID_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

[0837] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 - 13.09 (m, 1 H) 10.90 - 10.99 (m, 1 H) 8.26 (s, 1 H) 8.14 (s, 0.268 H) 7.55 (s, 1 H) 7.43 (br d, J=7.78 Hz, 1 H) 7.29 (d, J=8.78 Hz, 1 H) 7.12 - 7.24 (m, 3 H) 6.99 - 7.10 (m, 2 H) 6.76 (d, J=8.53 Hz, 1 H) 6.56 - 6.70 (m, 4 H) 5.05 (dd, J=13.43, 4.89 Hz, 1 H) 4.15 - 4.39 (m, 2 H) 3.60 (br d, J=10.79 Hz, 2 H) 3.29 (br d, J=4.27 Hz, 8 H) 3.12 (br s, 2 H) 2.84 - 2.95 (m, 1 H) 2.54 - 2.63 (m, 3 H) 2.36 (br dd, J=13.93, 5.14 Hz, 2 H) 2.26 (br d, J=8.28 Hz, 1 H) 2.16 - 2.22 (m, 4 H) 1.92 - 2.00 (m, 1 H) 1.71 - 1.81 (m, 2 H) 1.59 - 1.69 (m, 1 H) 1.08 - 1.20 (m, 2 H)

Example 20. Synthesis of (S)-3-(5-(4-((1-(4-(7-(2,4-dichlorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-49



[0838] *Step 1.* A mixture of compound 1 (120 mg, 206.70 umol, 1.0 eq.), compound 2 (47.33 mg, 248.04 umol, 1.2 eq.), Na_2CO_3 (43.82 mg, 413.40 umol, 2.0 eq.), $Pd(dtbpf)Cl_2$ (13.47 mg, 20.67 umol, 0.1eq) in dioxane (12 mL) and H_2O (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hr under N_2 atmosphere. The mixture was concentrated in reduced pressure. The residue was poured into water (15 mL). The aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (15 mL), dried with Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate= 3/1). Compound 3 (100 mg, 154.64 umol, 74.82% yield) was obtained as a white solid.

[0839] LC-MS (ESI^+) m/z: 646.4 $(M+H)^+$.

[0840] *Step 2.* To a solution of 3 (100 mg, 154.64 umol, 1.0 eq.) in DCM (3 mL) was added TFA (17.63 mg, 154.64 umol, 11.45 uL, 1.0 eq.). The mixture was stirred at 25 °C for 3 hr. The

mixture was concentrated to give compound 4 (50 mg, 96.81 umol, 62.60% yield) was obtained as oil.

[0841] LC-MS (ESI^+) m/z: 516.3 $(M+H)^+$.

[0842] ***Step 3.*** To a solution of compound 4 (105 mg, 174.83 umol, 1.0 eq.) and compound 034 (57.41 mg, 174.83 umol, 1.0 eq.) in MeOH (3 mL) and DCM (3 mL) was added $NaBH(OAc)_3$ (74.11 mg, 349.66 umol, 2.0 eq.) and NMM (1.77 mg, 17.48 umol, 0.1 eq.). The mixture was stirred at 25 °C for 5 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 25%-55%, 10min) to give (S)-3-(5-(4-((1-(4-(7-(2,4-dichlorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (38 mg, 45.85 umol, 26.22% yield) as a white solid.

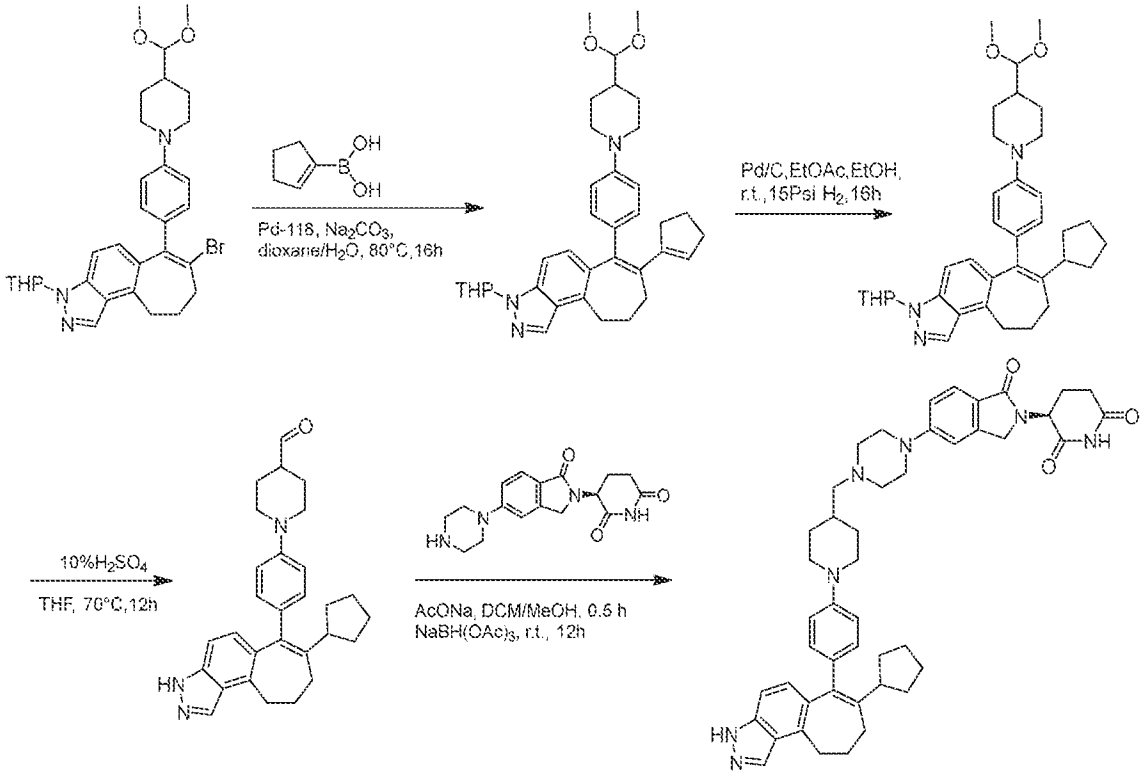
[0843] LCMS (ESI^+) m/z: 828.5 $(M+H)^+$.

[0844] HPLC: 98.74% purity at 220 nm.

[0845] ^1H NMR (500 MHz, METHANOL-d4) & = 8.43 (s, 1H), 8.19 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.16 - 7.06 (m, 4H), 6.87 (d, J = 8.5 Hz,1H), 6.77 - 6.71 (m, 4H), 5.11 - 5.06 (m, 1H), 4.38 (d, J = 8.9 Hz, 2H), 3.61 (br d, J = 12.1 Hz, 2H), 3.37 (br d, J = 4.6 Hz, 4H), 3.18 - 3.12 (m, 1H), 2.92 - 2.85 (m, 1H), 2.78 - 2.74 (m,

[0846] 1H), 2.69 - 2.58 (m, 6H), 2.48 - 2.42 (m, 1H), 2.41 - 2.26 (m, 7H), 2.16 - 2.11 (m, 1H), 1.86 (br d, J = 13.4 Hz, 2H), 1.79 - 1.71 (m, 1H), 1.35 - 1.29 (m, 2H)

Example 21. Synthesis of (3S)-3-[5-[4-[[1-[4-(7-cyclopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-60



[0847] ***Step 1.*** A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (300 mg, 516.8 μmol, 1 eq), cyclopenten-1-ylboronic acid (69.4 mg, 620.1 μmol, 1.2 eq), Na_2CO_3 (164.3 mg, 1.55 mmol, 3 eq), Pd-118 (33.7 mg, 51.7 μmol, 0.1 eq) in dioxane (4 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hr. under N_2 atmosphere. TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The reaction mixture was diluted with 20 mL H_2O and extracted with 30 mL ethyl acetate (15 mL * 2). The combined organic layers were washed with brine 20 mL (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/ethyl acetate=3/1). The residue was further purified by flash silica gel chromatography (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 95%-100%, 7min). Compound 7-(cyclopenten-1-yl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (120 mg, 211.36 μmol, 40.9% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 568.4 $(M+H)^+$.

[0848] ***Step 2.*** To a solution of 7-(cyclopenten-1-yl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (120 mg, 211.36 μmol, 1 eq) in EtOAc (4 mL) and EtOH (4 mL) was added Pd/C (10%, 0.11 g) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 psi) at 25 °C for 16 hr. TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product 7-cyclopentyl-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (100 mg, 105.30 μmol, 49.82% yield, 60% purity) was used into the next step without further purification. Compound 7-cyclopentyl-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (100 mg, 105.30 μmol, 49.82% yield, 60% purity) was obtained as a yellow oil. LC-MS (ESI+) m/z: 570.2 $(M+H)^+$.

[0849] ***Step 3.*** To a solution of 7-cyclopentyl-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (100 mg, 175.51 μmol, 1 eq) in THF (4 mL) was added 10% H_2SO_4 (4 mL). The mixture was stirred at 70 °C for 12 hr. The reaction mixture was quenched by saturated $NaHCO_3$ aqueous solution addition 20 mL at 25 C, and then diluted with H_2O 5 mL and extracted with 30 mL ethyl acetate (15 mL * 2). TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The combined organic layers were washed with brine 10 mL (5 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product 1-[4-(7-cyclopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (40 mg, 87.35 μmol, 49.77% yield, 96% purity) was used into the next step without further purification. Compound 1-[4-(7-cyclopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (40 mg, 87.35 μmol, 49.77% yield, 96% purity) was obtained as a yellow solid.LC-MS (ESI^+) m/z: 440.3 $(M+H)^+$.

[0850] ***Step 4.*** To a solution of 1-[4-(7-cyclopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (40 mg, 91 μmol, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (45.6 mg, 91 μmol, 1 eq, $PhSO_3H$ salt) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (22.4 mg, 273 μmol, 3 eq) and then stirred at 25 °C for 0.5 hr. The mixture was stirred at 25 °C for 12 hr after the mixture was added $NaBH(OAc)_3$(38.6 mg, 182 μmol, 2 eq) and acetic acid (16.4 mg, 273 μmol, 15.6 μL, 3 eq). TLC (DCM/MeOH=10:1, R_f =0.4) showed new spot was formed. The reaction mixture was diluted

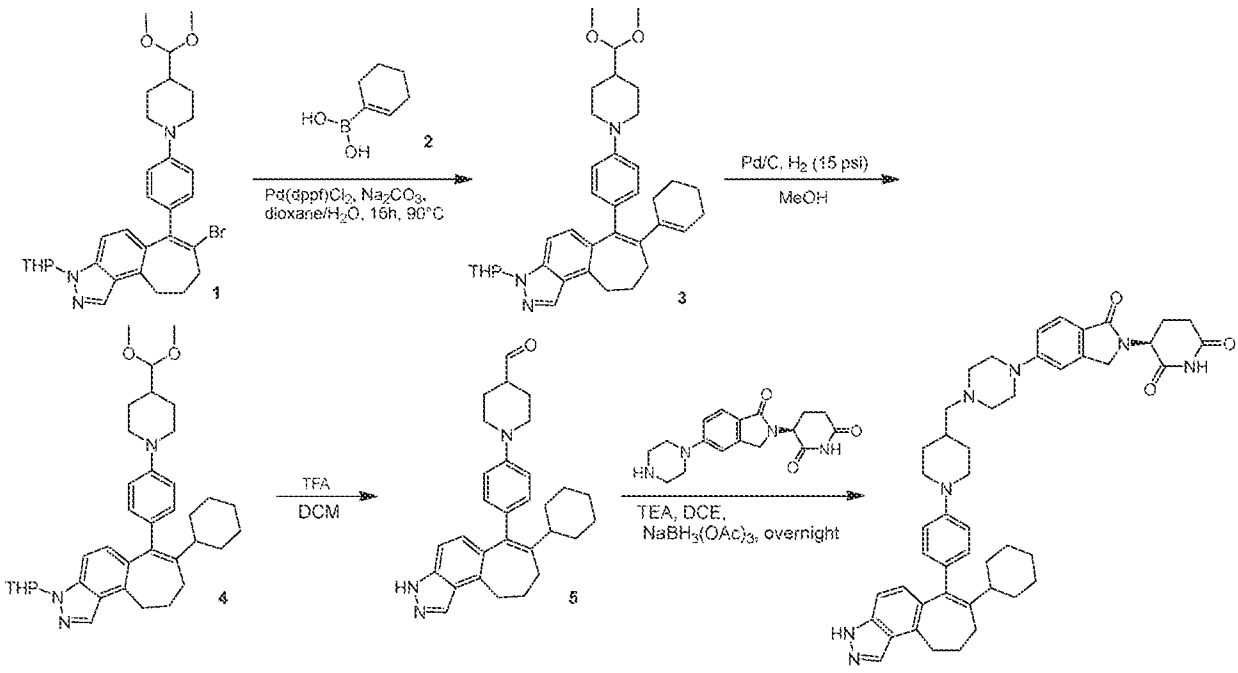
with 10 mL H_2O and extracted with 20 mL DCM (10 mL * 2). The combined organic layers were washed with brine 10 mL (5 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; gradient: 26%-56% B over 7 min). (3S)-3-[5-[4-[[1-[4-(7-cyclopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (3.2 mg, 4.26 μmol, 4.68% yield) was obtained as a white solid.LC-MS (ESI^+) m/z: 752.3 $(M+H)^+$.

[0851] HPLC: 100%, purity at 220 nm.

[0852] SFC: Rt: 4.022 min; Area, 96.374%; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

[0853] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.91 - 12.97 (m, 1 H) 10.91 - 11.02 (m, 1 H) 8.37 - 8.49 (m, 0.505 H) 8.18 (s, 1 H) 7.53 (d, J=8.46 Hz, 1 H) 7.19 (d, J=8.58 Hz, 1 H) 7.04 - 7.10 (m, 2 H) 6.88 (s, 4 H) 6.63 (d, J=8.58 Hz, 1 H) 5.01 - 5.09 (m, 1 H) 4.30 - 4.38 (m, 1 H) 4.16 - 4.25 (m, 1 H) 3.65 - 3.74 (m, 2 H) 3.30 (br s, 8 H) 2.88 - 3.00 (m, 4 H) 2.66 - 2.69 (m, 1 H) 2.20 - 2.29 (m, 4 H) 1.81 - 1.87 (m, 4 H) 1.65 - 1.74 (m, 5 H) 1.42 - 1.57 (m, 5 H) 1.15 - 1.32 (m, 5 H)

Example 22. Synthesis of (S)-3-(5-(4-((1-(4-(7-cyclohexyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-115



[0854] ***Step 1.*** To a solution of compound 1 (150 mg, 258.37 μmol, 1 eq) and compound 2 (80.65 mg, 387.56 μmol, 1.5 eq) in dioxane (4.5 mL) and H_2O (1.5 mL) was added $Pd(dppf)Cl_2$ (18.91 mg, 25.84 μmol, 0.1 eq) and Na_2CO_3 (54.77 mg, 516.75 μmol, 2 eq), purged with N_2 for 3 times. The mixture was stirred under N_2 at 90 °C for 12 h. The reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (PE/EtOAc = 5/2, TLC: PE/EtOAc = 5/1, R_f = 0.69) to yield compound 3 (110 mg, 158.82 μmol, 84% purity) as a white solid. LC-MS (ESI^+) m/z 582.5 $[M+H]^+$.

[0855] ***Step 2.*** To a solution of compound 3 (100 mg, 144.38 μmol, 1 eq) in MeOH (10 mL) was added Pd/C (100 mg, 144.38 μmol, 10% purity, 1 eq). The mixture was stirred under H_2 (15 Psi) at 25 °C for 1 h. The reaction mixture was filtered and concentrated to yield compound 4 (50 mg, 51.39 μmol, 60% purity) as a yellow solid which was used in the next step without further purification. LC-MS (ESI^+) m/z 584.5 $[M+H]^+$.

[0856] ***Step 3.*** To a solution of compound 4 (50 mg, 51.39 μmol, 1 eq) in DCM (3 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 130.99 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition saturation solution of $NaHCO_3$ (10 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield compound 5 (30 mg, crude) as a yellow solid which was used in the next step without further purification. LC-MS (ESI^+) m/z 454.4 $[M+H]^+$.

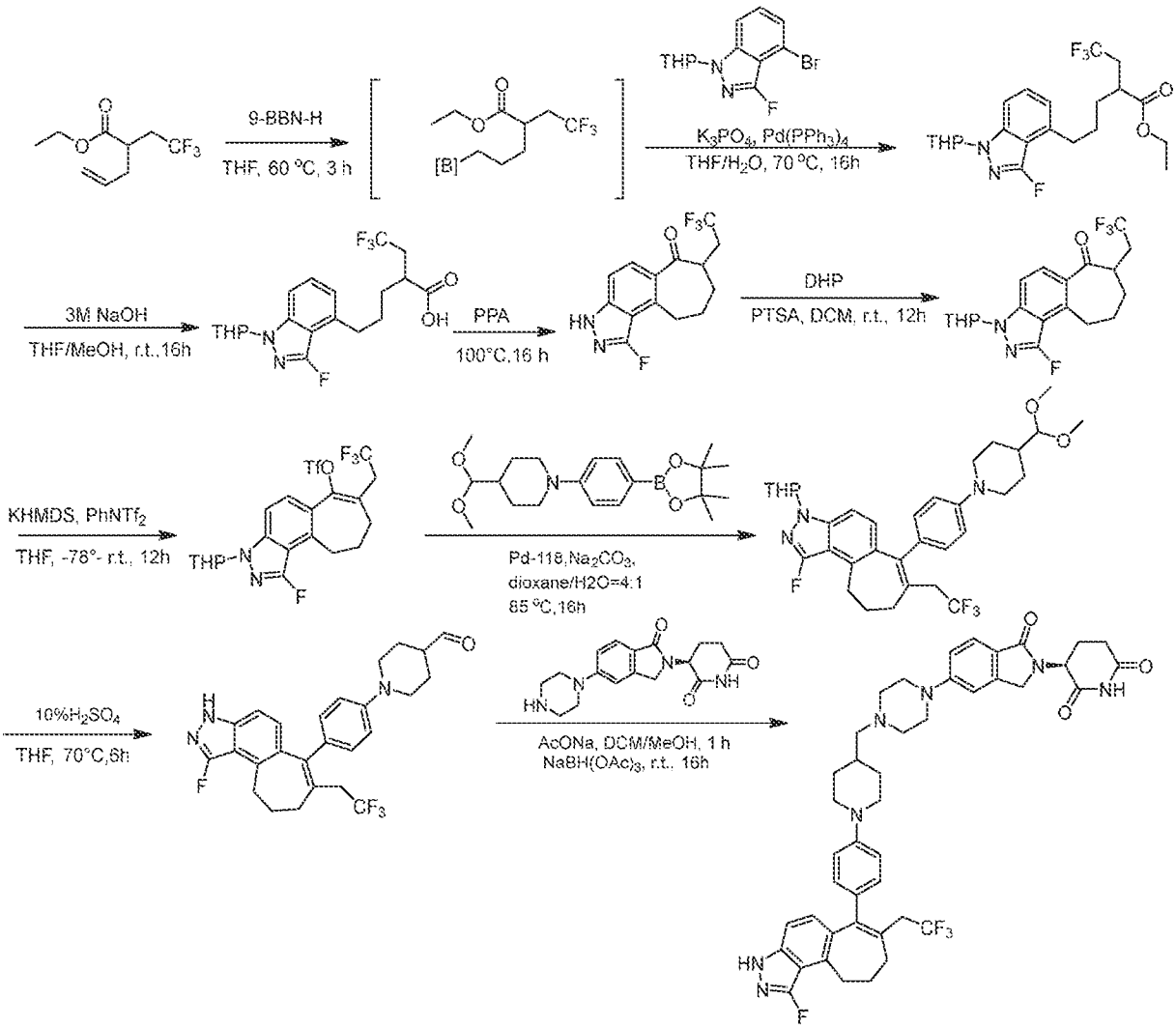
[0857] ***Step 4.*** To a solution of compound 5 (30 mg, 66.14 μmol, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (21.72 mg, 66.14 μmol, 1 eq) in DCM (3 mL) and MeOH (3 mL) , after stirred 30 min was added $NaBH(OAc)_3$ (42.05 mg, 198.41 μmol, 3 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to yield a residue. The residue was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; gradient: 19%-49% B over 10 min), followed by lyophilization to yield (S)-3-(5-(4-((1-(4-(7-cyclohexyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (9.3 mg, 12.14 μmol, 18.36% yield, 100% purity) as a white solid. LC-MS (ESI^+) m/z 766.6 $[M+H]^+$.

[0858] Step 5. LCMS: calc. for C47H55N7O3: 765.44, found: $[M+H]^+$ 766.6.

[0859] HPLC: 100% purity at 220 nm.

[0860] ^{1}H NMR (400MHz, MeOD-d_4) δ = 8.45 (s, 1H), 8.12 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.12 - 7.07 (m, 2H), 6.96 (s, 4H), 6.77 (d, J = 8.8 Hz, 1H), 5.10 (dd, J = 5.2, 13.3 Hz, 1H), 4.47 - 4.34 (m, 2H), 3.71 (br d, J = 12.4 Hz, 2H), 3.41 (s, 4H), 3.04 (t, J = 7.0 Hz, 2H), 2.92 - 2.84 (m, 1H), 2.79 (d, J = 2.4 Hz, 1H), 2.77 - 2.65 (m, 7H), 2.64 - 2.57 (m, 1H), 2.52 - 2.39 (m, 3H), 2.30 (t, J = 7.2 Hz, 2H), 2.15 (dd, J = 5.2, 10.4 Hz, 1H), 2.00 - 1.90 (m, 4H), 1.77 (s, 3H), 1.72 - 1.64 (m, 3H), 1.52 - 1.36 (m, 3H), 1.26 - 1.17 (m, 3H)

Example 23. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-55



[0861] ***Step 1.*** A mixture of ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (5.97 g, 1.7 Eq, 28.4 mmol) , 9-Borabicyclo[3.3.1]nonane solution (3.47 g, 56.8 mL, 0.5 M, 1.7 Eq, 28.4 mmol) in

THF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 3 h under N_2 atmosphere. And then was added 4-bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (5.00 g, 1 Eq, 16.7 mmol) , Tetrakis(triphenylphosphine)palladium(0) (966 mg, 0.05 Eq, 836 μmol), K_3PO_4(10.6 g, 4.15 mL, 3 Eq, 50.1 mmol) , THF (50 mL) and H_2O (250 mL)in mixture solution. The mixture was stirred at 70 °C for 16 hour. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.4 UV) showed one main new spot was observed. The reaction mixture was quenched by addition of water (150 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (petroleum ether/ethyl acetate from 100/0 to 90/10) to yield a product. Compound ethyl 5-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoate (3.4 g, 7.9 mmol, 47 % yield) was obtained as yellow oil.

[0862] ***Step 2.*** To a solution of ethyl 5-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoate (3.40 g, 1 Eq, 7.90 mmol) in THF (15 mL) and MeOH (15 mL) was added sodium hydrate (1.26 g, 10.5 mL, 3 molar, 4 Eq, 31.6 mmol). The mixture was stirred at 25 °C for 16 hour .TLC (petroleum ether: ethyl acetate=3:1 UV R_f=0.5) showed one main new spot was observed. The reaction was adjust to pH=~3 with 1N HCl (10 mL).Then the mixture was added water(100 mL) and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine(100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 5-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoic acid (1.6 g, 4.0 mmol, 50 % yield) as a yellow solid. LC-MS (ESI$^+$) m/z: 403.1 $(M+H)^+$

[0863] ***Step 3.*** A solution of 5-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoic acid (1.6 g, 1 Eq, 4.0 mmol) in PPA (20 mL) stirred at 100 °C for 16 hour. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4 UV) showed a new spot was desired. The reaction was poured into 200 mL water and extracted with ethyl acetate(100 mL*2). The organic layer washed with aq.$NaHCO_3$ (50 mL).The organic layer was washed with brine(100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 1-fluoro-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (320 mg, 1.00 mmol, 25 % yield, 93.9% purity) as a white solid. LC-MS (ESI$^+$) m/z: 301.0 $(M+H)^+$

[0864] ***Step 4.*** 1-fluoro-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (320 mg, 1 Eq, 1.07 mmol) was added to a solution of the 4-methylbenzenesulfonic acid (55.1 mg, 0.3 Eq, 320 μmol), DHP(717 mg, 775 μL, 8 Eq, 8.53 mmol), and DCM (10 mL) at room temperature. The reaction was stirred under N_2 for 12 hour. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (360 mg, 908 μmol, 85.2 % yield, 96.97% purity) as a white solid.

[0865] ***Step 5.*** A mixture of KHMDS solution (280 mg, 1.40 mL, 1 molar, 1.5 Eq, 1.40 mmol) in THF (2 mL) at -78 °C. Then the mixture was stirred until it reached -78 °C. 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (360 mg, 1 Eq, 937 μmol) in THF (8 mL) was added to the mixture and stirred at -78 °C for 1 hour, then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (502 mg, 1.5 Eq, 1.40 mmol) was add to the mixture at -78 °C and stirred at 25 °C for 12 hour. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.3 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (550 mg, 1.07 mmol, crude product) as a white solid.

[0866] ***Step 6.*** A mixture of1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (69.4 mg, 0.1 Eq, 107 μmol) , 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (550 mg, 1 Eq, 1.07 mmol), sodium carbonate (339 mg, 3 Eq, 3.20 mmol) 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (385 mg, 1 Eq, 1.07 mmol) in 1,4-dioxane (8.0 mL) and H_2O (1.6 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred

at 85 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.5 UV) showed one main new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (270 mg, 449 μmol, 42.1% yield) as a white solid.

[0867] ***Step 7.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (270 mg, 1 Eq, 449 μmol) in 10%H_2SO_4 (4 mL) and THF (4 mL) was stirred at 70 °C for 6 hour. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4 UV) showed a new spot was desired. The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (10 mL).Then the mixture was added water (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (200 mg, 424 μmol, 94.5 %) as a yellow solid.

[0868] ***Step 8.*** To a solution of 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (200 mg, 1 Eq, 424 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, $PhSO_3H$ salt(318 mg, 1.5 Eq, 636 μmol) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (104 mg, 69.5 μL, 3 Eq, 1.27 mmol) was stirred at 25 °C for 60 mins, Then sodium triacetoxyborohydride (180 mg, 126 μL, 2 Eq, 848 μmol) and acetic acid (76.4 mg, 73.2 μL, 3 Eq, 1.27 mmol) was added .The mixture was stirred at 25 °C for 16 hour. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 27%-57%,7min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (37.3 mg, 46.5 μmol, 11.0 %, 97.7% purity) was obtained as a white solid.

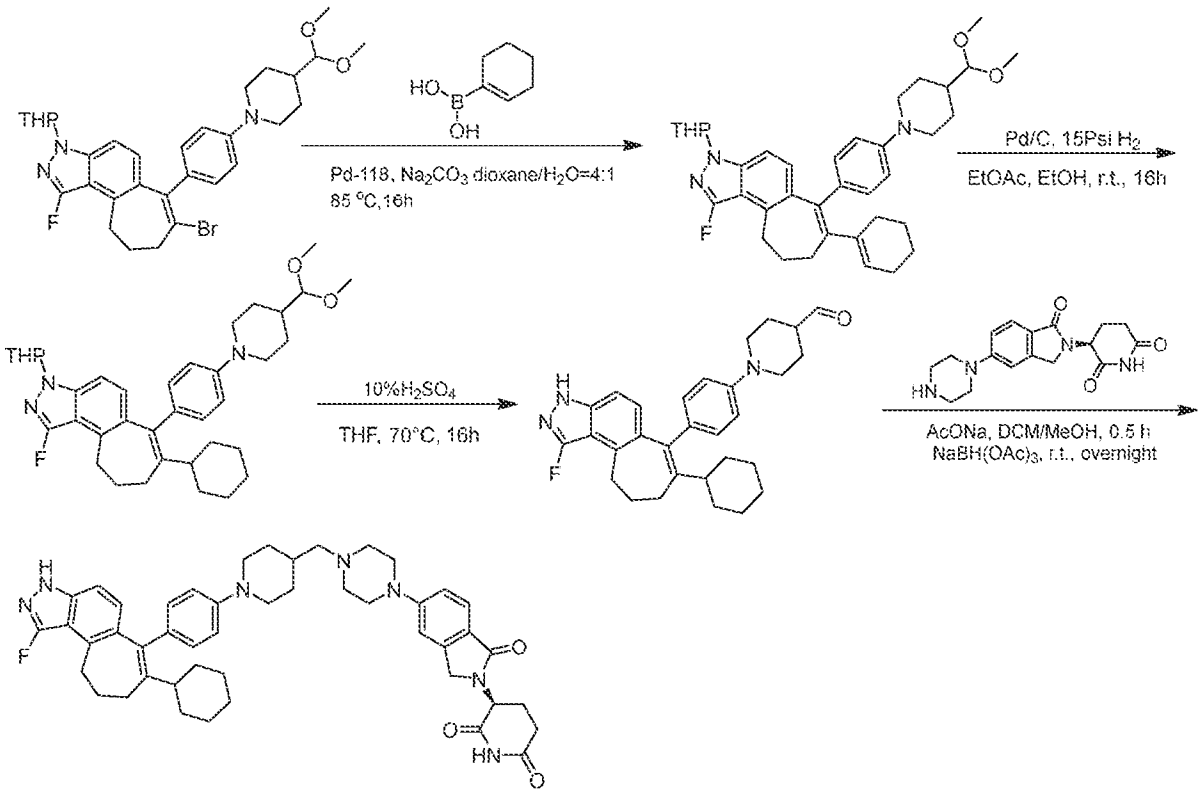
[0869] LCMS: calc. for $C_{43}H_{45}F_4N_7O_3$: 783.87, found: $[M+H]^+$ 784.2.

[0870] HPLC: 97.668% purity at 220 nm.

[0871] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.50 (s, 1H), 10.95 (s, 1H), 8.16 (s, 0.307H), 7.52 (d, J = 8.5 Hz, 1H), 7.19 (dd, J = 2.0, 8.8 Hz, 1H), 7.10 - 7.02 (m,2H), 6.92 (s, 4H), 6.77 (d, J = 8.5 Hz, 1H), 5.05 (dd, J = 4.9, 13.2 Hz, 1H), 4.37 - 4.25 (m, 1H), 4.24 - 4.16 (m, 1H), 3.72 (br d, J = 12.0 Hz, 2H), 3.34 (br s,10H), 2.96 (br d, J = 6.8 Hz, 2H), 2.93 - 2.83 (m, 1H), 2.67 (br t, J = 11.5 Hz, 2H), 2.58 (br d, J = 16.1 Hz, 1H), 2.36 - 2.26 (m, 3H), 2.23 (br d, J = 6.8 Hz,2H), 2.03 (br t, J = 6.7 Hz, 2H), 1.99 - 1.90 (m, 1H), 1.83 (br d, J = 11.5 Hz, 2H), 1.77 - 1.65 (m, 1H), 1.28 - 1.14 (m, 2H)

[0872] SFC: retention time, 2.657 min; Area, 93.371%; method: IC_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

Example 24. Synthesis of (3S)-3-[5-[4-[[1-[4-(7-cyclohexyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-61



[0873] ***Step 1***. A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (300 mg, 501.2 μmol, 1 eq) , cyclohex-1-en-1-ylboronic acid (75.8 mg, 601.5 μmol, 1.2 eq), Na_2CO_3 (159.4 mg, 1.50 mmol, 3

eq), Pd-118(40.9 mg, 50.1 μmol, 0.1 eq) was added in dioxane (4 mL) and H_2O (1 mL) and purged with N_2 for 3 times, the mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. LCMS showed 82% desired MS was detected. Then the reaction was cooled to room temperature. The mixture was treated with H_2O (50 mL), extracted with EtOAc (50 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~20% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuo to give 7-(cyclohex-1-en-1-yl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (270 mg, 450.17 μmol, 89.82% yield) as a white solid. LC-MS (ESI^+) m/z: 600.3 $(M+H)^+$

[0874] ***Step 2.*** A mixture of 7-(cyclohex-1-en-1-yl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (270 mg, 450.2 μmol, 1 eq) and Pd/C (2.39 g, 10% purity) was added in EtOAc (4 mL) and EtOH (4 mL)and purged with H_2 for three times, the mixture was stirred at 50 °C for 12 hr. LCMS showed 77% desired MS was detected. the reaction mixture was filtered and concentrated under reduced pressure to give a 7-cyclohexyl-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (250 mg, 415.3 μmol, 92.28% yield) as a white solid.

[0875] ***Step 3.*** To a solution of 7-cyclohexyl-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (135 mg, 224.3 μmol, 1 eq) in 10% H_2SO_4 (10 mL) and THF (10 mL). The mixture was stirred at 70 °C for 16 hour. LCMS showed desired MS was detected. The solvent was removed under vaccum. The aqueous solution was added saturated aqueous $NaHCO_3$ to adjust pH=6. The reaction mixture was treated by addition H_2O 50 mL at 25°C, and then treated with H_2O 50 mL and extracted with Ethyl acetate 50 mL (50 mL * 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give 1-(4-(7-cyclohexyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (100 mg, 212 μmol, 94.5% yield), LC-MS (ESI+) m/z: 472 (M+H)+

[0876] ***Step 4.*** A mixture of (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (159.2 mg, 318.1 μmol, 1.5 eq, $PhSO_3H$ salt), 1-(4-(7-cyclohexyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (100 mg, 212 μmol, 1

eq), sodium acetate (52.2 mg, 636.1 μmol, 3 eq) was added in DCM (5 mL) and MeOH (5 mL), the mixture was stirred at 25 °C for 0.5h, and then $NaBH(OAc)_3$ (89.9 mg, 424.1 μmol, 2 eq), acetic acid (175.7 mg, 636.1 μmol, 167.3 μL, 3 eq) was added in the mixture, the mixture was stirred at 25 °C for 12 hr, The reaction was treated with H_2O (20 mL), extracted with EtOAc (20 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep. HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN];gradient:34%-64% B over 7 min). The aqueous phase was lyophilized to dryness to give (3S)-3-[5-[4-[[1-[4-(7-cyclohexyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (16.5 mg, 21.05 μmol, 4.73% yield) as a white solid.

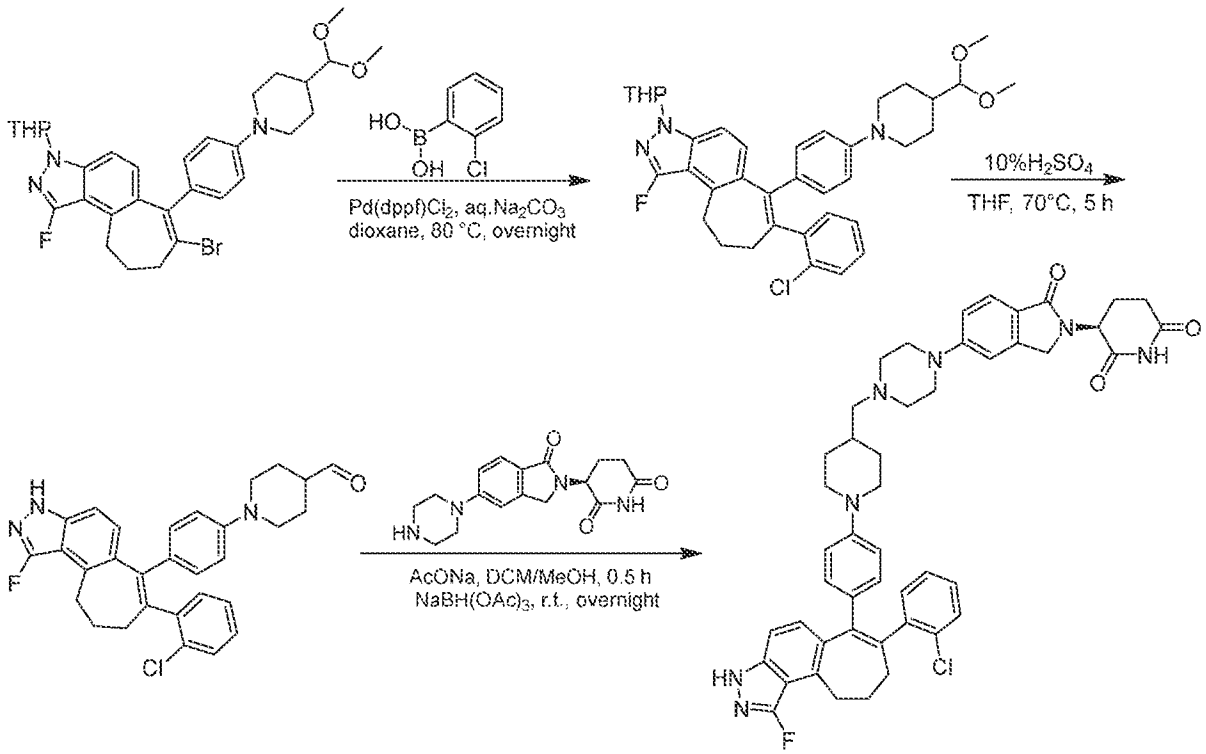
[0877] LC-MS (ESI+) m/z: 784.3 (M+H) +

[0878] HPLC: 98.928%, purity at 220 nm.

[0879] SFC: retention time, 3.808 min; Area, 92.345; method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.lcm

[0880] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.46 - 12.34 (m, 1H), 11.07 - 10.89 (m, 1H), 8.16 (s, 0.351H), 7.57 - 7.50 (m, 1H), 7.16 - 7.03 (m, 3H), 6.94 - 6.81 (m, 4H), 6.71 (d, J = 8.8 Hz, 1H), 5.06 (dd, J = 5.2, 13.2 Hz, 1H), 4.43 - 4.13 (m, 2H), 3.76 - 3.66 (m, 2H), 3.33 - 3.27 (m, 8H), 3.01 - 2.87 (m, 3H), 2.74 - 2.55(m, 4H), 2.41 - 2.33 (m, 1H), 2.29 - 2.16 (m, 4H), 2.02 - 1.94 (m, 1H), 1.90 - 1.78 (m, 4H), 1.76 - 1.67 (m, 3H), 1.66 - 1.57 (m, 3H), 1.50 - 1.39 (m, 2H), 1.31- 1.10 (m, 5H).

Example 25. Synthesis of (S)-3-(5-(4-((1-(4-(7-(2-chlorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-56



[0881] ***Step 1.*** A 8 mL thread vial was equipped with magnetic stirrer. $Pd(dppf)Cl_2$(13.643 mg, 0.1 Eq, 16.707 μmol) was added to a mixture suspension of 7-bromo-6-(4-(4-(dimethoxymethyl) piperidin-1-yl) phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3, 8, 9, 10-tetrahydrocyclohepta[e]indazole (100 mg, 1 Eq, 167 μmol) and sodium carbonate (53.1 mg, 3 Eq, 501.2 μmol) and (2-chlorophenyl)boronic acid (31.3 mg, 1.2 Eq, 200.5 μmol) in 1,4-dioxane (3 mL) and H_2O (0.6 mL). The mixture was stirred at 90 °C for 16 hour. LCMS showed 82.5% desired MS. TLC (petroleum ether: ethyl acetate=5:1, UV) showed one main new spot was observed. 50 mL water was added, and the mixture was extracted with dichloromethane (100 mLx2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a yellow oil. The yellow oil was purified by flash column (petroleum ether/ethyl acetate from 100/0 to 0/100) and the organic layer was concentrated in vacuo to give 7-(2-chlorophenyl)-6-(4-(4-(dimethoxymethyl)piperidine-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole(95 mg, 0.15 mmol) as a yellow solid. LC-MS (ESI+) m/z: 630.2 $(M+H)^+$

[0882] *Step 2.* To a solution of 7-(2-chlorophenyl)-6-(4-(4-(dimethoxymethyl)piperidine-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (95 mg, 1 Eq, 0.15 mmol) in THF (2 mL) and 10 % H_2SO_4 (2 mL) was stirred at 70 °C for 5 h. The reaction mixture was quenched by addition aq.$NaHCO_3$ (10 mL) at 0°C, then extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (20 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(4-(7-(2-chlorophenyl)-1-fluoro-3, 8, 9, 10-tetrahydrocyclohepta[e]indazol-6-yl) phenyl)piperidine-4-carbaldehyde (100 mg, 95 % yield) as a yellow solid. LC-MS (ESI^+) m/z: 500.1 $(M+H)^+$.

[0883] *Step 3.* A mixture of (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione benzenesulfonate (72.98 mg, 150.00 µmol, 1.5 eq), 1-(4-(7-(2-chlorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (50 mg, 100 µmol, 1 eq) and sodium acetate (41 mg, 500 µmol, 5 eq) and acetic acid (12 mg, 200 µmol, 2 eq) in THF (2 mL) and MeOH (2 mL) at 30 °C for 1 h, then $NaBH(OAc)_3$ (42.39 mg, 200 µmol, 2 eq) was added to the mixture and was stirred at 25 °C for 15 h. The reaction mixture was quenched by addition H_2O (15 mL) at 25 °C, and then diluted with DCM (5 mL) and extracted with DCM (15 mL * 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 150*40mm*10um; mobile phase:[water(FA)-ACN]; B%: 27%-57%,7min). Compound (S)-3-(5-(4-((1-(4-(7-(2-chlorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (14 mg, 17.23 µmol, 17.23% yield) was obtained as a white solid.

[0884] LC-MS (ESI+) m/z: 812.2 $(M+H)^+$

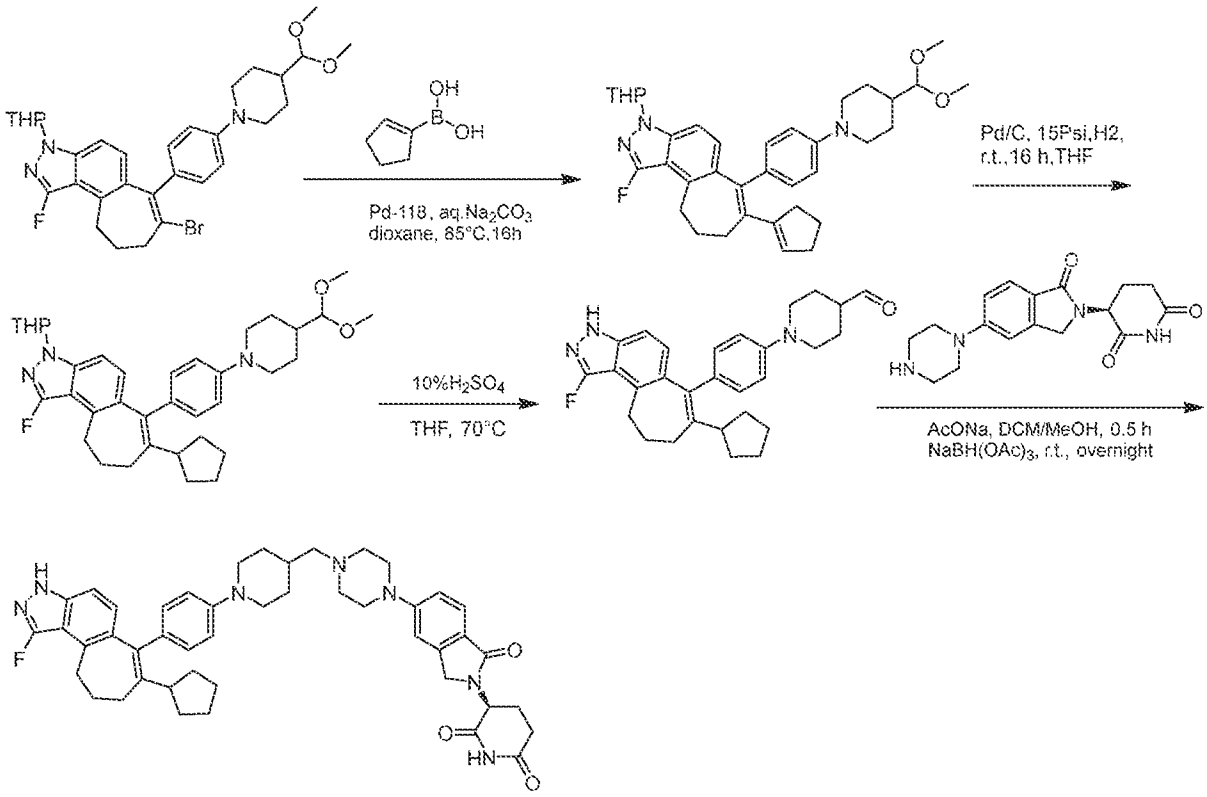
[0885] HPLC: 100% purity at 220 nm.

[0886] ^1H NMR (400 MHz, DMSO-d_6) δ= 9.39 (s, 1H), 8.14 (s, 0.183H), 8.00 (s, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.13 (s, 1H),7.12 - 7.08 (m, 1H), 7.03 - 6.99 (m, 3H), 6.90 (s, 1H), 6.80 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 5.23 (dd, J = 5.1, 13.1 Hz, 1H), 4.41 (s, 1H), 4.30(s, 1H), 3.64 (br d, J = 10.5 Hz, 2H), 3.38 (br s, 5H), 3.11 (br d, J = 8.3 Hz, 1H), 2.92 (br s, 2H), 2.65 (br s, 6H), 2.34 (br s, 7H), 2.27 - 2.19 (m, 1H), 1.87(br s, 2H), 1.48 - 1.20 (m, 3H)

[0887] SFC: retention time, 3.698 min; Area, 95.647%; method:

[0888] ID_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

Example 26. Synthesis of (S)-3-(5-(4-((1-(4-(7-cyclopentyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-116



[0889] ***Step 1.*** A mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (300 mg, 501.2 μmol, 1 eq), cyclopent-1-en-1-ylboronic acid (61.71 mg, 551.34 μmol, 1.1 eq), disodium carbonate (159.4 mg, 1.50 mmol, 3 eq), Pd-118(32.7 mg, 50.1 μmol, 0.1 eq) in H_2O (2 mL) and dioxane (8 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 16 hr under N_2 atmosphere. The reaction mixture was quenched by addition **100** mL H_2O at 25 °C, and then diluted with **50** mL ethyl acetate and extracted with ethyl acetate(**100** mL * **3**). The combined organic layers were washed with brine **100** mL, dried over **drying Na_2SO_4**, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (**ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min**). Compound 7-(cyclopent-1-en-1-yl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-

3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 143.6 μmol, 28.65% yield, 84.109% purity) was obtained as a yellow solid.

[0890] LC-MS (ESI^+) m/z: 586.2 $(M+H)^+$

[0891] ***Step 2.*** To a solution of 7-(cyclopenten-1-yl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (200 mg, 341.44 μmol, 1 eq) in THF (10 mL) was added **Pd/C (10%, 100 mg)** under N_2 atmosphere. The suspension was degassed and purged with H_2 for **3** times. The mixture was stirred under H_2 (**15** Psi) at 25 °C for 16 hr . The reaction mixture was filtered and the filter was concentrated. The residue was purified by prep-HPLC (**column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];gradient:70%-100% B over 7 min**) to give desired compound (**85** mg, yield **42.35%**) as a white solid, which was further separated by SFC (**column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [CO2-EtOH(0.1%NH3H2O)];B%:40%%, isocratic elution mode**). The crude product 7-cyclopentyl-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (55 mg, 93.57 μmol, 27.41% yield) as colorless oil was used into the next step without further purification.

[0892] LC-MS (ESI^+) m/z: 588.3 $(M+H)^+$

[0893] ***Step 3.*** To a solution of 7-cyclopentyl-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (55 mg, 93.57 μmol, 1 eq) in H2SO4 (3 mL) and THF (3 mL) .The mixture was stirred at 70 °C for 16 hr. The mixture was added with $NaHCO_3$ to pH=7~8. The reaction mixture was diluted with 50 mL H_2O and extracted with EA (50 mL * 2). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product 1-(4-(7-cyclopentyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (40 mg, 87.42 μmol, 93.42% yield) as white solid was used into the next step without further purification.

[0894] ***Step 4.*** A mixture of 1-[4-(7-cyclopentyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (40 mg, 87.42 μmol, 1 eq) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione benzenesulfonate (63.8 mg, 131.1 μmol, 1.5 eq) and sodium acetate (21.5 mg, 262.3 μmol, 3 eq) and acetic acid (10.5 mg, 174.8 μmol, 10 μL, 2 eq) in MeOH (2 mL) and DCM (2 mL) at 30 °C for 0.5 hour, then $NaBH(OAc)_3$(37.1 mg, 174.8 μmol, 2 eq) was added to the mixture and was stirred at 30

°C for 16 hr. The reaction mixture was quenched by addition H_2O **20** mL at 25 °C, and then diluted with **20** mL ethyl acetate and extracted with ethyl acetate (**20** mL * **3**). The combined organic layers were washed with **20** mL **brine**, dried over **drying Na_2SO_4**, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (**column: Xtimate C18 150*40mm*5um; mobile phase: [water(FA)-ACN];gradient:20%-60% B over 9 min**). Compound (S)-3-(5-(4-((1-(4-(7-cyclopentyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (10 mg, 12.99 μmol, 14.86% yield, 100% purity) was obtained as a white solid.

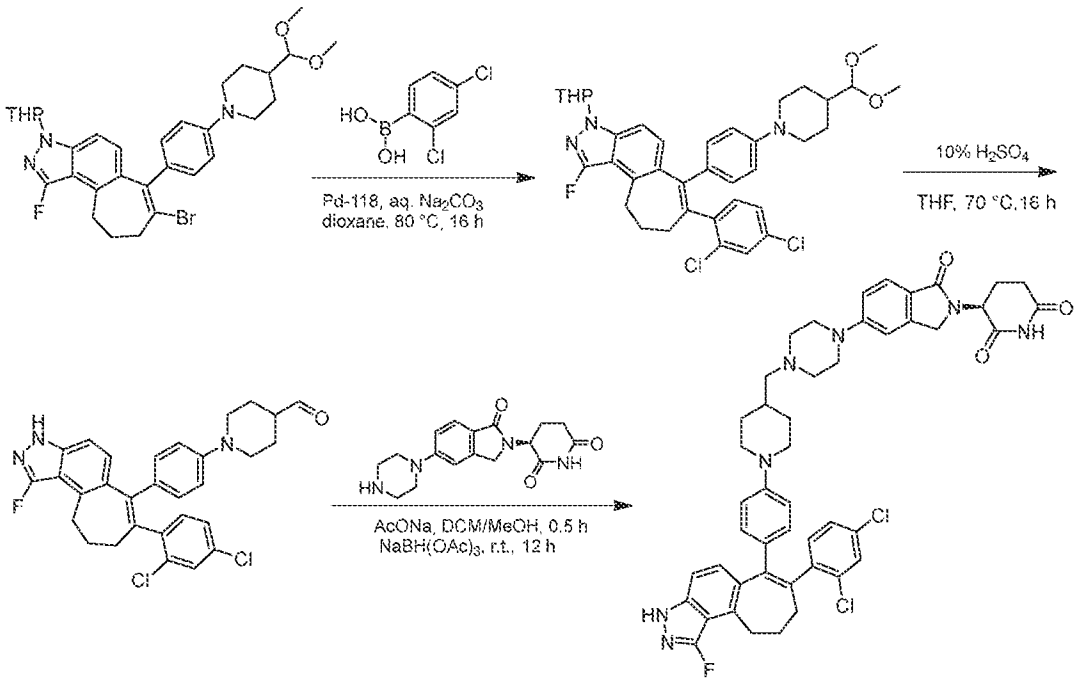
[0895] LC-MS (ESI^+) m/z: 770.6 $(M+H)^+$

[0896] HPLC: 98.277% purity at 220 nm.

[0897] ^1H NMR (400 MHz, DMSO-d_6) δ= 12.42 (s, 1H), 10.96 (s, 1H), 8.26 (s, 0.247H), 7.53 (d, J = 8.8 Hz, 1H), 7.14 (dd, J = 2.3, 8.8 Hz, 1H), 7.08 (s, 2H), 6.88(s, 4H), 6.70 (d, J = 8.8 Hz, 1H), 5.05 (dd, J = 5.0, 13.1 Hz, 1H), 4.31 (s, 1H), 4.23 (s, 1H), 3.69 (br d, J = 12.3 Hz, 2H), 3.30 (br s, 6H), 2.94 (br d, J = 5.5Hz, 4H), 2.66 (br s, 3H), 2.42 - 2.32 (m, 2H), 2.23 (br d, J = 7.0 Hz, 4H), 2.00 - 1.91 (m, 1H), 1.85 (br s, 4H), 1.68 (br s, 6H), 1.49 (br s, 4H), 1.22 (br d, J =13.6 Hz, 2H)

[0898] SFC: retention time, 3.447 min; Area, 87.534%; method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM

Example 27. Synthesis of (3S)-3-[5-[4-[[1-[4-[7-(2,4-dichlorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-59



[0899] ***Step 1.*** A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (130 mg, 217.2 μmol, 1 eq) , (2,4-dichlorophenyl)boronic acid (41.4 mg, 217.2 μmol, 1 eq) , Pd-118 (14.16 mg, 21.7 μmol, 0.1 eq) , Na_2CO_3(69.1 mg, 651.6 μmol, 3 eq) in dioxane (4 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hr under N_2 atmosphere. LCMS showed desired 83% MS. TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The reaction mixture was diluted with 30 mL H_2O and extracted with 40 mL ethyl acetate (20 mL* 2). The combined organic layers were washed with brine 20 mL (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate= 10/1). Compound 7-(2,4-dichlorophenyl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (70 mg, 105.32 μmol, 48.49% yield) was obtained as a white solid. LC-MS (ESI+) m/z: 664.1 $(M+H)^+$

[0900] ***Step 2.*** To a solution of 7-(2,4-dichlorophenyl)-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (70 mg, 105.3 μmol, 1 eq) in THF (4 mL) was added 10% H_2SO_4 (4 mL). The mixture was stirred

at 70 °C for 16 hr. LCMS showed desired 61% MS. The reaction mixture was quenched by saturated $NaHCO_3$ aqueous solution addition 10 mL at 25 °C, and then diluted with 10 mL H_2O and extracted with 30 mL ethyl acetate (15 mL * 2). The combined organic layers were washed with brine 20 mL (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product 1-[4-[7-(2,4-dichlorophenyl)-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (60 mg, 97.00 μmol, 92.10% yield) was used into the next step without further purification Compound 1-[4-[7-(2,4-dichlorophenyl)-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (60 mg, 97.00 μmol, 92.10% yield) was obtained as a white solid.LC-MS (ESI+) m/z: 552.0 $(M+H)^+$.

[0901] ***Step 3.*** To a solution of 1-[4-[7-(2,4-dichlorophenyl)-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (60 mg, 97.0 μmol, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (72.8 mg, 145.5 μmol, 1.5 eq, $PhSO_3H$ salt) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (15.91 mg, 194.0 μmol, 2 eq) .The mixture was stirred at 25 °C for 0.5 h. After, the mixture which was added $NaBH(OAc)_3$ (41.12 mg, 194.0 μmol, 2 eq) and acetic acid (17.47 mg, 291.00 μmol, 16.64 μL, 3 eq) stirred at 25 °C for 16 hr. LC-MS showed 56% desired mass. The reaction mixture was diluted with 10 mL H_2O and extracted with 20 mL ethyl acetate (10 mL * 2). The combined organic layers were washed with brine 10 mL (5 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 30%-60%, 7min). The aqueous phase was lyophilized to dryness to give compound (3S)-3-[5-[4-[[1-[4-[7-(2,4-dichlorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (14 mg, 16.6 μmol, 17.0% yield) as a white solid.

[0902] LC-MS (ESI^+) m/z: 846.4 $(M+H)^+$.

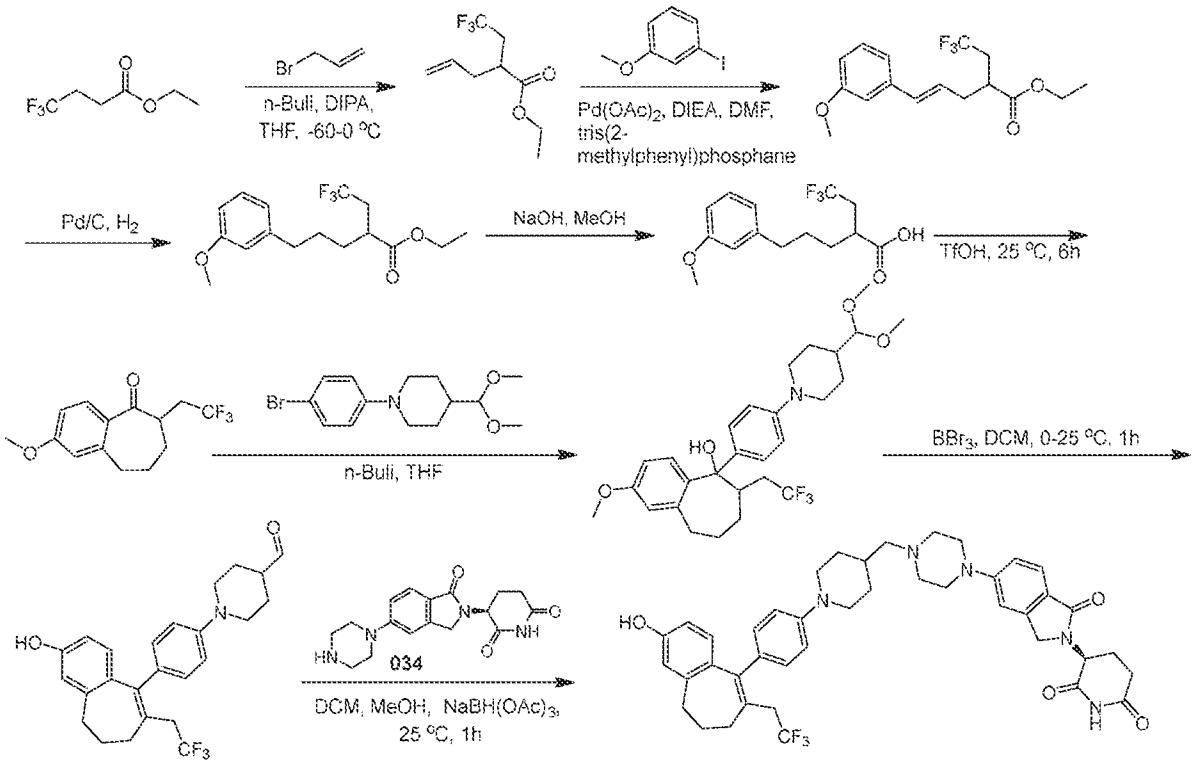
[0903] HPLC: 94.498%, purity at 220 nm.

[0904] SFC: Rt: 4.042 min; Area, 82.285%; method: ID_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

[0905] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.56 (s, 1 H) 10.96 (s, 1 H) 8.20 (s, 0.252 H) 7.60 (d, J=2.15 Hz, 1 H) 7.52 (d, J=8.82 Hz, 1 H) 7.18 - 7.31 (m, 3 H) 7.02 - 7.09 (m, 2 H) 6.80 - 6.86 (m, 1 H) 6.62 - 6.74 (m, 4 H) 5.05 (dd, J=13.23, 5.01 Hz, 1 H) 4.15 - 4.38 (m, 2 H) 3.63 (br

d, J=10.37 Hz, 2 H) 3.23 - 3.31 (m, 8 H) 2.99 - 3.14 (m, 2 H) 2.85 - 2.95 (m, 1 H) 2.55 - 2.64 (m, 3 H) 2.32 - 2.46 (m, 2 H) 2.24 - 2.28 (m, 1 H) 2.13 - 2.21 (m, 4 H) 1.92 - 2.00 (m, 1 H) 1.72 - 1.81 (m, 2 H) 1.60 - 1.71 (m, 1 H) 1.09 - 1.21 (m, 2 H)

Example 28. Synthesis of (3S)-3-[5-[4-[[1-[4-[2-hydroxy-6-(2,2,2-trifluoroethyl)-8,9-dihydro-7H-benzo[7]annulen-5-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-68



[0906] ***Step 1.*** To a solution of DIPA (7.73 g, 76.41 mmol, 10.80 mL) in THF (100 mL) was added n-BuLi (2.5 M, 28.21 mL) dropwise at 0 °C under N_2 atmosphere and stirred at 0 °C for 0.5 h. Then the mixture was cooled to -60 °C and ethyl 4,4,4-trifluorobutanoate (10 g, 58.78 mmol) in THF (100 mL) was added dropwise at -60 °C and stirred at -60 °C for 0.5 h. 3-Bromoprop-1-ene (9.24 g, 76.41 mmol) in THF (10 mL) was added dropwise at -60 °C and stirred at -60 °C for 3 h. The reaction was quenched with sat.aq. NH_4Cl (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 5%) to give ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (6.1 g, 44.4% yield) as yellow liquid.

[0907] ^{1}HNMR (400MHz, $CDCl_3$): δ 5.79 - 5.61 (m, 1H), 5.24 - 5.04 (m, 2H), 4.26 - 4.13 (m, 2H), 2.81 - 2.73 (m, 1H), 2.67 - 2.54 (m, 1H), 2.44 (td, J = 7.0, 13.9 Hz, 1H), 2.38 - 2.28 (m, 1H), 2.27 - 2.17 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H).

[0908] ***Step 2.*** A mixture of ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (2.67 g, 11.42 mmol), 1-iodo-3-methoxy-benzene (3.21 g, 13.70 mmol, 1.63 mL), $Pd(OAc)_2$ (128.17 mg, 570.90 μmol), DIEA (3.54 g, 27.40 mmol, 4.77 mL) and tris-o-tolylphosphane (347.53 mg, 1.14 mmol) in DMF (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The reaction was quenched with water (50 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 10%) to give the product of ethyl (E)-5-(3-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pent-4-enoate (1.5 g, 40.3% yield) as a yellow oil. LC-MS (ESI^+) m/z: 317.2 $(M+H)^+$.

[0909] ***Step 3.*** To a solution of Pd/C (1.5 g, 10% purity) in MeOH (10 mL) was added ethyl (E)-5-(3-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pent-4-enoate (1.5 g, 4.60 mmol) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 50 °C for 2 h. The reaction mixture was filtered and the filter was concentrated to give ethyl 5-(3-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pentanoate (1.3 g, 87.9% yield) as a yellow oil. LC-MS (ESI^+) m/z: 319.2 $(M+H)^+$.

[0910] ***Step 4.*** To a solution of ethyl 5-(3-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pentanoate (1.3 g, 4.04 mmol) in MeOH (12 mL) and H_2O (3 mL) was added NaOH (404.30 mg, 10.11 mmol). The mixture was stirred at 25 °C for 6 h. The reaction mixture was adjust pH to ~5 with 2 M HCl and concentrated under reduced pressure to remove solvent. The residue was added DCM/MeOH (20/1, 20 mL), and stirred at 20 °C for 2 h. The slurry was filtered, and the cake was rinsed with DCM (2 x 3 mL). The solid was collected and dried in vacuo to give 5-(3-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pentanoic acid (1.1 g, 89.0% yield) as a colorless oil. LC-MS (ESI^+) m/z: 291.1 $(M+H)^+$.

[0911] ***Step 5.*** A solution of 5-(3-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pentanoic acid (900 mg, 2.82 mmol) in TfOH (2.12 g, 14.11 mmol, 1.25 mL) was stirred at 25 °C for 6 h. The reaction was quenched with sat.aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica

gel chromatography (ethyl acetate in petroleum ether= 0% to 8%) to give the product of 2-methoxy-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydrobenzo[7]annulen-5-one (250 mg, 30.9% yield) as a colorless gum. LC-MS (ESI^+) m/z: 273.3 $(M+H)^+$.

[0912] ***Step 6.*** To a solution of 1-(4-bromophenyl)-4-(dimethoxymethyl)piperidine (274.10 mg, 872.32 μmol) in THF (3 mL) was added n-BuLi (2.5 M, 523.39 μL) at -60 °C and stirred at -60 °C for 0.5 h. Then 2-methoxy-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydrobenzo[7]annulen-5-one (250 mg, 872.32 μmol) in THF (3 mL) was added at -60 °C. The mixture was stirred at -60 °C for 3 h. The reaction was quenched with sat.aq. NH_4Cl (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 25%) to give the product of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-2-methoxy-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydrobenzo[7]annulen-5-ol (220 mg, 42.23% yield) as a white solid. LC-MS (ESI^+) m/z: 508.4 $(M+H)^+$.

[0913] ***Step 7.*** To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-2-methoxy-6-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydrobenzo[7]annulen-5-ol (200 mg, 334.92 μmol) in DCM (2 mL) was added BBr_3 (419.53 mg, 1.67 mmol, 161.36 μL) at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction was quenched with sat.aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the product of 1-[4-[2-hydroxy-6-(2,2,2-trifluoroethyl)-8,9-dihydro-7H-benzo[7]annulen-5-yl]phenyl]piperidine-4-carbaldehyde (150 mg, 93.8% yield) as a yellow oil. LC-MS (ESI^+) m/z: 430.3 $(M+H)^+$.

[0914] ***Step 8.*** To a solution of 1-[4-[2-hydroxy-6-(2,2,2-trifluoroethyl)-8,9-dihydro-7H-benzo[7]annulen-5-yl]phenyl]piperidine-4-carbaldehyde (150 mg, 314.34 μmol) in DCM (5 mL) and MeOH (5 mL) was added (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (113.54 mg, 345.77 μmol, BENZENESULFONIC ACID) and stirred at 25 °C for 0.5 h. Then $NaBH(OAc)_3$ (333.10 mg, 1.57 mmol) was added and stirred at 25 °C for 0.5 h. The solvent was removed to yield a residue. The residue was purified by preparative HPLC (column: Welch Xtimate C18 150*25 mm*5 um; mobile phase: [water (FA)-ACN]; B%: 23% - 53%, 11 min), followed by lyophilization to give the product of (3S)-3-[5-[4-[[1-[4-[2-hydroxy-6-(2,2,2-trifluoroethyl)-8,9-dihydro-7H-benzo[7]annulen-5-yl]phenyl]-4-piperidyl]methyl]piperazin-1-

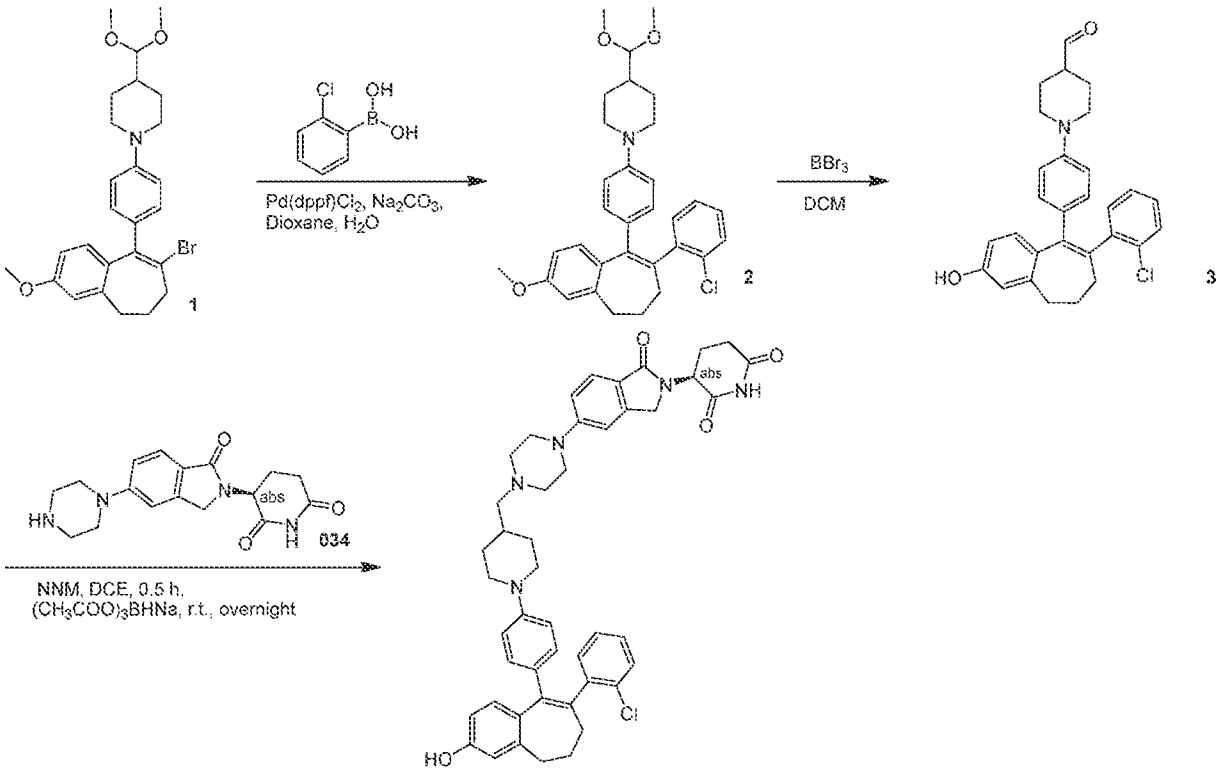
yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (60 mg, 25.7% yield) as a white solid. LC-MS (ESI^+) m/z: 742.5 $(M+H)^+$.

[0915] LCMS: calc. for $C_{42}H_{46}F_3N_5O_4$: 741.8, found: $[M+H]^+$ 742.5.

[0916] HPLC: 99.8% purity at 220 nm.

[0917] ^{1}HNMR (500MHz, MeOD-d4): δ 7.64 (d, J = 8.5 Hz, 1H), 7.12 - 7.05 (m, 2H), 7.01 - 6.93 (m, 4H), 6.66 (d, J = 2.6 Hz, 1H), 6.60 - 6.56 (m, 1H), 6.53 - 6.48 (m, 1H), 5.10 (dd, J = 5.2, 13.4 Hz, 1H), 4.48 - 4.33 (m, 2H), 3.72 (d, J = 12.4 Hz, 2H), 3.43 - 3.35 (m, 4H), 3.11 (q, J = 11.3 Hz, 2H), 2.95 - 2.85 (m, 1H), 2.81 - 2.69 (m, 3H), 2.68 - 2.62 (m, 6H), 2.46 (dq, J = 4.7, 13.2 Hz, 1H), 2.34 (d, J = 7.2 Hz, 2H), 2.25 - 2.08 (m, 5H), 1.93 (d, J = 11.6 Hz, 2H), 1.78 (ddd, J = 3.8, 7.3, 11.0 Hz, 1H), 1.39 (dq, J = 3.7, 12.3 Hz, 2H).

Example 29. Synthesis of (S)-3-(5-(4-((1-(4-(8-(2-chlorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-51



[0918] *Step 1.* A mixture of compound 1 (500 mg, 1.03 mmol, 1.0 eq.), 2-ChlorophenylboronicAcid (193 mg, 1.23 mmol, 1.2 eq.), Na_2CO_3 (327 mg, 3.08 mmol, 3.0 eq.) and $Pd(dppf)Cl_2$ (83.9 mg, 103 μmol, 0.1 eq.) in Dioxane (20 mL) and water (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hour

under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition EA 10 mL at 20 °C, and then diluted with water 30 mL and extracted with EA 30 mL (10 mL x 3). The combined organic layers were washed with EA 30 mL (10 mL x 3), dried over Na_2So_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 5/1) to give compound 2 (350 mg, 676 μmol, 65.7 % yield) as a yellow solid.

[0919] LC-MS (ESI^+) m/z: 518.1 $(M+H)^+$.

[0920] ^1H NMR (500 MHz, DMSO-d_6) δ: ppm 7.40 (dd, J = 7.86, 0.99 Hz, 1 H), 7.08 - 7.22 (m, 3 H), 6.89 (d, J = 2.59 Hz, 1 H), 6.68 - 6.77 (m, 2 H), 6.57 - 6.68 (m, 4 H), 5.07 (s, 1 H), 4.05 (d, J = 6.56 Hz, 1 H), 3.77 (s, 2 H), 3.71 - 3.82 (m, 1 H), 3.53 - 3.64 (m, 2 H), 3.25 (s, 6 H), 2.74 - 2.89 (m, 2 H), 2.12 - 2.23 (m, 2 H), 2.05 - 2.11 (m, 2 H), 1.62 - 1.68 (m, 3 H), 1.26 (s, 2 H), 0.90 - 0.99 (m, 1 H), 0.83 - 0.86 (m, 2 H).

[0921] ***Step 2.*** To a solution of compound 2 (350 mg, 676 μmol, 1.0 eq.) in DCM (10 mL) was added BBr_3 (846 mg, 3.38 mmol, 5.0 eq.). The mixture was stirred at 20 °C for 1 hour and then water (1 mL) in DCM (10 mL) was added dropwise at 20 °C. The resulting mixture was stirred at 20 °C for 2 hour. LCMS showed the reaction was completed. The mixture was concentrated and then water (20 mL) was added. The mixture was extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The mixture was concentrated in vacuo to give crude product 3. No further purification as it is used for the next step directly.

[0922] LC-MS (ESI+) m/z: 458.2$(M+H)^+$

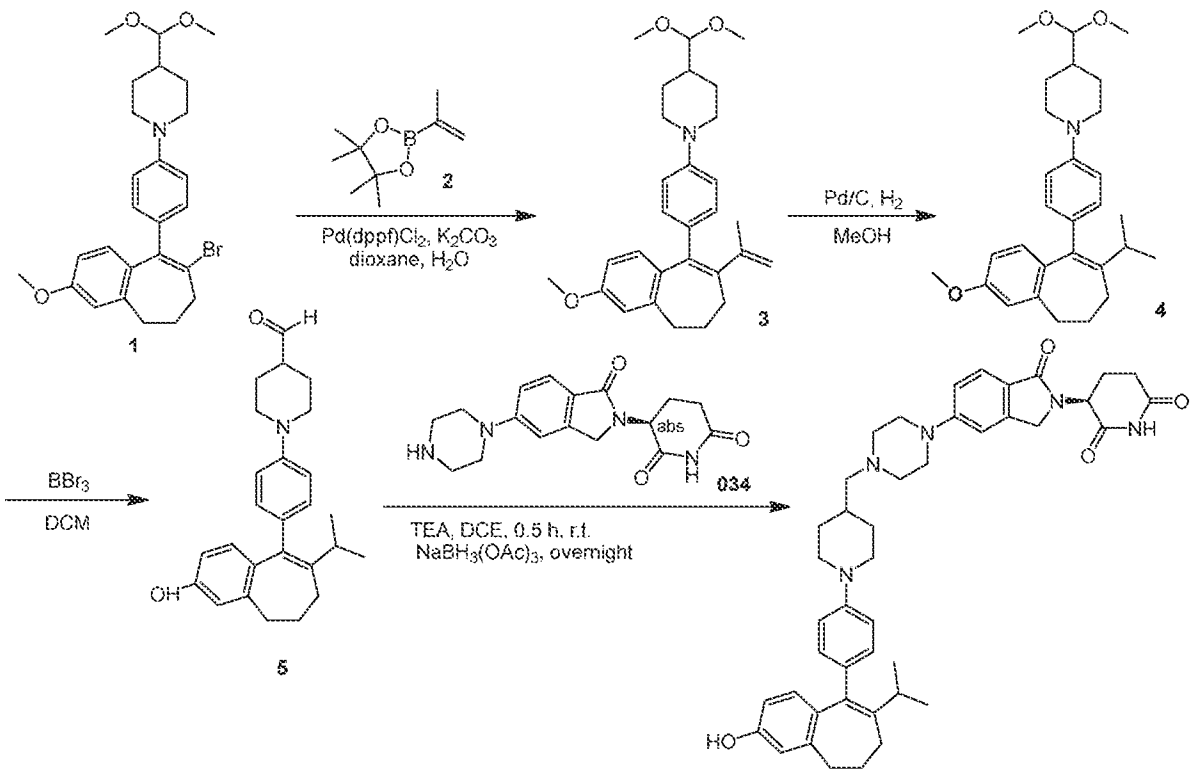
[0923] ***Step 3.*** To a solution of compound 3 (250 mg, 546 μmol, 1.0 eq.) and (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (197 mg, 600 μmol, 1.1 eq.) in DCE (10 mL) was added dropwise 4-methylmorfolin (55.2 mg, 546 μmol, 1.0 eq.) to pH = 7 at 20 °C. After addition, the mixture was stirred at this temperature for 0.5 hour, and then Sodium triacetoxyborohydride (347 mg, 1.64 mmol, 3.0 eq.) was added dropwise at 20 °C. The resulting mixture was stirred at 20 °C for 2 hour. LCMS showed the reaction was completed. The crude was purified by prep-HPLC together (Boston Green ODS 150*30mm*5um, water (FA)-ACN as a mobile phase, from 20% to 50%, Gradient Time (min): 12, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(4-(8-(2-chlorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (120.5 mg, 156.4 μmol, 28.7 % yield) as a pink solid.

[0924] LCMS: calc. for $C_{46}H_{48}ClN_5O_4$:769.33, found: $[M+H]^+$ 770.3

[0925] HPLC: 100.00% purity at 220 nm.

[0926] ^1H NMR (400 MHz, METHANOL-d_4) δ: ppm 8.36 (s, 1 H), 7.65 (d, J = 8.34 Hz, 1 H), 7.32 (d, J = 7.87 Hz, 1 H), 7.05 - 7.12 (m, 5 H), 6.75 - 6.79 (m, 2 H), 6.65 - 6.72 (m, 4 H), 6.59 (d, J = 2.50 Hz, 1 H), 5.10 (dd, J = 13.23, 5.25 Hz, 1 H), 4.35 - 4.46 (m, 2 H), 3.59 (d, J = 11.92 Hz, 2 H), 3.42 (d, J=4.17 Hz, 4 H), 2.84 - 2.95 (m, 2 H), 2.79 (d, J = 1.43 Hz, 6 H), 2.62 (s, 2 H), 2.47 (d, J = 6.56 Hz, 3 H), 2.28 (s, 2 H), 2.10 - 2.17 (m, 3 H), 1.83 - 1.89 (m, 2 H), 1.73 - 1.81 (m, 1 H), 1.28 - 1.38 (m, 2 H).

Example 30. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-isopropyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-58



[0927] ***Step 1.*** To a mixture of compound 1 (500 mg, 1.03 mmol, 1.0 eq.) and compound 2 (207 mg, 1.2 Eq., 1.23 mmol) in Water (5 mL) and 1,4-Dioxane (20 mL)was added $PdCl_2$(dppf) (113mg, 0.15 eq., 154 μmol) and K_2CO_3 (426 mg, 3 eq., 3.08 mmol) in one portion at 25 °C under N_2.The mixture was heated to 90 °C for 2 hours. LCMS showed that the desired compound was detected. The mixture was cooled to 25 °C and concentrated in reduced pressure. The residue was poured into water (100 mL)， and the aqueous phase was extracted with ethyl

acetate (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatograph on silica gel eluted with (PE/EtOAc = 20/1 to 5/1) to give compound 3 (336 mg, 0.75 mmol, 73.0 % yield) as brown oil.

[0928] LC-MS (ESI^+) m/z: 448.3 $(M+H)^+$.

[0929] ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm : 6.94 - 7.05 (m, 2 H) , 6.75 - 6.83 (m, 3 H) , 6.61 - 6.69 (m, 1 H) , 4.85 (br d, J = 8.70 Hz, 2 H) , 4.11 (dd, J = 14.01, 6.97 Hz, 1 H) , 3.79 - 3.84 (m, 3 H) , 3.68 - 3.75 (m, 2 H) , 3.38 (s, 6 H) , 2.67 (br d, J = 6.56 Hz, 3 H) , 2.11 - 2.15 (m, 3 H) , 1.86 (br d, J = 11.92 Hz, 2 H), 1.76 (s, 3 H), 1.43 - 1.49 (m, 2 H) , 1.24 - 1.30 (m, 2 H) , 0.79 - 1.00 (m, 2 H) .

[0930] ***Step 2.*** To a solution of compound 3(300 mg, 1 eq., 670 μmol) in MeOH (10 mL) was added Pd/C (143 mg, 10% Wt, 134 μmol, 0.2 eq.). The suspension was degassed under vacuum and purged with H_2 several times. The mixture was heated to 25 °C (15 psi) and stirred for 3 hours. LCMS showed that the desired compound was detected. The crude product was filtered and the filter was concentrated to give the crude as a grey solid. The residue was purified by column chromatograph on silica gel eluted with (PE/EtOAc = 20/1 to 8/1) to afford compound 4 (120 mg, 267 μmol, 39.8 % yield) as a colorless solid.

[0931] LC-MS (ESI^+) m/z: 450.5 $(M+H)^+$.

[0932] ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm : 6.97 (br d, J = 8.58 Hz, 2 H) , 6.87 (br d, J = 8.23 Hz, 2 H) , 6.75 (d, J = 2.50 Hz, 1 H) , 6.69 (s, 1 H) , 6.60 - 6.64 (m, 1 H) , 4.10 (d, J=7.27 Hz, 1 H) , 3.79 (s, 3 H) , 3.39 (s, 6 H) , 2.91 (dt, J = 13.53, 6.82 Hz, 1 H) , 2.67 (br t, J=6.91 Hz, 3 H) , 2.15 (quin, J=7.00 Hz, 2 H) , 1.82 - 1.97 (m, 5 H) , 1.73 - 1.80 (m, 2 H) , 1.42 - 1.53 (m, 3 H), 1.05 (d, J=6.79 Hz, 6 H).

[0933] ***Step 3.*** To a mixture of compound 4 (110 mg, 245 μmol, 1.0 eq.) in DCM (15 mL)was added tribromoborane (613 mg, 2.45 mmol, 10.0 eq.) in one portion .The mixture was stirred at 25 °C for 2 hours. LCMS showed the reaction was completed. The mixture was concentrated afford the crude compound 5 (60 mg, 0.15 mmol, 63 % yield).

[0934] LC-MS (ESI^+) m/z: 390.4 $(M+H)^+$.

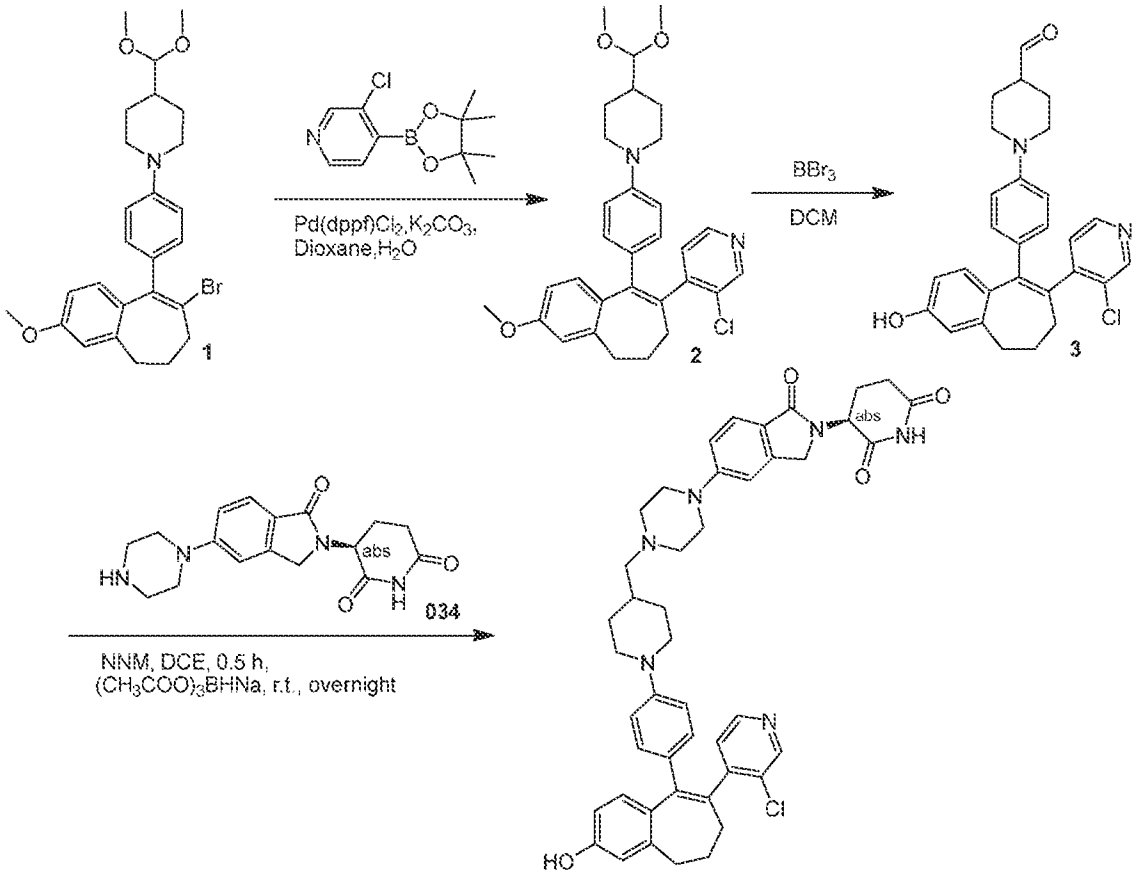
[0935] ***Step 4.*** To a solution of compound 5 (60 mg, 0.15 mmol, 1.0 eq.) in DCE (5 mL) was added Compound 034 (92 mg, 1.2 eq., 0.18 mmol, 1.2 eq.) and Sodium triacetoxyborohydride (98 mg, 68 μL, 0.46 mmol, 3.0 eq.). The mixture was adjusted to pH 5-6 with DIEA. The

mixture was stirred at 25 °C for 16 hours. LCMS showed the reaction was completed. The mixture was concentrated and then water (30 mL) was added. The mixture was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by HPLC (Column C18-1 150*30mm*5um ; Condition water(NH_4HCO_3)-ACN ; Begin B 59 ; End B 89 ; Gradient Time(min) 11 ; 100%B Hold Time(min) 2 ;FlowRate (ml/min) 25) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-isopropyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (22 mg, 31 μmol, 20 % yield) as a white solid .

[0936] LC-MS (ESI^+) m/z: 702.4 $(M+H)^+$.

[0937] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm : 7.64 (d, J=8.46 Hz, 1 H) ,7.07 - 7.12 (m, 2 H) , 6.95 (s, 4 H) , 6.63 (d, J=2.38 Hz, 1 H) , 6.45 - 6.54 (m, 2 H) , 5.10 (dd, J=13.35, 5.13 Hz, 1 H) , 4.36 - 4.46 (m, 2 H) , 3.68 (br d, J=12.76 Hz, 2 H) , 3.37 - 3.40 (m, 4 H) , 2.84 - 2.93 (m, 2 H) , 2.69 - 2.81 (m, 3 H) , 2.61 (br s, 6 H) , 2.43 - 2.52 (m, 1 H) , 2.34 (br d, J = 6.91 Hz, 2 H) , 2.10 - 2.19 (m, 3 H) , 1.90 - 1.96 (m, 4 H) , 1.74 - 1.82 (m, 1 H) , 1.40 (br dd, J = 11.74, 2.56 Hz, 2 H) ,1.05 (d, J = 6.79 Hz, 6 H).

Example 31. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-isopropyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-54



[0938] ***Step 1.*** A mixture of compound 1 (250 mg, 514 μmol, 1.0 eq.), 3-Chloro pyridine-4-Boronic acid, Pinacol ester (135 mg, 565 μmol, 1.1 eq) , K_2CO_3 (213 mg, 3 eq., 1.54 mmol) and Pd (dppf)Cl_2 (37.6 mg, 51.4 μmol, .0.1 eq.) in Dioxane (10 mL) and Water (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hour under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition EA 30 mL at 20 C, and then diluted with water 30 mL and extracted with EA 90 mL (30 mL x 3). The combined organic layers were washed with EA 30 mL (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 3/1) to give compound 2 (200 mg, 385 μmol, 75.0 %) as a yellow solid.

[0939] LC-MS (ESI^+) m/z: 519.2 $(M+H)^+$

[0940] ^1H NMR (500 MHz, DMSO-d_6) δ: ppm 8.54 (s, 1 H), 8.32 (d, J = 4.88 Hz, 1 H), 7.21 (d, J = 4.88 Hz, 1 H), 6.92 (d, J = 2.59 Hz, 1 H), 6.75 - 6.78 (m, 1 H), 6.69 - 6.73 (m, 1 H), 6.60 -

6.68 (m, 4 H), 4.03 - 4.08 (m, 1 H), 3.95 (s, 2 H), 3.78 (s, 3 H), 3.63 (d, J = 12.21 Hz, 2 H), 3.25 (s, 6 H), 2.83 (t, J = 6.79 Hz, 2 H), 2.18 (d, J = 5.49 Hz, 2 H), 2.05 - 2.11 (m, 2 H), 1.66 (d, J=9.46 Hz, 3 H), 1.20 - 1.27 (m, 2 H).

[0941] ***Step 2.*** To a solution of compound 2 (200 mg, 385 μmol, 1.0 eq.) in DCM (10 mL) was added BBr_3 (483 mg, 1.93 mmol, 5.0 eq.). The mixture was stirred at 20 °C for 2 hour and then water (2 mL) in DCM (10 mL) was added dropwise at 20 °C. The resulting mixture was stirred at 20 °C for 30 min. LCMS showed the reaction was completed. The mixture was concentrated and then water (20 mL) was added. The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The mixture was concentrated in vacuo to give crude product. No further purification as it is used for the next step directly.

[0942] LC-MS (ESI+) m/z: 459.2$(M+H)^+$

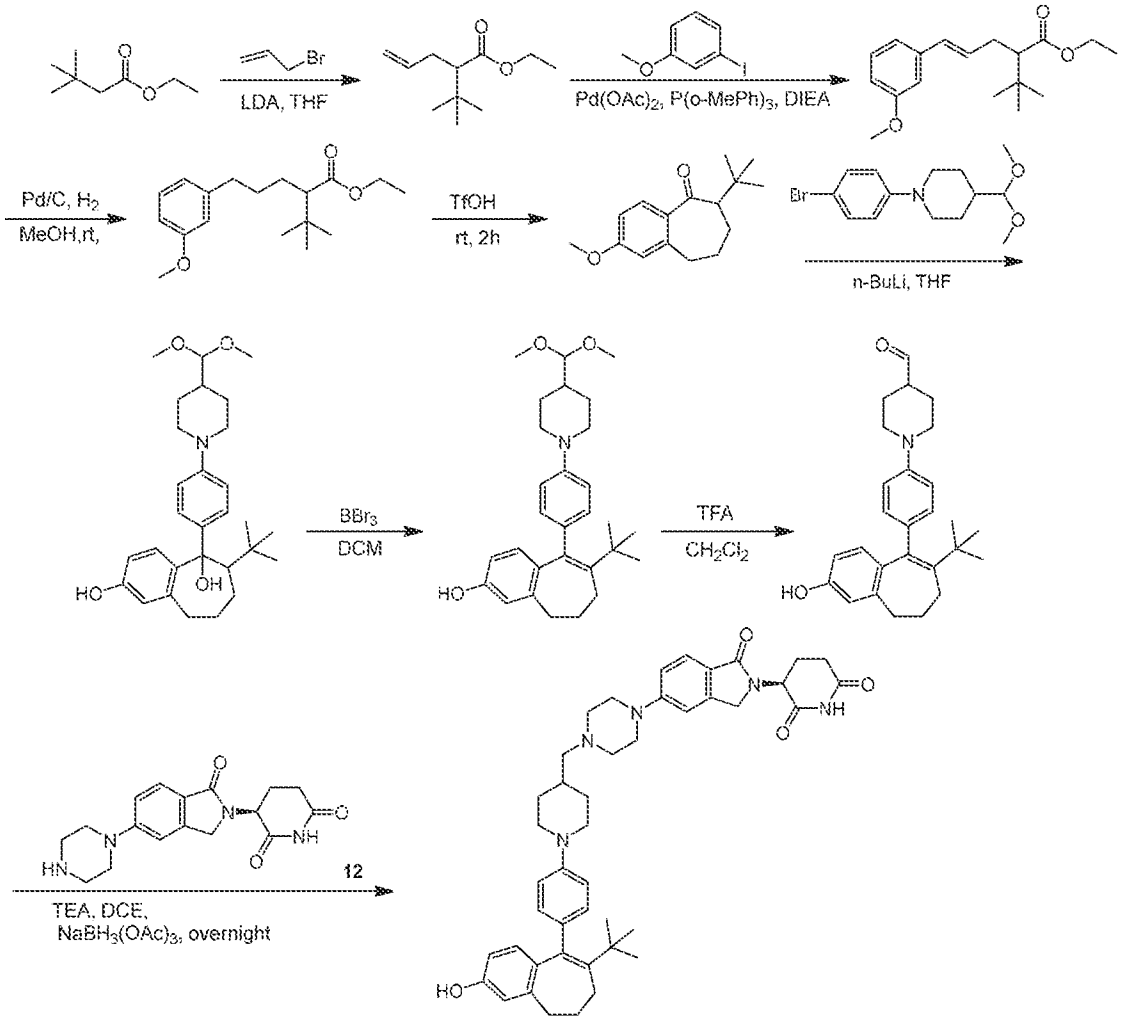
[0943] ***Step 3.*** To a solution of compound 3 (250 mg, 545 μmol, 1.0 eq.) and compound 034 (233 mg, 1.3 eq., 708 μmol) in DCE (10 mL) was added sodium triacetoxyhydroborate (289 mg, 1.36 mmol, 2.5 eq.). The mixture was stirred at 20 °C for 3 hour. LCMS showed the reaction was completed. The crude was purified by prep-HPLC together (Boston Green ODS 150*30mm*5um, water (FA)-ACN as a mobile phase, from 12% to 42%, Gradient Time (min): 14, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-isopropyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (162 mg, 210 μmol, 38.6 %) as an off white solid.

[0944] LCMS: calc. for $C_{46}H_{47}ClN_6O_4$:770.33, found: $[M+H]^+$ 771.6

[0945] HPLC: 100.00% purity at 220 nm.

[0946] ^1H NMR (400 MHz, METHANOL-d_4) δ: ppm 8.43 (s, 1 H), 8.33 - 8.35 (m, 1 H), 8.18 - 8.25 (m, 1 H), 7.61 - 7.68 (m, 1 H), 7.19 (d, J = 5.01 Hz, 1 H), 7.09 (s, 2 H), 6.70 - 6.78 (m, 5 H), 6.66 - 6.69 (m, 1 H), 6.61 (d, J = 2.62 Hz, 1 H), 5.10 (dd, J =13.23, 5.13 Hz, 1 H), 4.34 - 4.48 (m, 2 H), 3.64 (d, J = 12.76 Hz, 2 H), 3.42 (d, J = 4.53 Hz, 4 H), 2.84 - 2.95 (m, 2 H), 2.74 - 2.83 (m, 6 H), 2.61 - 2.68 (m, 2 H), 2.39 - 2.51 (m, 3 H), 2.31 (t, J = 6.32 Hz, 2 H), 2.11 - 2.18 (m, 3 H), 1.84 - 1.92 (m, 2 H), 1.80 (d, J = 3.70 Hz, 1 H), 1.33 (dd, J = 12.04, 2.03 Hz, 2 H).

Example 32. Synthesis of (S)-3-(5-(4-((1-(4-(8-(tert-butyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-67



[0947] ***Step 1.*** A mixture of ethyltert-butylacetate (10.00 g, 69.34 mmol, 1.0 eq.) in THF (50 ml) was degassed and purged with N_2 for 3 times, and then the mixture was slowly added LDA (35.37 ml, 70.73 mmol, 2 M, 1.02 eq.) and stirred at -78 °C for 1 hour under N_2 atmosphere. 1 hour later, the 3-bromoprop-1-ene (9.228 g, 76.28 mmol, 1.1 eq.) was added in to the reaction. Within three hours, the reaction temperature rose from -78° to 0 °C. TLC indicated reactant 1 was consumed completely and one new spot formed. The reaction was clean according to TLC (Iodine reagent color). The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with NH_4Cl 200 ml and extracted with ethly acetate 200 ml (20 ml x 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to offer ethyl 2-(tert-butyl)pent-4-enoate (13.55 g, 59 mmol, 85 % yield, 80% Purity).

[0948] 1H NMR (400 MHz, METHANOL-d_4) δ ppm: 5.58 - 5.71 (m, 1 H), 4.88 - 4.99 (m, 2 H), 3.99 - 4.08 (m, 2 H), 2.12 - 2.32 (m, 3 H), 1.14 - 1.20 (m, 3 H), 0.90 - 0.93 (m, 9 H).

[0949] ***Step 2.*** A mixture of ethyl 2-(tert-butyl)pent-4-enoate (5.00 g, 27.1 mmol, 1.0 eq.), 1-iodo-3-methoxybenzene (6.99 g, 29.8 mmol, 1.1 eq.) , diacetyl (oxo) palladium (566 mg, 2.71 mmol, 0.1 eq.), DIEA (7.01 g, 54.3 mmol, 2.0 eq.) and Phosphine,tris(2-methylphenyl)- (826 mg, 2.71 mmol, 0.1 eq.) in DMF (20 ml) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 6 hours under N_2 atmosphere. TLC indicated Reactant 1 was consumed completely and one new spot (one new spot is more large) formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with brine 200 ml and extracted with ethly acetate 200 ml (200 ml x 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1) to offer benzyl 2-(tert-butyl)-5-(3-methoxyphenyl) pentanoate (2.03 g, 4.6 mmol, 17 % yield , 80% Purity).

[0950] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm: 7.12 - 7.21 (m, 2 H), 6.90 (s, 2 H), 6.33 - 6.41 (m, 1 H), 6.06 - 6.17 (m, 1 H), 4.05 - 4.14 (m, 2 H), 3.85 (s, 3 H), 2.49 (s, 2 H), 2.33 (br d, J = 4.02 Hz, 1 H), 1.15 - 1.22 (m, 3 H), 1.00 - 1.06 (m, 9 H).

[0951] ***Step 3.*** A mixture of compound 3 (2.00 g, 1 eq, 6.89 mmol), Pd/C (147 mg, 0.2 eq, 1.38 mmol) in MeOH (20 ml) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 50 °C for 12 hours under H_2 atmosphere. The reaction solution is filtered with diatomaceous earth to remove Pd/C, the reaction solution is filtered with diatomaceous earth and the diatomaceous earth containing Pd/C is poured into a special recycling bucket. The reaction mixture was concentrated under reduced pressure to remove solvent to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1) to offer ethyl 2-(tert-butyl)-5-(3-methoxyphenyl) pentanoate (1.05 g, 3.1 mmol, 44 % yield, 85% Purity).

[0952] ^{1}H NMR (500 MHz, METHANOL-d4) δ ppm 7.13 - 7.18 (m, 4 H) 4.07 - 4.15 (m, 2 H) 3.83 - 3.86 (m, 4 H) 2.52 - 2.68 (m, 2 H) 2.15 - 2.19 (m, 1 H) 1.45 - 1.69 (m, 4 H) 1.22 - 1.25 (m, 3 H) 0.92 - 0.94 (m, 9 H).

[0953] ***Step 4.*** To a solution of ethyl 2-(tert-butyl)-5-(3-methoxyphenyl) pentanoate (2.00 g, 1 eq, 6.84 mmol) in TfOH (10 ml). The mixture was stirred at 20 °C for 2 hours. LCMS showed Reactant 6 was consumed completely and one main peak with desired MS was detected. The

reaction mixture was quenched by addition Saturated sodium sulfite solution 100 ml at 0 °C, and then diluted with water 50 ml and extracted with ethyl acetate 100 mL (100 mL x 2). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. LC-MS (ESI^+) m/z: 247.2$(M+H)^+$.

[0954] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm: 7.46-7.51 (m, 1 H), 6.79-6.83 (m, 2 H), 3.81- 3.85 (m, 3 H), 2.96-3.06 (m, 2 H), 2.77-2.85 (m, 1 H), 1.93-2.18 (m, 2 H), 1.46-1.71 (m, 2 H), 1.02-1.06 (m, 9 H).

[0955] ***Step 5.*** A mixture of compound 7 (1.99 g, 6.33 mmol, 1.3 eq.) in THF (20 ml) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at -68 °C for 10 minters under N_2 atmosphere. The reaction solution was slowly dripped with n-Butyllithium, 2.5 Minhexane (468 mg, 3.65 mL, 2.0 molar, 1.5 eq, 7.31 mmol) and kept at a temperature of -68 °C. After half an hour, the reaction liquid becomes milky white and raw material6-(tert-butyl)-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1.20 g, 1 eq, 4.87 mmol) is added to the reaction droplet. After an hour, test the reaction fluid LC-MS showed Reactant 7 was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with brine 20 mL and extracted with ethyl acetate 20 ml (20 ml x 2). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1) to offer 6-(tert-butyl)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (980 mg, 850 μmol, 17.4 % yield, 41.776% Purity). LC-MS (ESI^+) m/z: 482.3$(M+H)^+$.

[0956] ***Step 6.*** To a solution of compound 9 (1.10 g, 1 eq, 2.28 mmol) in CH_2Cl_2 (12 ml). The mixture was slowly added tribromoborane (2.86 g, 11.4 mmol, 5.0 eq.) and stirred at 20 °C for 1 hour LCMS showed reactant 9 was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by addition MeOH 100 ml at 0°C, and then diluted with Saturated K_2CO_3 solution 200 ml and extracted with ethyl acetate 50 ml (50 ml * 2). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3/1) to offer 1-(4-(8-(tert-butyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (850 mg, 650 μmol, 28.5 % yield, 30.88% Purity). LC-MS (ESI^+) m/z: 450.3 $(M+H)^+$.

[0957] *Step 7.* To a solution of 1-(4-(8-(tert-butyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (200 mg, 445 μmol, 1.0 eq.) in CH_2Cl_2 (4 ml) was added TFA (254 mg, 2.22 mmol, 5.0 eq.). The mixture was stirred at 20 °C for 2 hours. LCMS showed reactant 10 was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. Without further purification, product 1-(4-(8-(tert-butyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (325 mg, 221 μmol, 49.8 % yield, 27.5% Purity)is obtained directly. LC-MS (ESI^+) m/z: 404.2$(M+H)^+$.

[0958] *Step 8.* A mixture of 1-(4-(8-(tert-butyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 0.15 mmol, 1.0 eq.), compound 12 (54 mg, 0.16 mmol, 1.1 eq.) in DCM (2 ml). The PH of the reaction solution was adjusted to about 7 by DIEA, than the Sodium triacetoxyborohydride (63 mg, 0.30 mmol, 2 eq.) was added into the reaction and stirred until completely dissolved. Test the reaction solution after 6 hours. LC-MS showed Reactant 11 was consumed completely and one main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. Dissolve the residual solids with DMF, The residue was purified by prep-HPLC (FA condition) to give (S)-3-(5-(4-((1-(4-(8-(tert-butyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (41 mg, 40 μmol, 27 % yield, 100% Purity) was obtained by freeze-drying machine. LC-MS (ESI^+) m/z: 716.5 $(M+H)^+$.

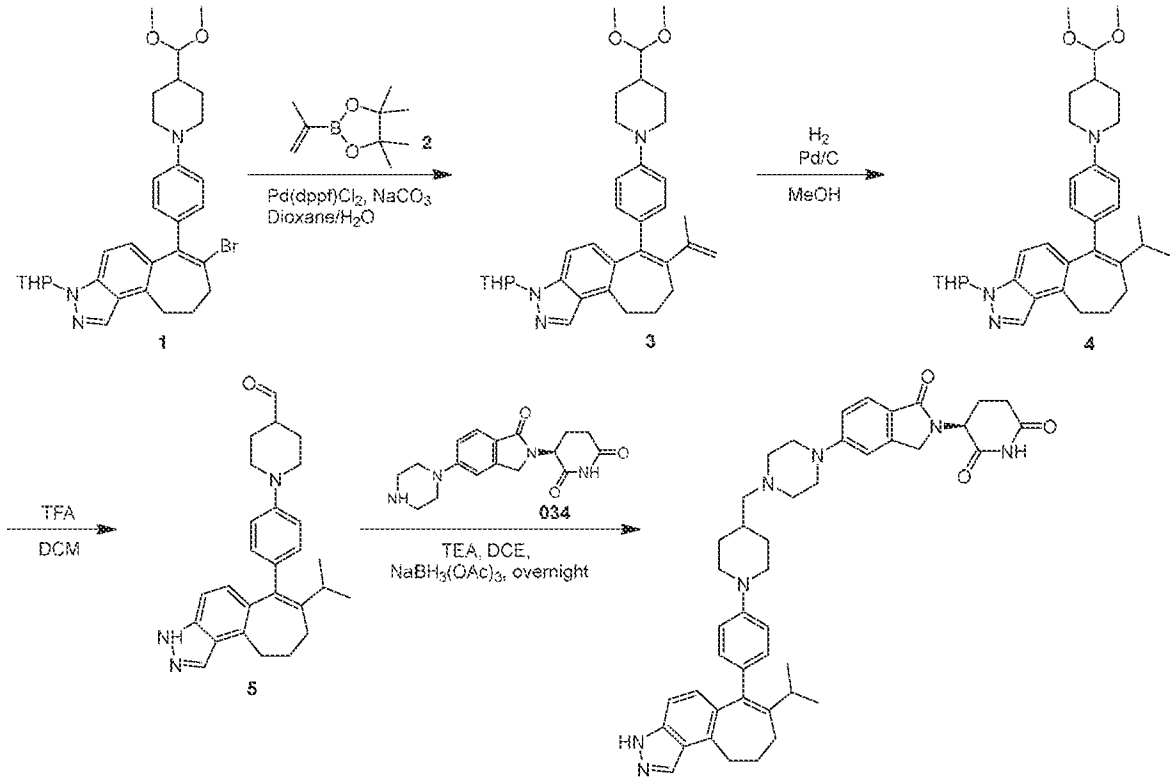
[0959] LCMS: calc. for $C_{44}H_{53}N_5O_4$:715.94, found: $[M+H]^+$ 716.5

[0960] HPLC: 97.645% purity at 220 nm.

[0961] 1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.93 - 10.97 (m, 1 H), 9.13 - 9.20 (m, 1 H), 8.18 - 8.23 (m, 1 H), 7.50 - 7.55 (m, 1 H), 7.04 - 7.10 (m, 3 H), 6.91(br d, J=11.32 Hz, 1 H), 6.83 (br d, J=8.11 Hz, 2 H), 6.55 - 6.59 (m, 1 H), 6.40 - 6.46 (m, 2 H), 5.02 - 5.09 (m, 1 H), 4.30 - 4.37 (m, 1 H), 4.18 - 4.25 (m,1 H), 3.62 - 3.76 (m, 4 H), 2.85 - 2.93 (m, 2 H), 2.68 (br d, J=1.31 Hz, 3 H), 2.31 - 2.37 (m, 2 H), 2.20 - 2.28 (m, 3 H), 1.93 - 2.08 (m, 5 H), 1.79 - 1.88(m, 3 H), 1.65 - 1.76 (m, 2 H), 1.17 - 1.29 (m, 4 H), 0.95 - 1.02 (m, 9 H).

Example 33. Synthesis of (S)-3-(5-(4-((1-(4-(7-isopropyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-

oxoisoindolin-2-yl)piperidine-2,6-dione, I-57



[0962] ***Step 1.*** To a solution of compound 1 (100 mg, 148.13 μmol, 1 eq) and compound 2 (37.34 mg, 222.20 μmol, 1.5 eq) in dioxane (3 mL) and H_2O (1 mL) was added $Pd(dppf)Cl_2$ (10.84 mg, 14.81 μmol, 0.1 eq) and Na_2CO_3 (31.40 mg, 296.27 μmol, 2 eq). The mixture was stirred at 90 °C for 12 h. The reaction mixture was quenched by addition of water (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (PE/EtOAc = 5/1, TLC: PE/EtOAc = 5/1, R_f = 0.69) to yield compound 3 (50 mg, 59.99 μmol, 40.50% yield, 65% purity) as a yellow solid. LC-MS (ESI^+) m/z 542.4 $(M+H)^+$

[0963] ***Step 2.*** To a solution of compound 3 (50 mg, 59.99 μmol, 1 eq) in MeOH (10 mL) was added Pd/C (50 mg, 10% purity). The mixture was stirred under H_2 (15 Psi) at 25 °C for 1 h. The reaction mixture was filtered and concentrated to yield compound 4 (40 mg, 55.17 μmol, 91.97% yield, 75% purity) as yellow oil which was used in the next step without further purification. LC-MS (ESI^+) m/z 544.5 $(M+H)^+$

[0964] ***Step 3.*** To a solution of compound 4 (35 mg, 48.28 μmol, 1 eq) in DCM (2.5 mL) was added TFA (671.54 mg, 5.89 mmol, 500 μL, 122.00 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition saturation solution of $NaHCO_3$ (10 mL),

extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield compound 5 (30 mg, 43.53 μmol, 90.16% yield, 60% purity) as a yellow solid which was used in the next step without further purification. LC-MS (ESI^+) m/z 414.3 $(M+H)^+$.

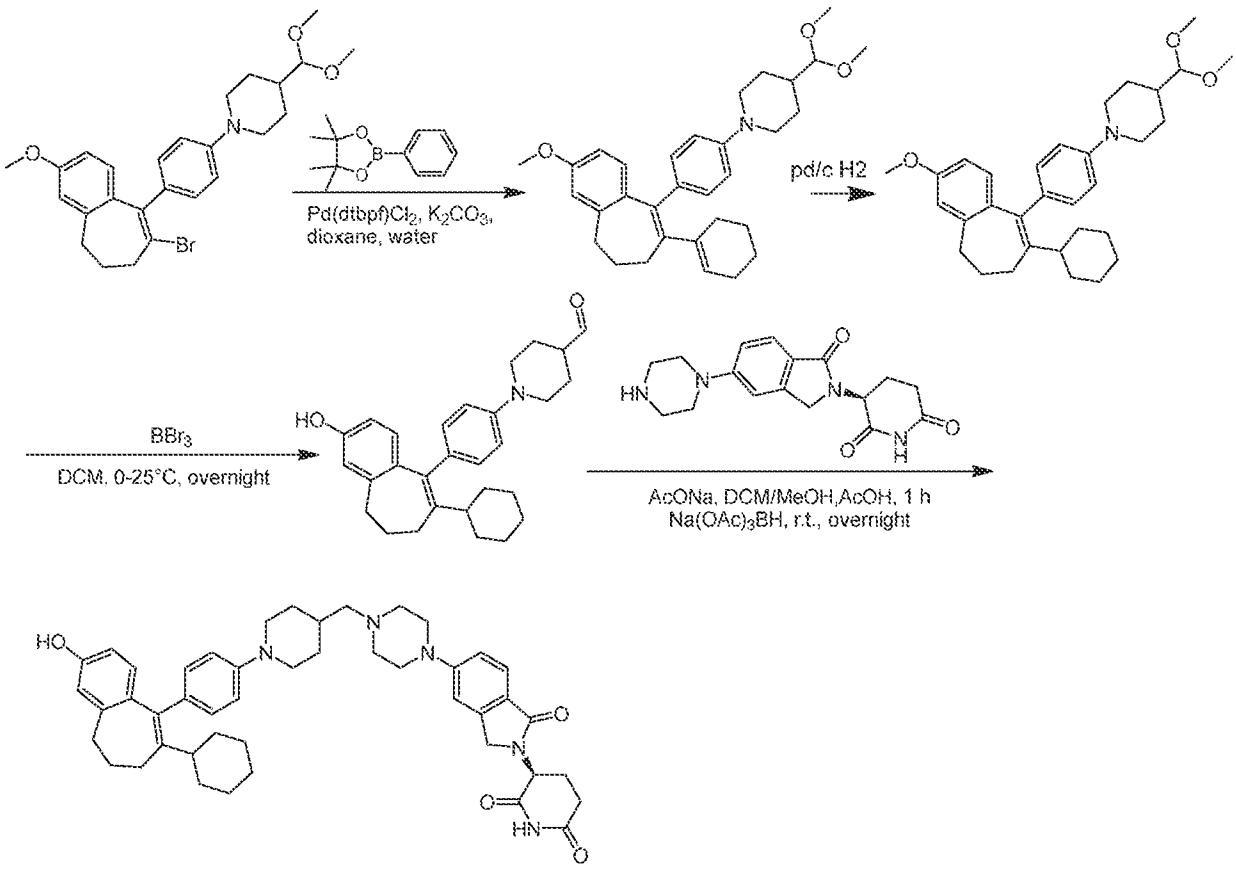
[0965] ***Step 4.*** To a solution of compound 5 (30 mg, 43.53 μmol, 1 eq) and Compound 034 (14.29 mg, 43.53 μmol, 1 eq) in DCM (2 mL) and MeOH (2 mL) ,after stirred 30 min was added $NaBH(OAc)_3$ (27.67 mg, 130.58 μmol, 3 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to yield a residue. The residue was purified by preparative HPLC (column: C18-1 150*30mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 52%-82%, 11 min), followed by lyophilization to yield a residue. The residue was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um;mobile phase: [water(FA)-ACN]; B%: 14%-44%, 12 min), followed by lyophilization to yield (S)-3-(5-(4-((1-(4-(7-isopropyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2.9 mg, 3.99 μmol, 9.18% yield, 100% purity) as a white solid. LC-MS (ESI^+) m/z 726.6 $[M+H]^+$.

[0966] LCMS: calc. for C44H51N7O3: 725.41, found: $[M+H]^+$ 726.6.

[0967] HPLC: 100% purity at 220 nm.

[0968] ^1H NMR (400MHz, METHANOL-d_4) δ = 8.13 (s, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.12 - 7.08 (m, 2H), 6.97 (s, 4H), 6.78 (d, J = 8.8 Hz, 1H), 5.10 (dd, J = 5.2, 13.4 Hz, 1H), 4.46 - 4.35 (m, 2H), 3.70 (d, J = 12.2 Hz, 2H), 3.41 (s, 4H), 3.06 (t, J = 6.9 Hz, 2H), 3.01 - 2.93 (m, 1H), 2.92 - 2.84 (m, 1H), 2.79 (d, J=2.9 Hz, 1H), 2.76 - 2.70 (m, 6H), 2.49 - 2.41 (m, 3H), 2.33 (t, J = 7.0 Hz, 2H), 2.19 - 2.12 (m, 1H), 1.99 - 1.91 (m, 4H), 1.80 (s, 1H), 1.48 - 1.36 (m, 2H), 1.11 (d, J = 6.8 Hz, 6H)

Example 34. Synthesis of (S)-3-(5-(4-((1-(4-(8-cyclohexyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-28



[0969] ***Step 1.*** To mixture of 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen -9-yl)phenyl)-4-(dimethoxymethyl)piperidine (117 mg, 1 Eq, 241 µmol), Cyclohexen-1-ylboronicacid (36.4 mg, 1.2 Eq, 289 µmol) , Na2CO3 (76.5 mg, 3 Eq, 722 µmol) , 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (15.7 mg, 0.1 Eq, 24.1 µmol) in Dioxane (5 mL)and whate (1ml) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 90°C for 8 hours under N2 atmosphere. LC-MS showed 0% of Reactant 1 was remained. Only one new peaks were shown on LC-MS and 94% of desired compound was detected. The reaction mixture was partitioned between brine 100 mL and Ethyl acetate 100 mL. The organic phase was separated, washed with whate 50 mL (50 mL *2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1) to give 1-(4-(8-(cyclohex-1-en-1-yl)-3-methoxy-6,7-dihydro-5H-benzo[7] annulen-9-yl)phenyl)-4-

(dimethoxymethyl)piperidine (115 mg, 0.22 mmol, 92 %, 94% Purity) was obtained as a white solid.LC-MS (ESI+) m/z: 461.9 (M+H)+.

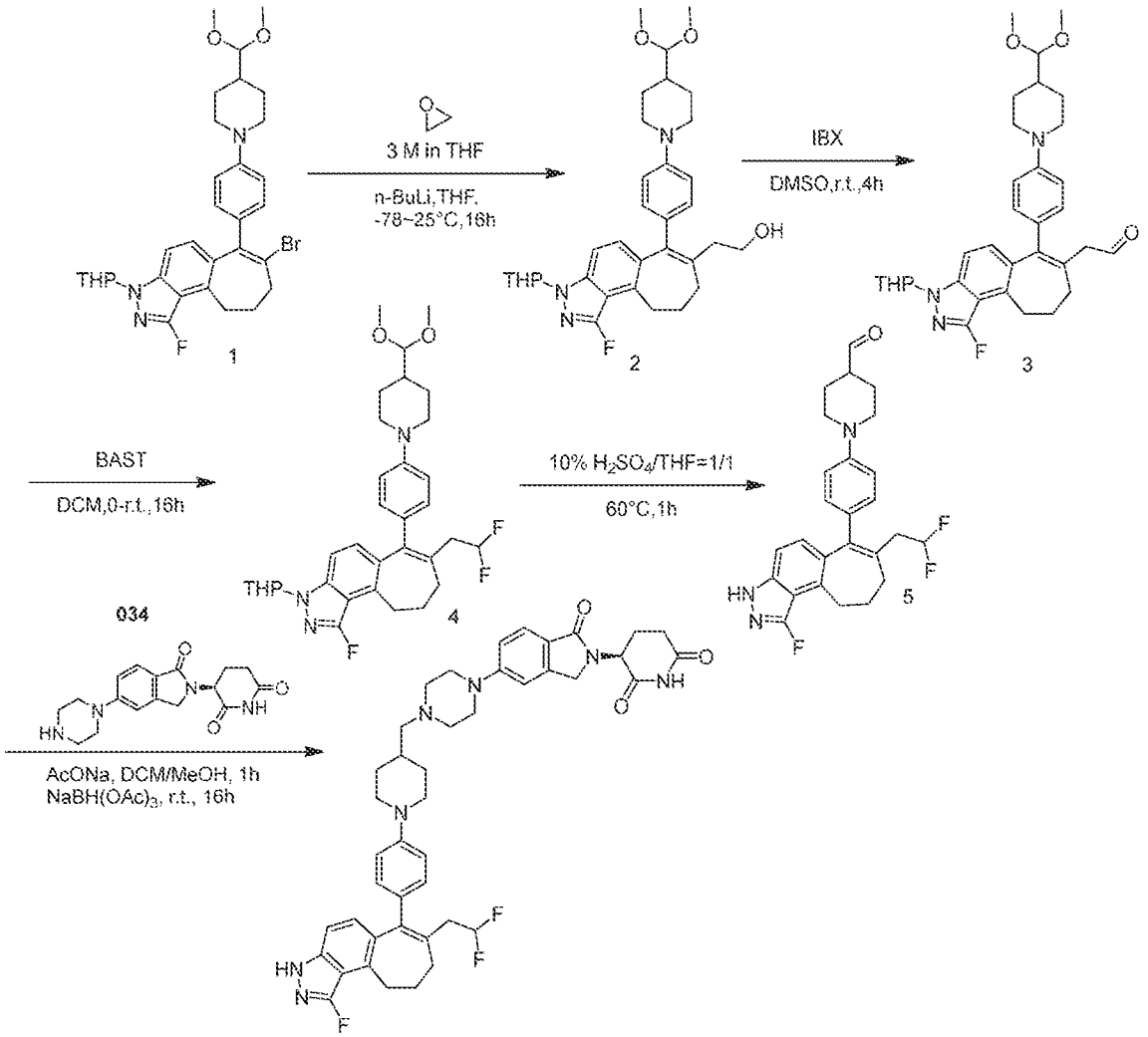
[0970] ***Step 2.*** To solution1-(4-(8-(cyclohex-1-en-1-yl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine in MeOH was added Pd-C under N2. The suspension was degassed under vacuum and purged with H2 several times. The mixture was stirred under H2 (xpsi) at 20°C for 16 hours. TLC (Petroleum ether/Ethyl acetate=3:1) or HPLC showed the starting material was consumed completely. The reaction mixture was filtered and the filter was concentrated. The crude product was purified by silica gel chromatography eluted with Petroleum ether/Ethyl acetate=3:1 to give 1-(4-(8-cyclohexyl-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine as white solid LC-MS (ESI+) m/z: 490 (M+H)+.

[0971] ***Step 3.*** To a mixture 1-(4-(8-cyclohexyl-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl) phenyl)-4-(dimethoxymethyl)piperidine (400 mg, 1 Eq, 817 μmol) in dcm (5 mL)at 25°C and stirred for ten minters.To a stirred solution of compound was added a solution of tribromoborane (1.02 g, 434 μL, 5 Eq, 4.08 mmol) in CH2Cl2 via syringe over 5 min.TLC (ethyl acetate: petroleum ether=1:3, iodide fuming) showed that the new spot was observed.The misture was added h2o (1 mL) and stirred for 30 minters.1H NMR showed the desired product was correct .The mixture was quenched with NH4Cl (20 mL, aqueous, sat.) under 25°C.The mixture was extracted with ethyl acetate (100 mL x 2),the combine organic layer was washed with water (200 mL), then washed with brine (200 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluted with petroleum / ethyl acetate=3:1 to give 1-(4-(8-cyclohexyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9- as yellow oil.

[0972] ***Step 4.*** To a mixture of 1-(4-(8-cyclohexyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl) phenyl)piperidine-4-carbaldehyde (400 mg, 1 Eq, 931 μmol) and (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (611 mg, 2 Eq, 1.86 mmol) in DCE (5 mL). The mixture was stirred at 25 °C for 10 min, pH was adjusted to around 6 by progressively adding 4-methylmorfolin (94.2 mg, 0.10 mL, 1 Eq, 931 μmol). Than added sodium triacetoxyhydroborate (395 mg, 2 Eq, 1.86 mmol) in the solution. The mixture was stirred for 2 hours.TLC showed the reaction was completed. LCMS show the product is correct. The aqueous phase was extracted with ethyl acetate (100mL*2). The combined organic phase was washed with brine (100 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified

by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1, N/1) to afford (S)-3-(5-(4-((1-(4-(8-cyclohexyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (98 mg, 0.13 mmol, 14 %, 97.3% Purity) as white solidLC-MS (ESI+) m/z: 805.3(M+H).

Example 35. Synthesis of (S)-3-(5-(4-((1-(4-(7-(2,2-difluoroethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-62



[0973] ***Step 1.*** To a mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (500 mg, 1 Eq, 835 μmol) in THF (10 mL) at r.t., and the mixture was degassed and purged with N_2 for 10 mintues. Then the mixture was stirred until it reached -78 °C. n-Butyllithium (80.3 mg, 501 μL, 2.5 M, 1.5 Eq, 1.25 mmol) was added to the mixture and stirred at -78 °C for 1 hour, then

ethylene oxide (736 mg, 5.57 mL, 3 M, 20 Eq, 16.7 mmol) was add to the mixture at -78 °C and stirred at 25 °C for 12 hour. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.6 UV) showed one main new spot was observed. The reaction was quenched with NH_4Cl (100 mL) and extracted with ethyl acetate (100 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a black soild. The black solid was subjected to column chromatography over silica gel (gradient elution: 0 – 80% EtOAc).The desired fractions were collected, and concentrated to dryness in vacuo to give 2-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)ethan-1-ol (270 mg, 479 μmol, 57.3%) as a yellow oil.

[0974] ***Step 2.*** To a solution of 2-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)ethan-1-ol (100 mg, 1 Eq, 177 μmol) in DMSO (2 mL) was added IBX (54.6 mg, 1.1 Eq, 195 μmol). The reaction mixture was heated at 25 °C for 4 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.5 UV) showed one main new spot was observed. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (15 mL*2). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% EtOAc).The desired fractions were collected, and concentrated to dryness in vacuo to give 2-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)acetaldehyde (36 mg, 64 μmol, 36 %) as a white solid.

[0975] Step 3. A mixture of 2-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)acetaldehyde (12 mg, 1 Eq, 21 μmol), Deoxo-Fluor (9.5 mg, 8.1 μL, 2 Eq, 43 μmol) in DCM (1 mL) at 0 °C for 0.5 hour, and the reaction was stirred at 25 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.5 UV) showed a new spot was observed. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 70%-100%,7min) to give 7-(2,2-difluoroethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (3 mg, 5 μmol, 20 %) was obtained as a white solid.

[0976] Step 4. To a solution of 7-(2,2-difluoroethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (3 mg, 1 Eq, 5 μmol) in 10%H_2SO_4 (2 mL) and THF (2 mL) was stirred at 60°C for 1 hour. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4, UV) showed a new spot was desired. The reaction was adjust to pH=~8 with aq.$NaHCO_3$ (5 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL).The combined organic layers were washed with brine(30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-(7-(2,2-difluoroethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (10 mg, 22 μmol, crude) as a yellow solid.

[0977] Step 5. To a solution of 1-(4-(7-(2,2-difluoroethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (10 mg, 1 Eq, 22 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, $PhSO_3H$ salt (11 mg, 1 Eq, 22 μmol) in DCM (1 mL) and MeOH (1 mL) was added sodium acetate (5.4 mg, 3.6 μL, 3 Eq, 66 μmol) was stirred at 25 °C for 60 mins, Then sodium $NaBH(OAc)_3$ (9.3 mg, 2 Eq, 44 μmol) and acetic acid (4.0 mg, 3.8 μL, 3 Eq, 66 μmol) was added. The mixture was stirred at 25 °C for 16 hour. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B% 70%-100%,7min) to give (S)-3-(5-(4-((1-(4-(7-(2,2-difluoroethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (1 mg, 1 μmol, 6 %, 93.15% purity) was obtained as a white solid.LC-MS (ESI^+) m/z: 766.6 $(M+H)^+$.

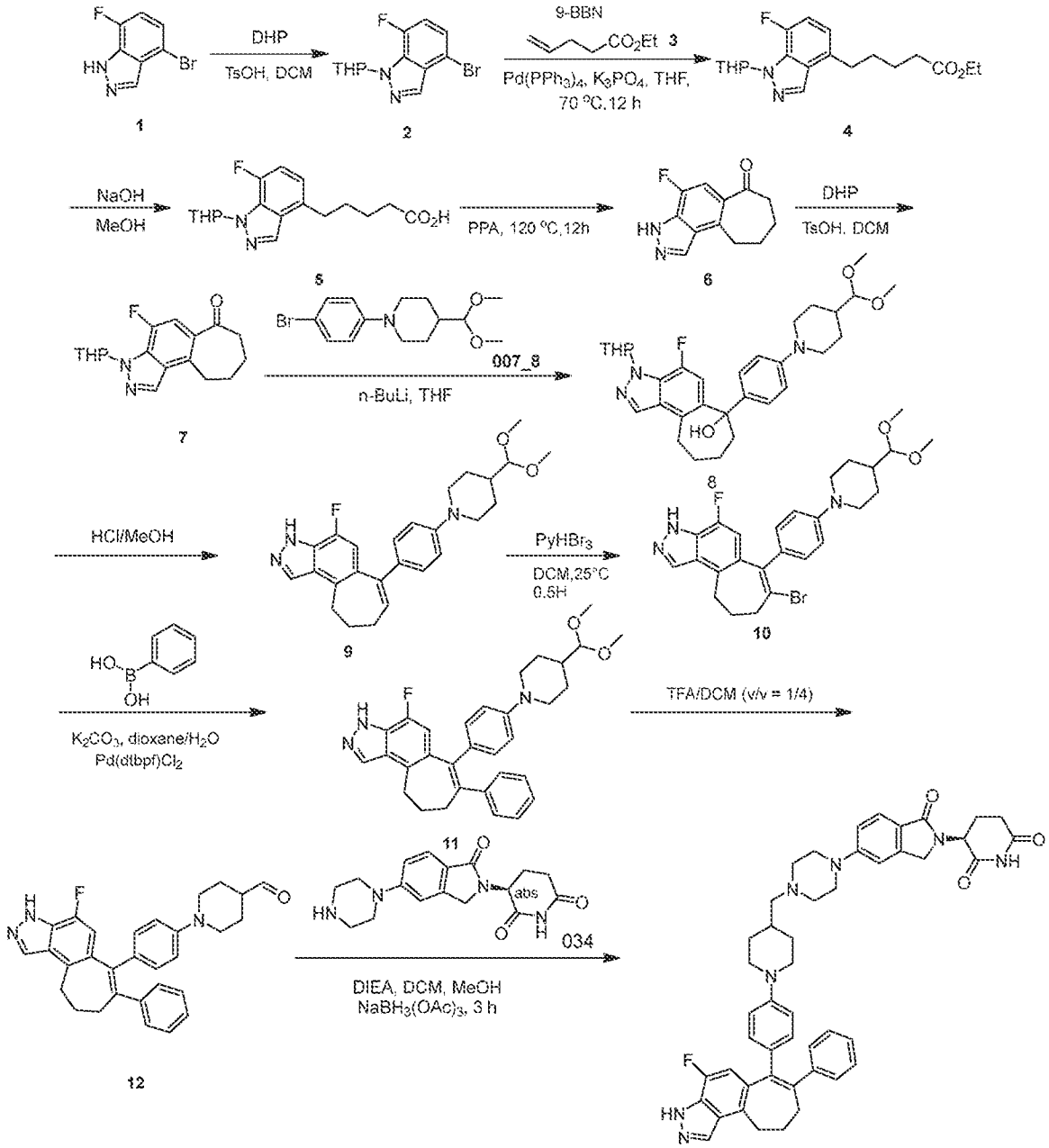
[0978] Step 6. LCMS: calc. for $C_{43}H_{46}F_3N_7O_3$: 765.88, found: $[M+H]^+$ 766.3

[0979] HPLC: 93.150% purity at 220 nm.

[0980] ^1H NMR (400 MHz, Methanol-d_4) δ = 7.66 (d, J = 8.5 Hz, 1H), 7.10 (s, 3H), 7.01 (s, 4H), 6.87 (d, J = 9.0 Hz, 1H), 6.19 - 5.87 (m, 1H), 5.12 (br dd, J =5.1, 13.2 Hz, 1H), 4.42 (d, J = 6.3 Hz, 2H), 3.75 (br d, J = 12.3 Hz, 2H), 3.46 - 3.36 (m, 4H), 3.08 (s, 2H), 2.90 (br d, J = 5.0 Hz, 3H), 2.83 - 2.71 (m, 3H),2.70 - 2.56 (m, 4H), 2.35 (br d, J = 6.8 Hz, 4H), 2.16 - 2.07 (m, 2H), 1.95 (br d, J = 12.8 Hz, 2H), 1.82 - 1.73 (m, 1H), 1.49 - 1.34 (m, 4H)

[0981] SFC: retention time, 3.024min; Area, 100.00 %; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 36. Synthesis of (S)-3-(5-(4-((1-(4-(4-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-65



[0982] *Step 1.* To a solution of compound 1 (5.1 g, 23.72 mmol, 1eq) in DCM (50 mL) was added DHP (5.99 g, 71.16 mmol, 6.51 mL, 3eq) and TsOH (816.87 mg, 4.74 mmol, 0.2eq). The mixture was stirred at 25 °C for 3 hr. The residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (50 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm,

100-200 mesh silica gel, Petroleum ether/Ethyl acetate=5:1) to afford compound 2 (5.1 g, 17.05 mmol, 71.88% yield) as a white solid.

[0983] LC-MS (ESI^+) m/z 299.0 $[M+H]^+$.

[0984] ***Step 2.*** To a mixture of compound 3 (2.04 g, 15.91 mmol, 1.7eq), 9-BBN (0.5 M, 31.82 mL, 1.7eq) in THF (28 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 3 h under N_2 atmosphere. And then was added 2 (2.8 g, 9.36 mmol, 1eq), $Pd(PPh_3)_4$ (540.81 mg, 468.01 μmol, 0.05eq), K_3PO_4 (5.96 g, 28.08 mmol, 3eq) and THF (15 mL) in mixture solution. The mixture was stirred at 70 °C for 12 h. The reaction mixture was quenched by addition of water (30 mL), extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1) to yield compound 4 (1.65 g, 4.74 mmol, 50.59% yield) as yellow oil.

[0985] LC-MS (ESI+) m/z 349.2 $[M+H]^+$.

[0986] ***Step 3.*** To a solution of compound 4 (1.12 g, 3.21 mmol, 1eq) in MeOH (8 mL), THF (3 mL) and H_2O (3 mL) was added NaOH (257.17 mg, 6.43 mmol, 2eq). The mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched by addition of water (8 mL), adjust pH to 6 by HCl(1 M), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 5 (888 mg, 2.77 mmol, 86.23% yield) as yellow oil which was used in the next step without further purification.

[0987] LC-MS (ESI^+) m/z 321.2 $[M+H]^+$.

[0988] ***Step 4.*** A mixture of compound 5 (1.2 g, 3.75 mmol, 1eq) in PPA (30 ml) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition of water (30 mL) under 0 °C, adjust pH to 7 by $NaHCO_3$, extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 1/1) to yield compound 6 (600 mg, 2.75 mmol, 73.40% yield) as a yellow solid.

[0989] LC-MS (ESI+) m/z 219.2 $[M+H]^+$.

[0990] *Step 5.* To a solution of compound 6 (124 mg, 568.22 μmol, 1eq) and TsOH (19.57 mg, 113.64 μmol, 0.2eq) in DCM (2 mL) was added DHP (95.60 mg, 1.14 mmol, 2eq) under 0 °C. The mixture was stirred at 25 °C for 12 h. The residue was concentrated and purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 10/1) to yield compound 7 (90 mg, 297.68 μmol, 52.39% yield) as yellow oil.

[0991] LC-MS (ESI+) m/z 303.2 $[M+H]^+$.

[0992] *Step 6.* A mixture of compound 007_8 (176.68 mg, 562.28 μmol, 1eq), n-BuLi (2.5 M, 269.89 μL, 1.2eq) in THF (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was added compound 7 (170 mg, 562.28 μmol, 1eq),Then the mixture was stirred at -78 °C for 3 hr under N_2 atmosphere. LCMS showed that the starting material was consumed and the desired product was detected. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (5 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3:1) to afford compound 8 (100 mg, 185.99 μmol, 33.08% yield) as oil.

[0993] LC-MS (ESI+) m/z 538.5 $[M+H]^+$.

[0994] *Step 7.* To a solution of compound 8 (40 mg, 76.98 μmol, 1 eq) in HCl/MeOH (3 mL) was stirred at 25 °C for 3hr. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was adjusted pH to 7 by $NaHCO_3$, extracted with EtOAc (6 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 9 (20 mg, 45.92 μmol, 59.66% yield) as yellow oil which was used in the next step without further purification.

[0995] LC-MS (ESI+) m/z 436.3 $[M+H]^+$.

[0996] *Step 8.* To a solution of compound 9 (33.53 mg, 76.98 μmol, 1eq) in DCM (3 mL) was added $PyHBr_3$ (19.69 mg, 61.58 μmol, 0.8eq). The mixture was stirred at 25 °C for 3 hr. The reaction mixture was quenched by addition of water (5 mL), extracted with DCM (6 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 5/1,) to yield 10 (15 mg, 29.16 μmol, 37.88% yield) as a yellow solid.

[0997] LC-MS (ESI+) m/z 516.2 [M+H]+.

[0998] ***Step 9.*** To a solution of compound 10 (36.5 mg, 70.95 μmol, 1 eq) and phenylboronic acid (12.98 mg, 106.43 μmol, 1.5eq) in dioxane (2 mL) and H_2O (0.5 mL) was added $Pd(dtbpf)Cl_2$ (4.62 mg, 7.10 μmol, 0.1eq) and K_2CO_3 (19.61 mg, 141.91 μmol, 2eq). The mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched by addition of water (3 mL), extracted with EtOAc (6 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from pure PE to PE/EtOAc = 2/1,) to yield 11 (25 mg, 48.86 μmol, 68.87% yield) as a white solid.

[0999] LC-MS (ESI+) m/z 512.4 $[M+H]^+$.

[1000] ***Step 10.*** To a solution of compound 11 (30 mg, 58.64 μmol, 1eq) in DCM (4 mL) was added TFA (6.69 mg, 58.64 μmol, 4.36 μL, 1eq). The mixture was stirred at 25 °C for 1hr. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure to give a residue which was used in the next step without further purification. Compound 12 (20 mg, 42.96 μmol, 73.26% yield) was obtained as yellow oil.

[1001] LC-MS (ESI+) m/z 466.3 [M+H]+.

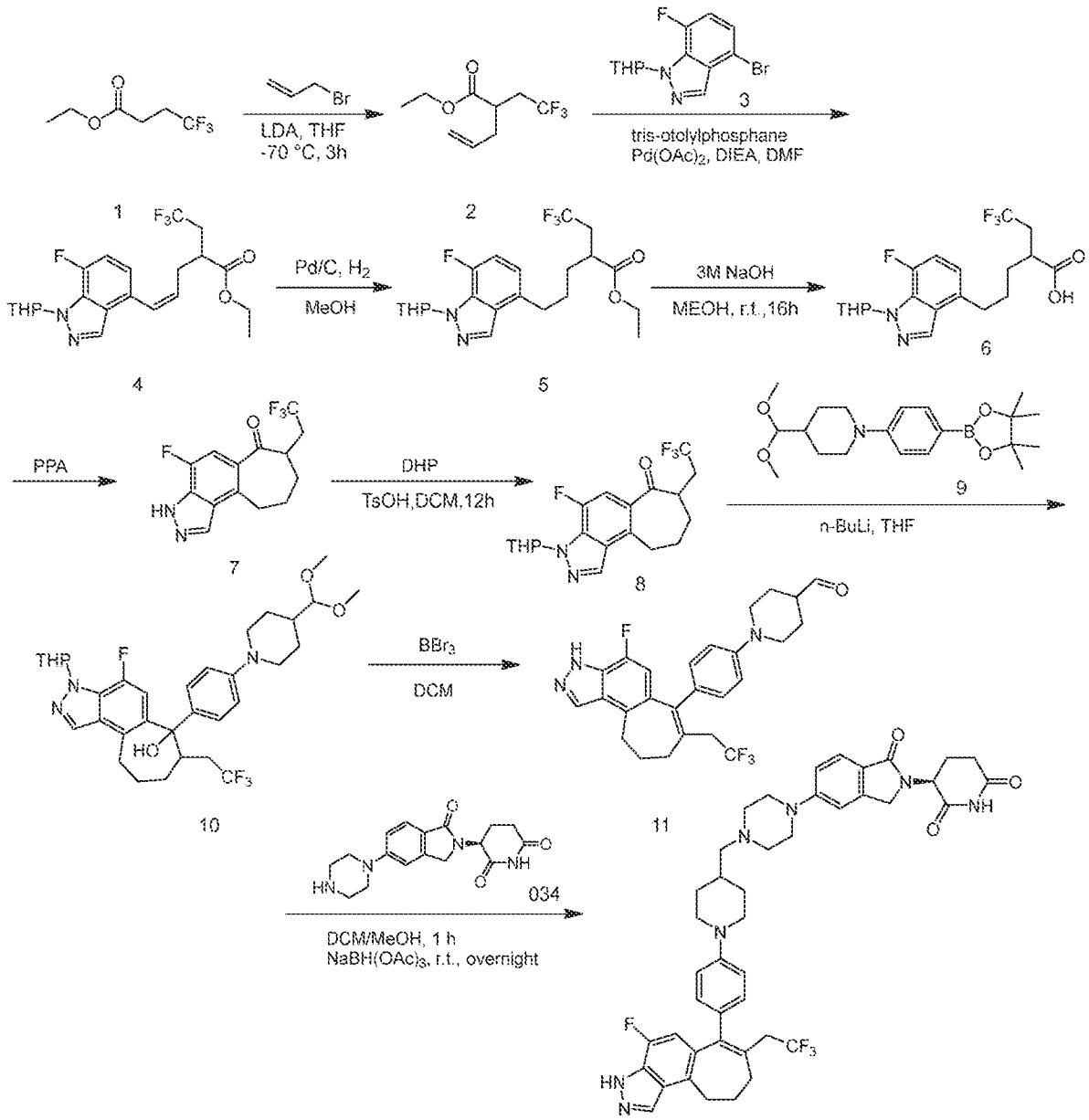
[1002] ***Step 11.*** To a solution of compound 12 (25 mg, 53.70 μmol, 1eq) in DCM (3 mL) and MeOH (2 mL) was added compound 034 (17.63 mg, 53.70 μmol, 1eq) and DIEA (6.94 mg, 53.70 μmol, 9.35 μL, 1eq) at 25 °C. After addition, the mixture was stirred at this temperature for 0.5 hr, and then $NaBH_3(OAc)_3$ (22.76 mg, 107.40 μmol, 2eq) was added at 25°C. The resulting mixture was stirred at 25°C for 3 hr. The reaction mixture was concentrated to yield a residue. The residue was purified by preparative HPLC (column: Boston Green ODS 150 * 30 mm * 5um; mobile phase: [water (FA) - ACN]; B%: 10%-40%,12min) , followed by lyophilization to yield (S)-3-(5-(4-((1-(4-(4-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (7.5 mg, 9.64 μmol, 17.95% yield) was obtained as a white solid. LC-MS (ESI^+) m/z: 778.6 $[M+H]^+$.

[1003] LCMS: calc. for $C_{47}H_{48}FN_7O_3$: 777.38, found: $[M+H]^+$ 778.6.

[1004] HPLC: 100 % purity at 220 nm.

[1005] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.47 - 8.49 (m, 1 H) 8.21 - 8.31 (m, 1 H) 7.65 (d, J=8.58 Hz, 1 H) 7.05 - 7.21 (m, 7 H) 6.73 (br s, 4 H) 6.55 (d, J=12.04 Hz, 1 H) 5.07 - 5.13 (m, 1 H) 4.35 - 4.47 (m, 2 H) 3.59 - 3.67 (m, 2 H) 3.39 (br d, J=5.25 Hz, 4 H) 3.11 (s, 2 H) 2.76 - 2.94 (m, 2 H) 2.61 - 2.71 (m, 6 H) 2.30 - 2.50 (m, 7 H) 2.09 - 2.20 (m, 1 H) 1.84 - 1.93 (m, 2 H) 1.66 - 1.80 (m, 1 H) 1.34 (br d, J=11.44 Hz, 2 H).

Example 37. Synthesis of (S)-3-(5-(4-((1-(4-(4-fluoro-7- (2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-66



[1006] *Step 1.* To a solution of ethyl 4,4,4-trifluorobutanoate (10.0 g, 58.8 mmol， 1.0 eq.) in THF (60 mL) was added dropwise LDA (70.5 mmol, 1.2 eq.) at -70 °C over 0.5 hour. After addition, the mixture was stirred at this temperature for 0.5 hour, and then 3-bromoprop-1-ene (8.53 g, 70.5 mmol, 1.2 eq.) in THF (60 mL) was added dropwise at -70 °C. The resulting mixture was stirred at -70 °C for 12 hour. TLC showed the reaction was completed. The reaction mixture was quenched by addition NH_4Cl 60 mL at 20 °C, and then diluted with water 30 mL and extracted with EA 150 mL (50 mL x 3). The combined organic layers were washed with EA 60 mL (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 1/0) to give ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (4.5 g, 21 mmol, 36 %) as colorless oil.

[1007] ^{1}H NMR (400 MHz, DMSO-d6) δ: ppm 5.73 (m, 1 H), 5.02 - 5.19 (m, 2 H), 4.10 (m, 2 H), 2.71 (m, 1 H), 2.53 - 2.64 (m, 1 H), 2.39 - 2.50 (m, 1 H), 2.32 (t, J=6.80 Hz, 2 H), 1.18 (t, J=7.20 Hz, 3 H).

[1008] *Step 2.* A mixture of ethyl 2-(2,2,2-trifluoroethyl)pent-4-enoate (2.19 g, 10.4 mmol, 1.2 eq.), 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (2.60 g, 8.69 mmol, 1.0 eq.), DIEA (2.70 g, 20.9 mmol, 2.4 eq.), Phosphine,tris(2-methylphenyl)- (265 mg, 869 μmol, 0.1 eq.) and Palladium diacetate (97.6 mg, 0.05 eq., 435 μmol) in DMF (30 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 hour under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition EA 30 mL at 20 °C, and then diluted with water 90 mL and extracted with EA 90 mL (30 mL x 3). The combined organic layers were washed with EA 30 mL (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 5/1) to give ethyl (Z)-5-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl)pent-4-enoate (2.8 g, 6.5 mmol, 75 %) as yellow oil.

[1009] LC-MS (ESI$^+$) m/z: 429.1 $(M+H)^+$

[1010] ^{1}H NMR (400 MHz, METHANOL-d_4) δ: ppm 8.28 (d, J=2.00 Hz, 1 H), 7.01 - 7.21 (m, 2 H), 6.79 (d, J=16.00 Hz, 1 H), 6.25 - 6.40 (m, 1 H), 5.90 (m, 1 H), 4.15 (m, 2 H), 4.00 (m, 1 H), 3.76 (m, 1 H), 2.92 (m, 1 H), 2.65 - 2.75 (m, 1 H), 2.58 - 2.63 (m, 2 H), 2.51 - 2.57 (m, 1 H), 2.42 (m, 1 H), 2.03 - 2.14 (m, 2 H), 1.74 - 1.83 (m, 1 H), 1.57 - 1.70 (m, 2 H), 1.18 - 1.22 (m, 3 H).

[1011] *Step 3.* To a solution of ethyl (Z)-5-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2 -trifluoroethyl) pent-4-enoate (2.20 g, 5.14 mmol, 1.0 eq.) in MeOH (20 mL) was added Pd/C (10wt%, 0.4 g) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hour. LCMS showed the reaction was completed. The mixture was filtered and the filtrate was concentrated give ethyl 5-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl) pentanoate (2.0 g, 4.6 mmol, 90 %) as colourless oil.

[1012] LC-MS (ESI^+) m/z: 427.1 $(M+H)^+$

[1013] ^1H NMR (400 MHz, METHANOL-d_4) δ: ppm 8.11 (d, J=2.00 Hz, 1 H), 7.01 (m, 1 H), 6.87 (d, J=4.00 Hz, 1 H), 5.86 (m, 1 H), 4.08 (m, 2 H), 3.94 - 3.99 (m, 1 H), 3.72 (m, 1 H), 3.27 (s, 1 H), 2.81 - 2.95 (m, 2 H), 2.62 - 2.71 (m, 1 H), 2.46 - 2.58 (m, 2 H), 2.22 (d, J=360 Hz, 1 H), 2.16 - 2.34 (m, 1 H), 2.01 - 2.11 (m, 2 H), 1.73 - 1.82 (m, 1 H), 1.57 - 1.71 (m, 6 H), 1.12 - 1.21 (m, 3 H).

[1014] *Step 4.* To a solution of ethyl 5-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(2,2,2- trifluoroethyl) pentanoate (2.000 g, 4.646 mmol, 1.0 eq.) in MeOH (40 mL) and Water (20 mL) was added NaOH (557.6 mg, 13.94 mmol, 3.0 eq.). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The mixture was adjusted to pH 6-7 with 1M HCl. The reaction mixture was quenched by addition EA 10 mL at 20 °C, and then diluted with water 30 mL and extracted with EA 30 mL (10 mL x 3). The combined organic layers were washed with EA 30 mL (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 5-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2 -(2,2,2-trifluoroethyl) pentanoic acid (1.6 g, 3.98 mmol, 90% yield) as a white solid.

[1015] LC-MS (ESI+) m/z: 403.3(M+H)+

[1016] ^1H NMR (500 MHz, DMSO-d_6) δ: ppm 12.56 (d, 1 H), 8.27 (d, J=1.50 Hz, 1 H), 7.10 - 7.17 (m, 1 H), 6.91 (m, 1 H), 5.82 (d, J=8.50 Hz, 1 H), 4.03 (m, 1 H), 3.90 (d, J=11.00 Hz, 1 H), 3.60 - 3.68 (m, 1 H), 2.81 - 2.93 (m, 2 H), 2.52 - 2.59 (m, 2 H), 2.39 - 2.47 (m, 2 H), 2.04 (d, J=10.50 Hz, 2 H), 1.60 - 1.74 (m, 4 H), 1.53 - 1.61 (m, 2 H).

[1017] *Step 5.* To a solution of 5-(7-fluoro-1H-indazol-4-yl)-2-(2,2,2-trifluoroethyl)pentanoic acid (1.60 g, 5.03 mmol, 1.0 eq.) in PPA (25 mL). The mixture was stirred at 120 °C for 12 hour. LCMS showed the reaction was completed. The reaction mixture was quenched by addition Na_2HCO_3 at 20 °C, and then diluted with water 30 mL and extracted with EA 150 mL

(50 mL x 3). The combined organic layers were washed with EA 60 mL (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 4/1) to give 4-fluoro-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (0.9 g, 3 mmol, 60 % yield) as yellow oil.

[1018] LC-MS (ESI+) m/z: 300.9(M+H)+

[1019] ^{1}H NMR (400 MHz, DMSO-d_6) δ: ppm 13.83 - 14.10 (m, 1 H), 8.51 (d, J=2.80 Hz, 1 H), 7.36 (d, J=11.60 Hz, 1 H), 3.50 - 3.58 (m, 1 H), 3.35 - 3.41 (m, 1 H), 3.35 - 3.41 (m, 1 H), 3.23 (m, 1 H), 3.00 (m, 1 H), 2.17 - 2.27 (m, 1 H), 2.04 - 2.15 (m, 1 H), 1.49 - 1.61 (m, 2 H).

[1020] ***Step 6.*** To a solution of DHP (252 mg, 3.00 mmol, 1.5 eq.) and 4-fluoro-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (600 mg, 1 eq., 2.00 mmol) in DCM (10 mL) was added TsOH (76.0 mg, 400 μmol, 0.2 eq.). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 5/1) to give compound 8 (600 mg, 1.56 mmol, 78.1 % yield) as yellow oil.

[1021] LC-MS (ESI+) m/z: 385.2(M+H)+

[1022] ^{1}H NMR (400 MHz, DMSO-d_6) δ: ppm 8.55 (d, J=2.00 Hz, 1 H), 7.40 (m, 1 H), 5.85 (d, J=9.20 Hz, 1 H), 3.90 (m, 1 H), 3.62 - 3.70 (m, 1 H), 3.48 - 3.58 (m, 1 H), 3.15 - 3.27 (m, 1 H), 2.91 - 3.06 (m, 1 H), 2.36 - 2.47 (m, 2 H), 2.15 - 2.29 (m, 1 H), 2.05 (d, J=10.40 Hz, 2 H), 1.69 - 1.77 (m, 1 H), 1.41 - 1.64 (m, 6 H).

[1023] ***Step 7.*** To a solution of 1-(4-bromophenyl)-4-(dimethoxymethyl)piperidine (441 mg, 1.40 mmol, 1.2 eq.) in THF (2 mL) was added dropwise n-butyllithium (1.64 mmol, 1.4 eq.) at -70 °C over 1h. After addition, the mixture was stirred at this temperature for -70 °C, and then 4-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (450 mg, 1.17 mmol, 1.0 eq.) in THF (2 mL) was added dropwise at -70 °C. The resulting mixture was stirred at -70 °C for 12 hour. LCMS showed the reaction was completed. The reaction mixture was quenched by addition NH_4Cl (aq.) 30 mL at 20 °C, and then diluted with water 30 mL and extracted with EA 90 mL (30 mL x 3). The combined organic layers were washed with EA 30 mL (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was

purified on silica gel column chromatography (from pure PE to PE/EtOAc = 5/1) to give compound 10 (250 mg, 403 μmol, 34.5 % yield) as a yellow solid.

[1024] LC-MS (ESI+) m/z: 620.3(M+H)+

[1025] ***Step 8.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-4-fluoro-3-(tetrahydro-2H- pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (250 mg, 1 eq., 403 μmol) in water (1 mL) was added BBr_3 (505 mg, 191 μL, 5 eq., 2.02 mmol). The mixture was stirred at 20 °C for 1 hour and then water (1 mL) in DCM (10 mL) was added dropwise at 20 °C. The resulting mixture was stirred at 20 °C for 1h. LCMS showed the reaction was completed. The mixture was concentrated and then water (20 mL) was added. The mixture was extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The mixture was concentrated in vacuo to give crude product. No further purification as it is used for the next step directly.

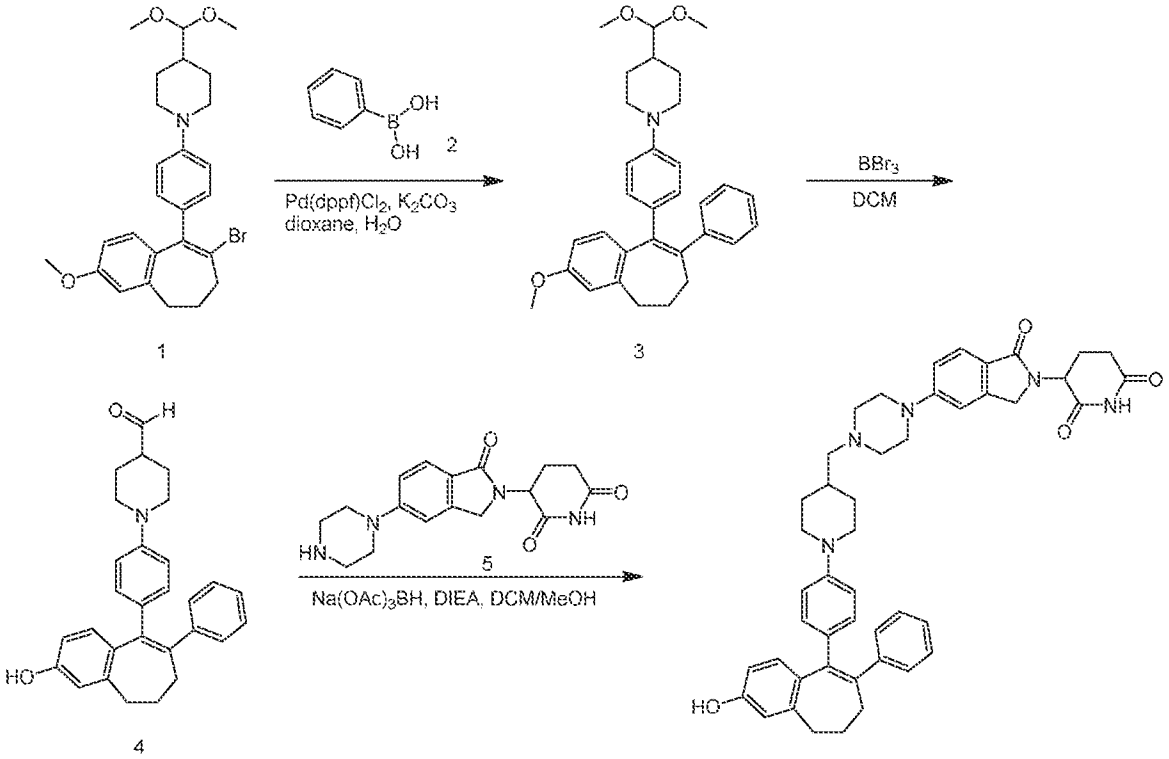
[1026] ***Step 9.*** To a solution of 1-(4-(4-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e] indazol-6-yl)phenyl)piperidine-4-carbaldehyde (100 mg, 1 eq., 212 μmol) in DCE (3 mL) and MeOH (3 mL) was added (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine -2,6-dione (83.6 mg, 1.2 eq., 255 μmol). The mixture was stirred at 20 °C for 0.5 hour. LCMS showed the reaction was completed. The crude was purified by prep-HPLC together (C18-1 150*30mm*5um, water (NH_4HCO_3)-CAN as a mobile phase, from 55% to 85%, Gradient Time (min): 11, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(4-(4-fluoro-7- (2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (44.7 mg, 57.0 μmol, 26.9 %) as a white solid.

[1027] LCMS: calc. for C43H45F4N7O3:783.35, found: $[M+H]^+$ 784.2

[1028] HPLC: 95.22% purity at 220 nm.

[1029] ^1H NMR (500 MHz, METHANOL-d_4) δ : ppm 8.23 (d, J=3.50 Hz, 1 H), 7.64 (d, J=8.50 Hz, 1 H), 7.06 - 7.11 (m, 2 H), 6.98 - 7.03 (m, 4 H), 6.49 (d, J=12.00 Hz, 1 H), 5.10 (m, 1 H), 4.34 - 4.46 (m, 2 H), 3.75 (d, J=12.50 Hz, 2 H), 3.36 - 3.40 (m, 4 H), 3.17 - 3.23 (m, 2 H), 3.05 (t, J=7.00 Hz, 2 H), 2.86 - 2.93 (m, 1 H), 2.73 - 2.80 (m, 3 H), 2.61 - 2.66 (m, 4 H), 2.38 - 2.51 (m, 3 H), 2.34 (d, J=7.00 Hz, 2 H), 2.13 - 2.17 (m, 3 H), 1.94 (d, J=12.50 Hz, 2 H),1.75 - 1.82 (m, 1 H), 1.35 - 1.43 (m, 2 H).

Example 38. Synthesis of 3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-122



[1030] ***Step 1.*** A mixture compound 1 (1.5 g, 3.08 mmol, 1 eq.), compound 2 (563.98 mg, 4.63 mmol, 1.5 eq.), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (200.97 mg, 308.36 μmol, 0.1 eq.), dipotassium;carbonate (1.28 g, 9.25 mmol, 3 eq.) and H_2O (10 mL) in dioxane (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 3 hr under N_2 atmosphere. LC-MS showed one main peak with desired mass was detected. The reaction mixture was partitioned between EA (60 mL×2) and water (60 mL). After quenching the reaction, the reaction mixture was poured into separatory funnel and separated. The crude product was purified by silica gel chromatography eluted with PE: EtOAc=3:1~2:1. Compound 3 (1.4 g, 2.89 mmol, 93.87% yield) was obtained as a brown liquid.

[1031] LC-MS (ESI^+) m/z: 484.2$(M+H)^+$.

[1032] ***Step 2.*** To a solution of compound 3 (300 mg, 620.30 μmol, 1 eq.) in DCM (10 mL) was added dropwise BBr_3 (310.79 mg, 1.24 mmol, 119.54 μL, 2 eq.) at 0 °C. After addition, the mixture was stirred at this temperature for 1 hr, and then H_2O was added dropwise. The resulting mixture was stirred at 25°C for 4hr. LC-MS showed one main peak with desired mass was detected. The reaction mixture was partitioned between DCM (100 mL×2) and water (100

mL). After quenching the reaction, the reaction mixture was poured into separatory funnel and separated. The crude product compound 4 (120 mg, 283.32 μmol, 45.68% yield) as brown solid was used into the next step without further purification.

[1033] LC-MS (ESI^+) m/z: 424.2 $(M+H)^+$.

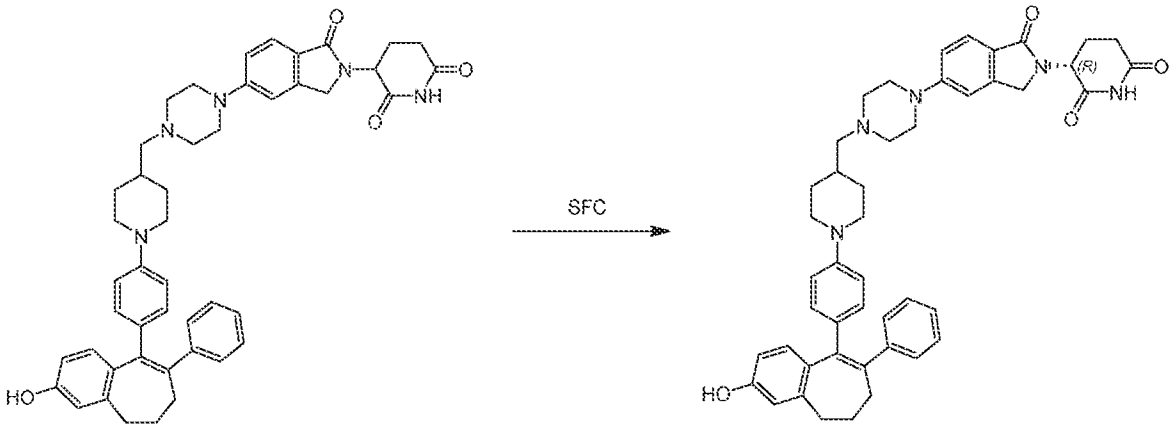
[1034] ***Step 3.*** To a solution of compound 4 (120 mg, 283.32 μmol, 1 eq.) and compound 5 (111.64 mg, 339.99 μmol, 1.2 eq.) in DCE (10 mL) was added sodium;triacetoxyboranuide (60.05 mg, 283.32 μmol, 1 eq.) and DIPEA (36.62 mg, 283.32 μmol, 49.35 μL, 1 eq.). The mixture was stirred at 25 °C for 6hr. LC-MS showed one main peak with desired mass was detected. After quenching the reaction, the reaction mixture was poured into separatory funnel and separated. The reaction mixture was partitioned between DCM (100 mL×2) and water (100 mL). The residue was purified by prep-HPLC(Column Boston Green ODS 150*30mm*5μm, Condition water(FA)-CAN, Begin B 25, End B 55, Gradient Time(min) 14, 100%B Hold Time(min) 2, FlowRate(ml/min) 25, Injections 8, HPLC 90). Compound 3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (110 mg, 149.47 μmol, 52.76% yield) was obtained as a white solid. LC-MS (ESI^+) m/z: 736.4 $(M+H)^+$.

[1035] LCMS: calc. for $C_{46}H_{49}N_5O_4$: 735.38, found: $[M+H]^+$ 736.4.

[1036] HPLC: 100.00% purity at 220 nm.

[1037] ^1H NMR: ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.37 (s, 1 H) 7.65 (d, J = 8.34 Hz, 1 H) 7.05 - 7.15 (m, 7 H) 6.74 - 6.78 (m, 2 H) 6.68 - 6.73 (m, 3 H) 6.63 - 6.67 (m, 1 H) 6.54 - 6.59 (m, 1 H) 5.10 (dd, J = 13.23, 5.13 Hz, 1 H) 4.35 - 4.46 (m, 2 H) 3.61 (br d, J = 12.52 Hz, 2 H) 3.40 - 3.45 (m, 4 H) 2.85 - 2.91 (m, 1 H) 2.73 - 2.80 (m, 6 H) 2.60 - 2.67 (m, 2 H) 2.42 - 2.50 (m, 3 H) 2.37 (t, J = 6.91 Hz, 2 H) 2.09 - 2.14 (m, 2 H) 1.88 (br d, J = 12.16 Hz, 2 H) 1.73 - 1.82 (m, 1 H) 1.29 - 1.39 (m, 4 H)

Example 39. Synthesis of (R)-3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-123



[1038] Compound (R)-3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (80 mg, 108.71 μmol, 1 eq.) was seperated by SFC. LCMS showed desired compound was detected. The solution was concentrated to dryness. Compound (R)-3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione was separated by chiral SFC (column: DAICEL CHIRALPAK ID (250mm*30mm,10μm); mobile phase: [Condition MeOH-ACN]; B%: 50%-50%. SFC: Rt=2.443, 3.420) to yield (R)-3-(5-(4-((1-(4-(3-hydroxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (21 mg, 28.54 μmol, 26.25% yield) as white solid.

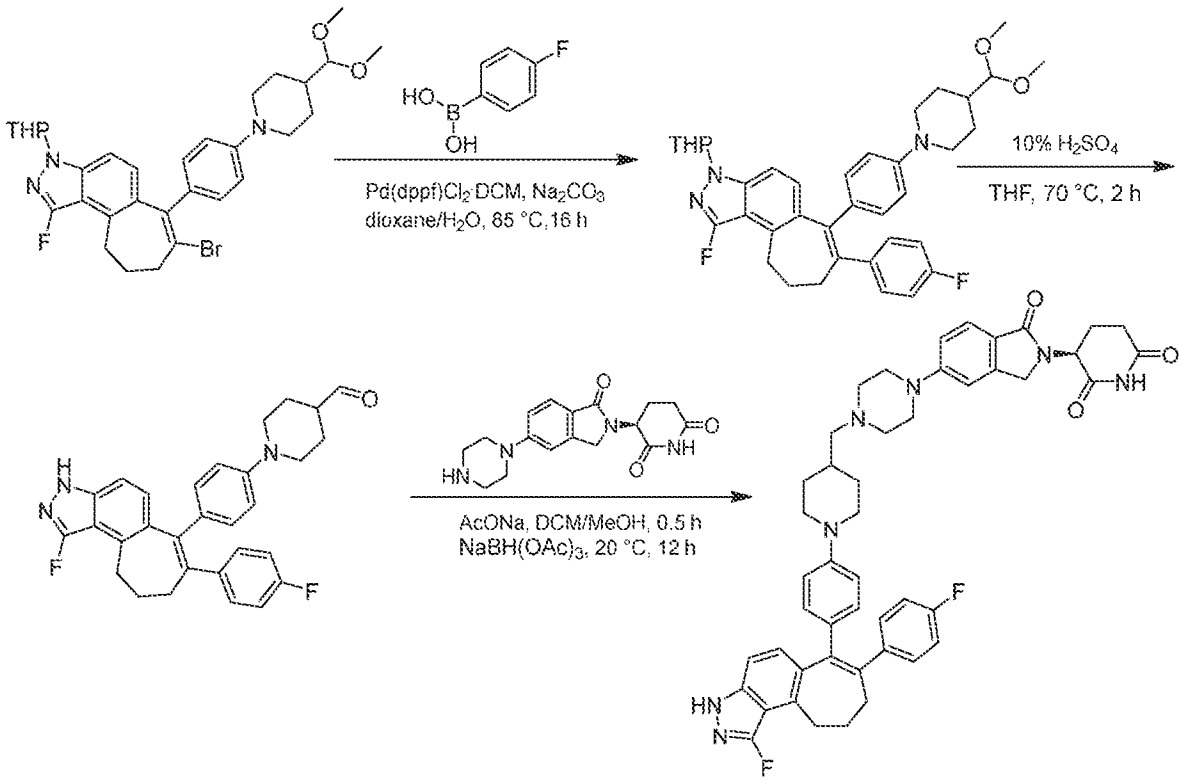
[1039] LC-MS (ESI^+) m/z: 736.4 $(M+H)^+$.

[1040] LCMS: calc. for $C_{46}H_{49}N_5O_4$: 735.38, found: $[M+H]^+$ 736.4.

[1041] HPLC: 98.27% purity at 220 nm.

[1042] ^1H NMR: ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.63 (d, J = 8.58 Hz, 1 H) 7.04 - 7.17 (m, 7 H) 6.63 - 6.78 (m, 6 H) 6.53 - 6.59 (m, 1 H) 5.10 (dd, J = 13.17, 4.95 Hz, 1 H) 4.33 - 4.45 (m, 2 H) 3.57 - 3.62 (m, 2 H) 3.36 (br d, J = 4.89 Hz, 4 H) 2.84 - 2.95 (m, 1 H) 2.71 - 2.81 (m, 3 H) 2.58 - 2.63 (m, 5 H) 2.43 - 2.52 (m, 1 H) 2.36 (br t, J = 6.85 Hz, 2 H) 2.30 (br d, J = 7.15 Hz, 2 H) 2.09 - 2.14 (m, 2 H) 1.85 - 1.91 (m, 2 H) 1.66 - 1.77 (m, 1 H) 1.32 (br d, J = 13.23 Hz, 3 H) 1.18 (t, J = 7.03 Hz, 1 H)

Example 40. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(4-fluorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-103



[1043] ***Step 1.*** A mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 1 Eq, 200 μmol), (4-fluorophenyl)boronic acid (30.9 mg, 1.1 Eq, 221 μmol) , Na_2CO_3 (64 mg, 3 Eq, 601 μmol), $Pd(dppf)Cl_2$·DCM (16 mg, 0.1 Eq, 20 μmol) in 1,4-dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.5 UV) showed one main new spot was observed. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a black solid. The black solid was subjected to column chromatography over silica gel (gradient elution: 0 – 30% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(4-fluorophenyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (87 mg, 0.14 mmol, 71 % yield) as a yellow solid.

[1044] *Step 2.* To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(4-fluorophenyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (87 mg, 1 Eq, 0.14 mmol) in THF (8 mL) was added 10% H_2SO_4 (4 g, 2 mL, 10% Wt, 4 mmol). The mixture was stirred at 70 °C for 2 hr. The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (10 mL). Then the mixture was added water (20 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a yellow oil of 1-(4-(1-fluoro-7-(4-fluorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 0.12 mmol, 88 % yield).

[1045] Step 3. A solution of 1-(4-(1-fluoro-7-(4-fluorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 1 Eq, 0.1 mmol) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (70 mg, 1.2 Eq, 0.1 mmol, $PhSO_3H$ salt) and sodium acetate (51 mg, 5 Eq, 0.6 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h, then acetic acid (15 mg, 14 μL, 2 Eq, 0.3 mmol) and sodium triacetoxyhydroborate (53 mg, 2 Eq, 0.25 mmol) was added. The mixture was stirred at 20 °C for 12 hour. The mixture was filtered and the filter cake was washed with ethyl acetate (50 mL). The filtrate was treated with H_2O (50 mL), extracted with ethyl acetate (50 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue.

[1046] The residue was purified by prep-HPLC:

[1047] Column: Phenomenex C18 80*30mm*3um

[1048] Condition:

[1049] A: water (FA)

[1050] B: ACN

[1051] At the beginning: A (72%) and B (28%)

[1052] At the end: A: (42%) and B (58%)

[1053] Gradient Time (min) 7; 100%B Hold Time (min) 3.7; Flow Rate (ml/min) 25.

[1054] The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(4-fluorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-

yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (21.4 mg, 26.4 μmol, 21 % yield, 98.2% purity) as a white solid.

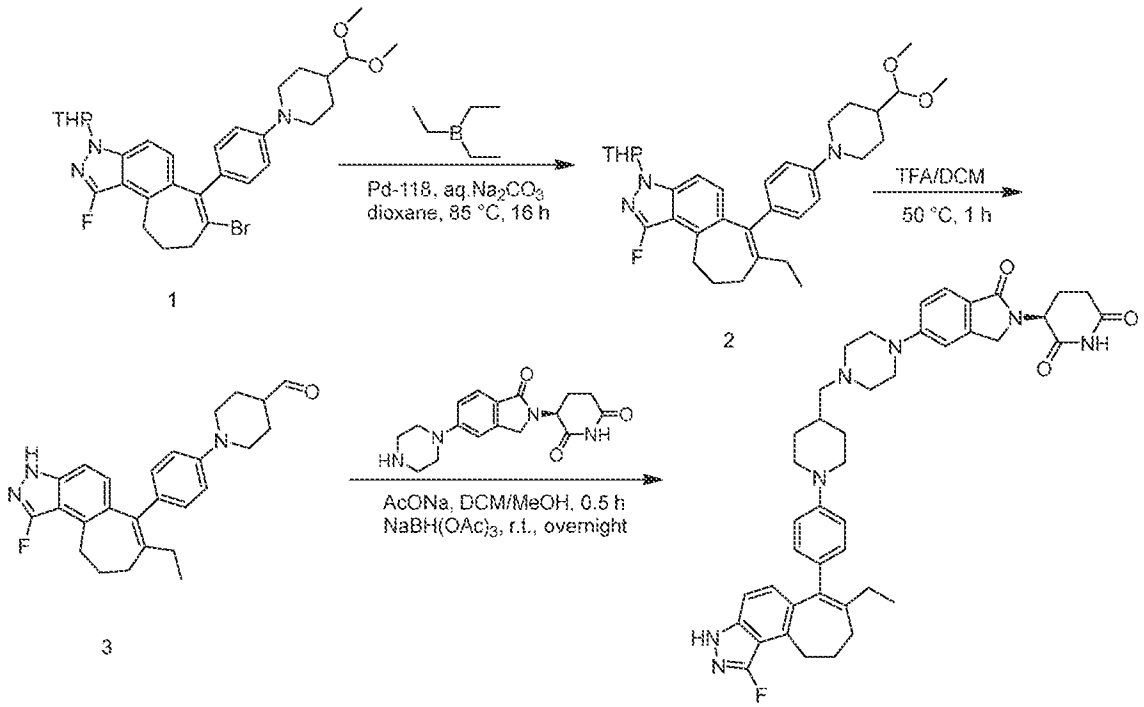
[1055] LCMS: calc. for $C_{47}H_{47}F_2N_7O_3$: 795.94, found: $[M+H]^+$ 796.2

[1056] HPLC: 98.21% purity at 220 nm.

[1057] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.52 (s, 1H), 10.96 (s, 1H), 8.16 (s, 0.368H), 7.52 (d, J = 8.7 Hz, 1H), 7.28 - 7.18 (m, 3H), 7.05 (br d, J = 14.1 Hz, 4H), 6.82 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 2.1 Hz, 4H), 5.05 (dd, J = 5.1, 13.4 Hz, 1H), 4.41 - 4.14 (m, 2H), 3.63 (br d, J = 11.6 Hz, 2H), 3.34 (br s, 8H), 3.07 (br s,2H), 2.98 - 2.85 (m, 1H), 2.63 - 2.55 (m, 3H), 2.37 (br dd, J = 4.4, 13.4 Hz, 1H), 2.30 - 2.16 (m, 6H), 2.05 - 1.90 (m, 1H), 1.79 (br d, J = 11.6 Hz, 2H), 1.73 - 1.60 (m, 1H), 1.17 (br d, J = 10.6 Hz, 2H)

[1058] SFC: retention time, 2.586 min; Area, 95.8%; Method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM

Example 41. Synthesis of (S)-3-(5-(4-((1-(4-(7-ethyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-70



[1059] ***Step 1.*** 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (13 mg, 0.1 Eq, 20 μmol) was added into a mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)pheny-l)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 1 Eq,

200 μmol), triethylborane (24 mg, 1.2 Eq, 240 μmol) and sodium carbonate (63 mg, 3 Eq, 601 μmol) in 1,4-dioxane (4 mL) and H_2O (1 mL). The mixture was bubbled with N_2 for 3 min and then stirred at 85 °C for 16 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL*2). The organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 40% ethyl acetate). The desired fractions were collected and concentrated to dryness in vacuo to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-7-ethyl-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (80 mg, 95 μmol, 47 % yield, 64.94% purity) as a white solid.

[1060] ***Step 2.*** A solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-7-ethyl-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (80 mg, 1 Eq, 95 μmol) in DCM/TFA (4:1, 10 mL) was stirred at 50 °C for 1h. The mixture was cooled to room temperature and poured into saturated aq.$NaHCO_3$ (30 mL), then the mixture was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-(7-ethyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (84 mg, crude) as a yellow solid.

[1061] ***Step 3.*** To a solution of 1-(4-(7-ethyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (84 mg, 1 Eq, 0.2 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (98 mg, 1 Eq, 0.2 mmol, $PhSO_3H$ salt) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (83 mg, 5 Eq, 1 mmol) was stirred at 25 °C for 0.5 h, then sodium triacetoxyborohydride (85 mg, 2 Eq, 0.4 mmol) and acetic acid (24 mg, 2 Eq, 0.4 mmol) was added. The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL*2). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B% 23%-53%, 7 min). The desired fractions were lyophilized under vacuum to give a white powder. The white powder was purified by prep-HPLC (column: Phenomenex C18 80*40mm*3um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B% 78%-100%, 7 min). The pure fractions were lyophilized under vacuum to give (S)-3-(5-(4-((1-(4-(7-ethyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-

yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (15.7 mg, 21.1 μmol, 10 % yield, 97.9% purity) as a white solid. LC-MS (ESI^+) m/z: 730.5 $(M+H)^+$.

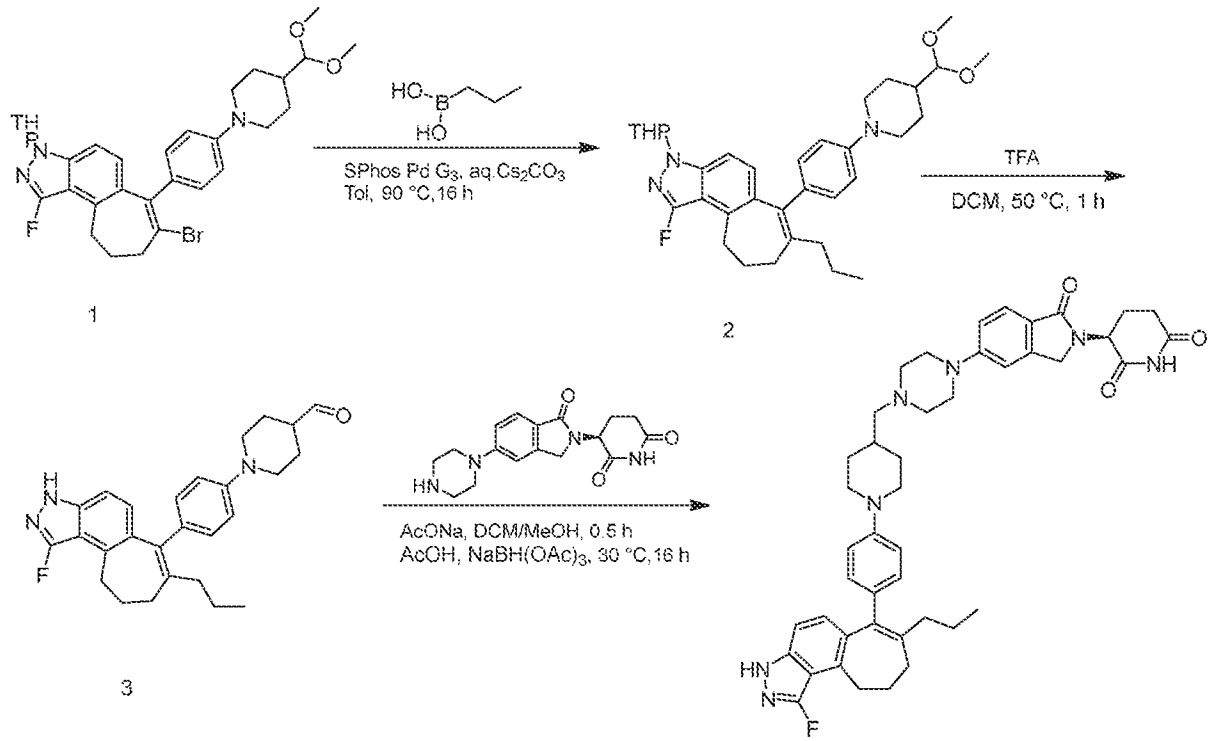
[1062] LCMS: calc. for $C_{43}H_{48}FN_7O_3$: 729.90, found: $[M+H]^+$ 730.5.

[1063] HPLC: 97.932% purity at 220 nm.

[1064] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.40 (s, 1H), 10.94 (s, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.15 (dd, J = 2.4, 8.7 Hz, 1H), 7.11 - 7.04 (m, 2H), 6.90 (s, 4H), 6.75 (d, J = 8.7 Hz, 1H), 5.05 (dd, J = 5.2, 13.1 Hz, 1H), 4.38 - 4.18 (m, 2H), 3.69 (br d, J = 12.3 Hz, 2H), 3.31 - 3.27 (m, 6H), 2.98 - 2.92 (m, 2H), 2.92 - 2.85 (m, 1H), 2.71 - 2.59 (m, 3H), 2.57 (br d, J = 1.8 Hz, 1H), 2.37 (br dd, J = 3.9, 12.8 Hz, 1H), 2.31 - 2.20 (m, 6H), 2.01 - 1.95 (m, 1H), 1.91 (br t, J = 6.8 Hz, 2H), 1.83 (br d, J = 11.9 Hz, 2H), 1.75 - 1.66 (m, 1H), 1.33 - 1.18 (m, 3H), 1.08 (t, J = 7.5 Hz, 3H)

[1065] SFC: retention time, 7.212 min; Area, 94.83%; method: IA_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

Example 42. Synthesis of (3S)-3-[5-[4-[[1-[4-(1-fluoro-7-propyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-71, I-124



[1066] *Step 1.* A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (200 mg, 334.14 μmol, 1 eq),

propylboronic acid (58 mg, 668 μmol, 2 eq), Sphos Pd G_3(48 mg, 66 μmol, 0.2 eq), dicesium carbonate (326 mg, 1 mmol, 3 eq) was added in toluene (5 mL) and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. The reaction was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the combined organic layer was washed with saturated salt water (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/Petroleum ethergradient @ 30 mL/min) to give compound 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (180 mg, 320 μmol) was obtained as a yellow oil. LC-MS (ESI+) m/z: 562.0 $(M+H)^+$

[1067] ***Step 2.*** A mixture of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (100 mg, 178 μmol, 1 eq) was added in DCM (8 mL) and TFA (2 mL) and purged with N_2 for 3 times, the mixture was stirred at 50 °C for 1 h under N_2 atmosphere. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the combined organic layer was washed with saturated salt water (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound 1-[4-(1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (80 mg, 124 μmol) was obtained as a white solid.

[1068] ***Step 3.*** A mixture of (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (81 mg, 222 μmol, 1.2 eq, HCl salt), 1-[4-(1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (80 mg, 155 μmol, 1 eq), AcONa (45 mg, 556 μmol, 3 eq) was added in the DCM (2 mL) and MeOH (2 mL), the mixture was stirred at 30 °C for 0.5 h, and then AcOH (33mg, 556 μmol, 31 μL, 3 eq), $NaBH(OAc)_3$ (78 mg, 370 μmol, 2 eq) was added in the mixture and was stirred at 30 °C for 16 h. the reaction was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];gradient:23%-53% B over 7 min) to give (3S)-3-[5-[4-[[1-[4-(1-fluoro-7-propyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-

piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (27 mg, 36 μmol) was obtained as a white solid.

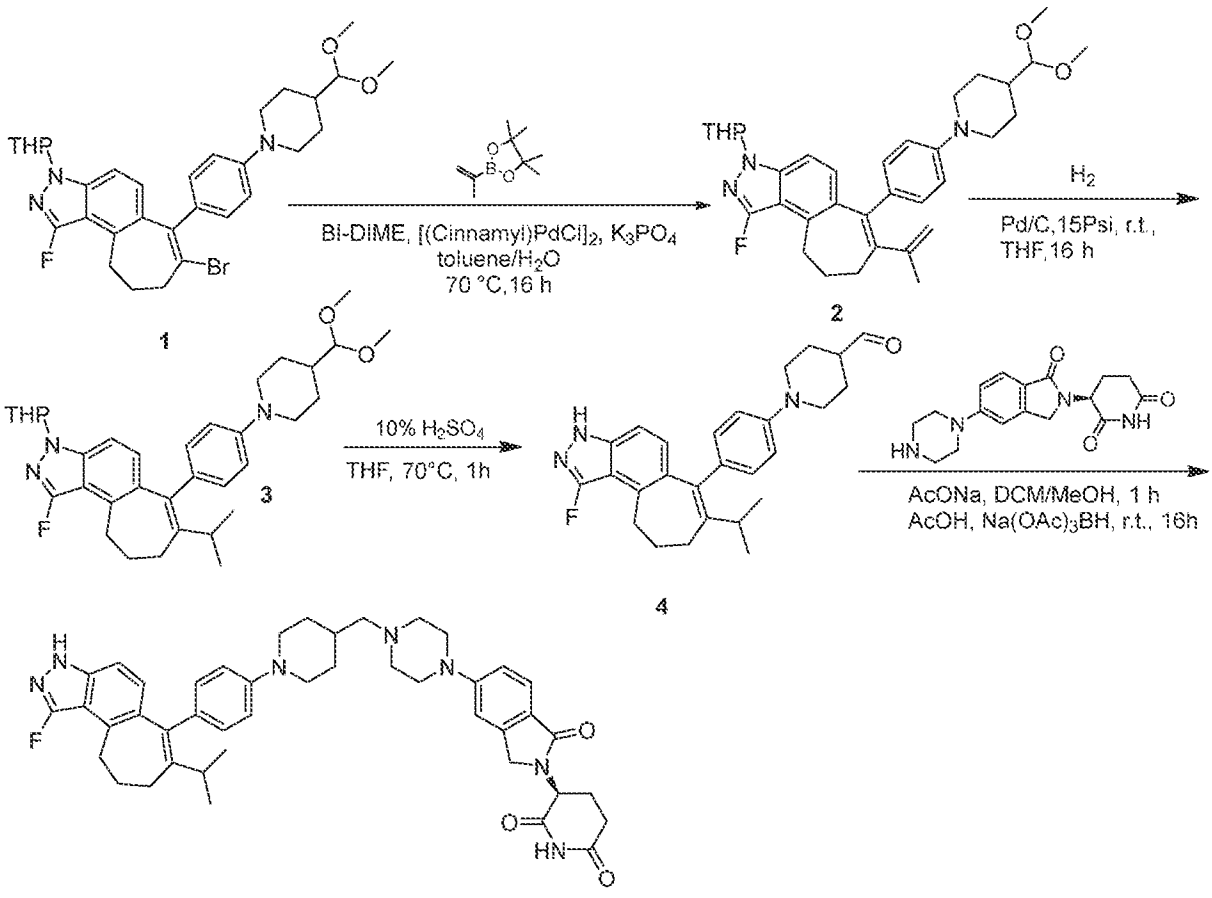
[1069] LC-MS (ESI+) m/z: 744.4 $(M+H)^+$

[1070] HPLC: 100% purity at 220 nm

[1071] SFC: Rt: 3.310 min; Area: 88%; Method: IC_MeOH_DEA_MeCN_50_1ML_15MIN_10CM

[1072] ^{1}H NMR (400 MHz, DMSO-d_6) δ= 12.41 (s, 1H), 10.95 (s, 1H), 8.16 (s, 0.237H), 7.53 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 2.6, 8.8 Hz, 1H), 7.10 - 7.04 (m, 2H), 6.89 (s, 4H), 6.75 (d, J = 8.8 Hz, 1H), 5.06 (dd, J = 5.1, 13.2 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.26 - 4.15 (m, 1H), 3.70 (br d, J = 12.3 Hz, 2H), 3.25(brs, 3H), 3.03 - 2.83 (m, 3H), 2.72 - 2.55 (m, 4H), 2.43 - 2.31 (m, 2H), 2.31 - 2.19 (m, 6H), 2.03 - 1.79 (m, 6H), 1.78 - 1.65 (m, 1H), 1.58 - 1.43 (m, 3H), 1.33 - 1.15 (m, 3H), 0.87 (t, J = 7.3 Hz, 3H).

Example 43. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-isopropyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-69



[1073] *Step 1.* A mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 334 μmol), di-mu-chlorobis[(1,2,3-nu)-1-phenyl-2-propen-1-yl]dipalladium (19 mg, 0.1 Eq, 33.4 μmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (112 mg, 2 Eq, 668 μmol), 3-(tert-butyl)-4-(2,6-dimethoxyphenyl)-2,3-dihydrobenzo[d][1,3]oxaphosphole (33 mg, 0.3 Eq, 100 μmol) and K_3PO_4(231 mg, 3 Eq, 1 mmol) in toluene (15 mL) and H_2O (3 mL) was bubbled with N_2 for 3 min and then stirred at 70 °C for 16 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (40 mL*2). The organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 30% ethyl acetate in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(prop-1-en-2-yl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (170 mg, 88.7 % yield, 97.539% purity) as a colorless oil. LC-MS (ESI^+) m/z: 560.3 $(M+H)^+$.

[1074] *Step 2.* A solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(prop-1-en-2-yl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (130 mg, 1 Eq, 232 μmol) in THF(8 mL) was added wet Pd/C (120 mg, 10% wt). The mixture was degassed and purged with H_2 for 3 times, then the mixture was stirred at r.t. under H_2(15 psi)for 16 h. The reaction mixture was filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B% 65%-95%, 7 min). The pure fractions were lyophilized under vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-isopropyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (90 mg, 100% purity, 69% yield) as a white solid. LC-MS (ESI^+) m/z: 562.3 $(M+H)^+$.

[1075] *Step 3.* A solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-isopropyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (90 mg, 1 Eq, 160 μmol) in 10% H_2SO_4 (3 mL) and THF (3 mL) was stirred at 70 °C for 60 min. The mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (30 mL), then the mixture was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give 1-(4-(1-fluoro-7-isopropyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-

yl)phenyl)piperidine-4-carbaldehyde (65 mg, crude) as a yellow solid. LC-MS (ESI^+) m/z: 432.3 $(M+H)^+$.

[1076] ***Step 4.*** To a solution of 1-(4-(1-fluoro-7-isopropyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (65 mg, 1 Eq, 0.15 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (60 mg, 1.1Eq, 0.17 mmol, HCl salt) in DCM (3 mL) and MeOH (3 mL) was added sodium acetate (83 mg, 5 Eq, 0.75 mmol). The mixture was stirred at 25 °C for 1 h, then sodium triacetoxyborohydride (64 mg, 2 Eq, 0.3 mmol) and acetic acid (18 mg, 2 Eq, 0.3 mmol) were added. The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL*2). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B% 28%-58%, 7 min). The desired fractions were lyophilized under vacuum to give a white powder. The pure fractions were lyophilized under vacuum to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-isopropyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (32.4 mg, 30 % yield, 100% purity) as a white solid. LC-MS (ESI^+) m/z: 744.6 $(M+H)^+$.

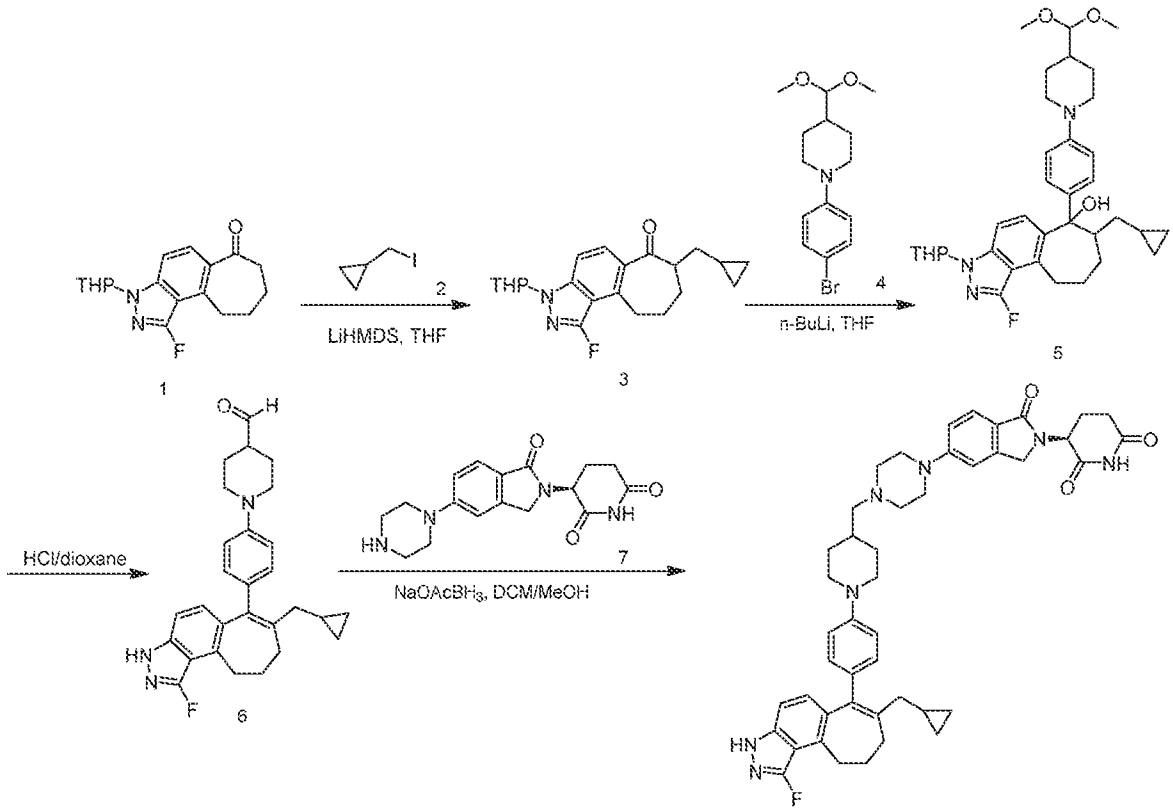
[1077] LCMS: calc. for $C_{44}H_{50}FN_7O_3$: 743.4, found: $[M+H]^+$ 744.6.

[1078] HPLC: 100% purity at 220 nm.

[1079] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.42 (s, 1H), 10.97 (s, 1H), 8.15 (s, 0.228H), 7.53 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 2.4, 8.8 Hz, 1H), 7.08 (s, 2H), 6.89 (s, 4H), 6.73 (d, J = 8.7 Hz, 1H), 5.05 (dd, J = 4.9, 13.4 Hz, 1H), 4.38 - 4.16 (m, 2H), 3.69 (br d, J = 11.4 Hz, 2H), 3.30 (br s, 6H), 3.00 - 2.83 (m, 5H), 2.66 (br s, 2H), 2.63 - 2.55 (m, 2H), 2.37 (br dd, J = 4.2, 13.2 Hz, 1H), 2.24 (br d, J = 7.3 Hz, 4H), 2.01 - 1.93 (m, 1H), 1.91 - 1.79 (m, 4H), 1.75 - 1.66 (m, 1H), 1.22 (br d, J = 11.4 Hz, 2H), 1.06 (d, J = 6.8 Hz, 6H)

[1080] SFC: retention time, 3.270 min; Area, 96.505%; method: C_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 44. Synthesis of (S)-3-(5-(4-((1-(4-(7-(cyclopropylmethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-100



[1081] ***Step 1.*** To a solution of compound 1 (900 mg, 2.98 mmol, 1.0 eq) in THF (10 mL) was added LiHMDS (697 mg, 4.17 mL, 4.17 mmol, 1.4 eq) at 0 °C and stirred at 0 °C for 0.5 h. Then a solution of compound 2 (813 mg, 4.47 mmol, 1.5 eq) in THF (3 mL) was added and the mixture was stirred at 40 °C for 16 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Phenomenex Gemini NX 150×30mm,5μm;mobile phase: [water(NH_4HCO_3)-ACN];gradient:65%-95% B over 11 min), followed by lyophilization to give compound 3 (150 mg, 14.1% yield) as a colorless gum.

[1082] LC-MS (ESI^+) m/z: 357.2 $(M+H)^+$.

[1083] ***Step 2.*** To a solution of compound 4 (198 mg, 631 μmol, 1.5 eq) in THF (3 mL) was added n-butyllithium (53.9 mg, 337 μL, 842 μmol, 2 eq) at -78 °C and stirred at -78 °C for 0.5 h. Then compound 3 (150 mg, 421 μmol, 1 eq) in THF (1 mL) was added at -78 °C. The mixture was stirred at 20 °C for 2 h. The reaction was quenched with sat.aq. NH_4Cl (30 mL) and

extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flashsilica gel chromatography (ethyl acetate in petroleum ether = 0% to 30%) to give compound 4 (90 mg, 36% yield) as a white solid.

[1084] LC-MS (ESI^+) m/z: 592.4 $(M+H)^+$.

[1085] ***Step 3.*** To a solution of compound 5 (30 mg, 51 μmol, 1 eq) in DCM (2 mL) was added HCl/dioxane (2 mL, 4M) at 20 °C. The mixture was stirred at 20 °C for 2 h. The solvent was removed to give a residue which was quenched with sat.aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 6 (20 mg, 89% yield) as a yellow solid.

[1086] LC-MS (ESI^+) m/z: 444.3 $(M+H)^+$.

[1087] ***Step 4.*** To a solution of compound 6 (20 mg, 45 μmol, 1 eq) in DCE (10 mL) and MeOH (1 mL) was added compound 7 (18 mg, 54 μmol, 1.2 eq) and stirred at 20 °C for 10 min. Then sodium triacetoxyhydroborate (29 mg, 0.14 mmol, 3 eq) was added and stirred at 20 °C for 10 min. The solvent was removed to yield a residue. The residue was purified by preparative HPLC (column: Phenomenex Gemini NX 150×30mm, 5μm; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 75%-95% B over 11 min), followed by lyophilization to give (S)-3-(5-(4-((1-(4-(7-(cyclopropylmethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2.3 mg, 6.7% yield) as a white solid.

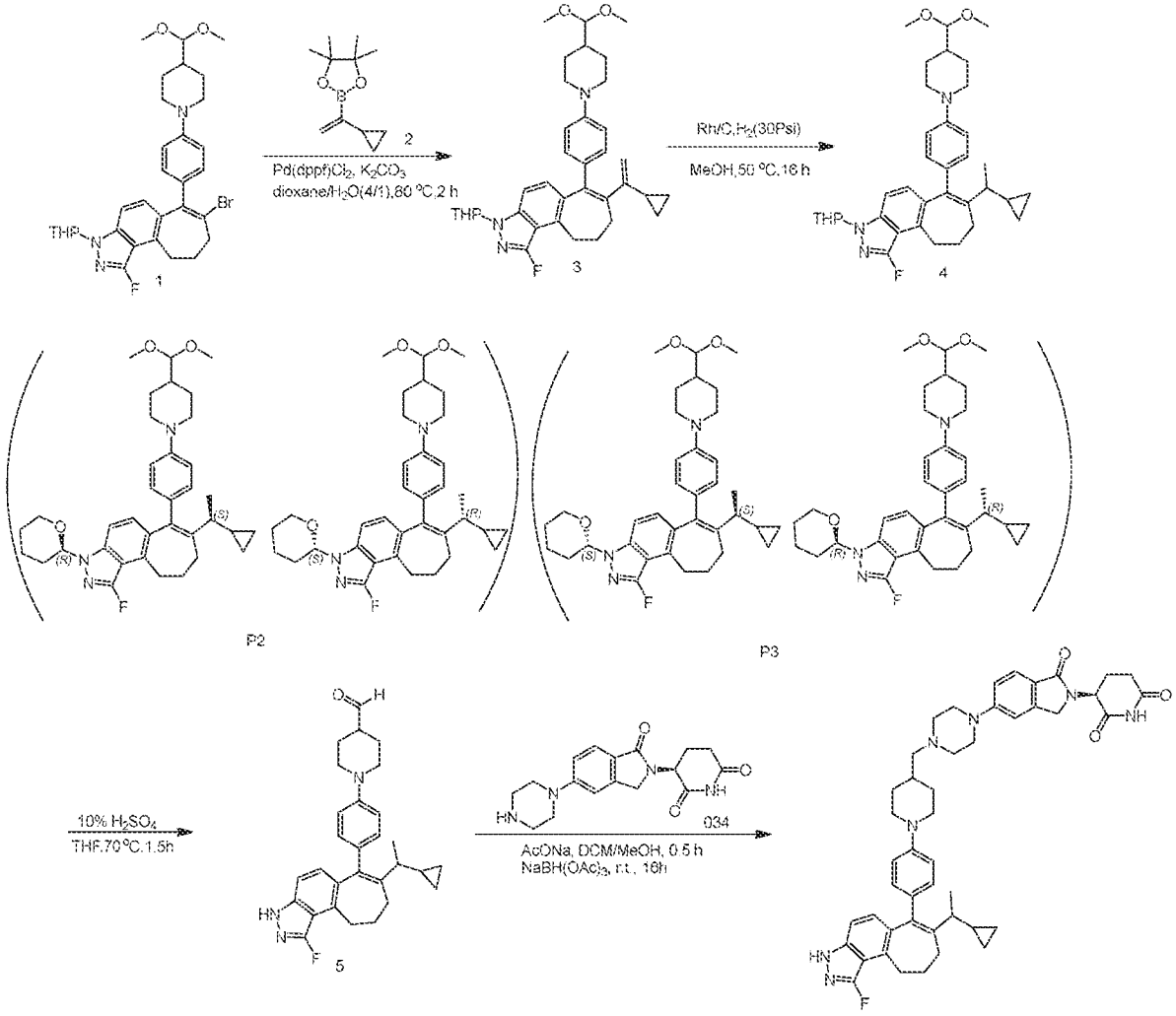
[1088] LC-MS (ESI^+) m/z: 756.4 $(M+H)^+$

[1089] LCMS: calc. for $C_{45}H_{50}FN_7O_3$: 755.94, found: $[M+H]^+$756.4.

[1090] HPLC: 99.32% purity at 220 nm.

[1091] ^1H NMR (400MHz, DMSO-d6) δ = 12.43 (s, 1H), 10.94 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 2.0, 8.7 Hz, 1H), 7.09 - 7.04 (m, 2H), 6.89 - 6.86 (m, 4H), 6.74 (d, J = 8.8 Hz, 1H), 5.04 (dd, J = 5.2, 13.2 Hz, 1H), 4.37 - 4.28 (m, 1H), 4.25 - 4.16 (m, 1H), 3.68 (d, J=12.0 Hz, 2H), 3.05 - 2.80 (m, 4H), 2.71 - 2.53 (m, 4H), 2.44 - 2.11 (m, 9H), 2.04 - 1.90 (m, 4H), 1.82 (d, J = 11.0 Hz, 2H), 1.70 (s, 1H), 1.28 - 1.14 (m, 4H), 0.85 (s, 2H), 0.48 - 0.42 (m, 2H), 0.03 (d, J = 4.6 Hz, 2H)

Example 45. Synthesis of (3S)-3-(5-(4-((1-(4-(7-(1-cyclopropylethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-101



[1092] ***Step 1.*** The mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (450 mg, 1 Eq, 752 μmol), 2-(1-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (292 mg, 2 Eq, 1.50 mmol), potassium carbonate (312 mg, 3 Eq, 2.26 mmol) and $Pd(dppf)Cl_2$(61 mg, 0.1 Eq, 75.2 μmol) were added in dioxane (8 mL) and H_2O (2 mL) at r.t. N_2 was bubbled into the mixture for 5 min. The reaction mixture was heated at 80°C for 2 hour. Then the reaction was cooled to room temperature. TLC (petroleum ether/ethyl acetate=2/1, R_f=0.5). The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL *2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the compound as a brown oil. The brown oil was purified by flash silica gel chromatography

(ISCO®; 20g SepaFlash® Silica Flash Column, petroleum ether/ethyl acetate from 100/0 to 30/70 @ 40 mL/min)) and the fraction was concentrated in vacuum to give 7-(1-cyclopropylvinyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (310 mg, 0.49 mmol, 65% yield, 92% purity) as a white solid. LC-MS (ESI^+) m/z: 586.6 $(M+1)^+$.

[1093] ***Step 2.*** To a solution of 7-(1-cyclopropylvinyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 92% purity, 1 Eq, 314 μmol) was added in MeOH (10 mL), then added Rh/C (200 mg, 6.19 Eq, 1.94 mmol) under H_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred at 50°C for 16 hour under H_2 (30 Psi). The reaction was filtered and concentrated to dryness in vacuum to give crude product as a colorless oil. The colorless oil was purified by preparative high-performance liquid chromatography. Condition: water (FA)-ACN. Column: Welch Xtimate C18 150*30mm*5um. Begin B: 90%, End B: 100%. Gradient time (min) 7; 100% B hold time (min) 3.7, Flow rate (ml/min) 25. The pure fractions were collected and the solvent was evaporated under vacuum. The aqueous layer was lyophilized to dryness to give P2 as a white solid (50 mg, 91% purity) and P3 as a white solid (40 mg, 85% purity). LC-MS (ESI^+) m/z: 588.4 $(M+1)^+$.

[1094] ***Step 3.*** To a solution of 7-(1-cyclopropylethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (40 mg, 91% purity, 1 Eq, 62 μmol) was added in THF (1 mL), then added 10% H_2SO_4 (3 mL) at 0 °C. The mixture was stirred at 70 °C for 1.5 hour. The mixture was adjusted to pH=8 by adding saturated aqueous $NaHCO_3$ (5 mL) at 0°C for 10 min. The reaction mixture was diluted with H_2O (15 mL) and extracted with ethyl acetate (20*2 mL). The combined organic layers were washed with 30 mL brine and dried over anhydrous Na_2SO_4. The organic layers were filtered and concentrated under reduced pressure to give crude product 1-(4-(7-(1-cyclopropylethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (25 mg, 55 μmol, 88% yield, 100% purity) as a colorless oil. LC-MS (ESI^+) m/z: 476.3$(M+H_2O)^+$

[1095] ***Step 4.*** A mixture of 1-(4-(7-(1-cyclopropylethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (25 mg, 100% purity, 1 Eq, 55 μmol) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (24 mg, 1.2 Eq, 66 μmol) and sodium acetate (22 mg, 5 Eq, 0.27 mmol) were added in DCM (2 mL) and MeOH (2 mL) at 25°C for 0.5 hour, then added acetic acid (9.8 mg, 9.4 μL, 3 Eq, 0.16

mmol) and sodium triacetoxyhydroborate (23 mg, 2 Eq, 0.11 mmol), then the mixture was stirred at 25°C for 16 hour. The reaction was dilute with water (50 mL) and extracted with ethyl acetate (50 mL*2). The combined organic layers were concentrated to give crude product as a yellow oil. The yellow oil was purified by preparative high-performance liquid chromatography. Condition: water (FA)-ACN. Column: Welch Xtimate C18 150*30mm*5um. Begin B: 24%, End B: 54%. Gradient time (min) 7; 100% B hold time (min) 3.3, Flow rate (ml/min) 25. The aqueous layer was lyophilized to dryness to give (3S)-3-(5-(4-((1-(4-(7-(1-cyclopropylethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (10.5 mg, 13.6 μmol, 25% yield, 100% purity) as a white solid.

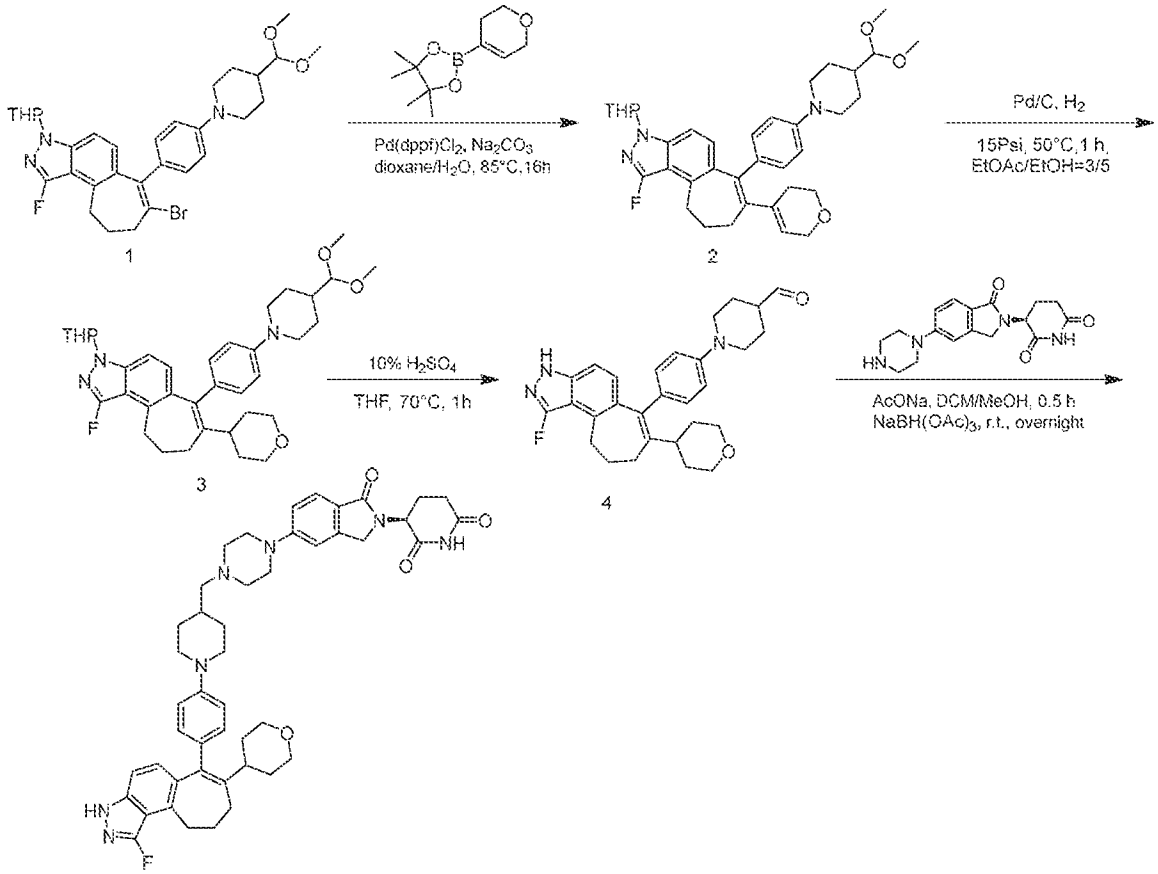
[1096] LCMS: calc. for $C_{46}H_{52}FN_7O_3$: 769.41, found: $[M+H]^+$ 770.3.

[1097] HPLC: 100% purity at 220 nm.

[1098] SFC: retention time, 2.668 min, 2.928 min; Area, 45.286%, 54.714 %; Method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

[1099] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.24 (br s, 1H), 8.11 (br s, 0.157H), 7.96 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.01 (dd, J = 1.9, 8.6 Hz, 1H), 6.97 - 6.84 (m, 7H), 5.21 (dd, J = 5.1, 13.2 Hz, 1H), 4.47 - 4.39 (m, 1H), 4.31 - 4.24 (m, 1H), 3.72 (br d, J = 12.6 Hz, 2H), 3.43 (br s, 3H), 3.30 - 3.21 (m, 1H), 3.01 (br d, J = 8.0 Hz, 1H), 2.93 - 2.82 (m, 2H), 2.81 - 2.66 (m, 5H), 2.49 - 2.28 (m, 5H), 2.25 - 2.15 (m, 2H), 2.01 - 1.78 (m, 7H), 1.51 - 1.38 (m, 2H), 1.20 (br d, J = 6.9 Hz, 3H), 0.90 - 0.80 (m, 1H), 0.53 - 0.45 (m, 1H), 0.39 (br d, J = 8.0 Hz, 1H), 0.00 (br d, J = 4.2 Hz, 2H)

Example 46. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(tetrahydro-2H-pyran-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-119



[1100] ***Step 1.*** To a solution of [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)Complex with dichloromethane (27 mg, 0.1 Eq, 33.414 μmol) was added to the mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 334.1 μmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 1 Eq, 334.1 μmol) and sodium carbonate (107 mg, 3 Eq, 1 mmol) in H_2O (1.5 mL) and 1,4-Dioxane (6 mL) at 25 °C, then the mixture was stirred at 85 °C for 16 hour. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.6, UV) showed one main new spot was observed. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 50% ethyl acetate).The desired fractions were collected, and concentrated to dryness in vacuum to give 7-(3,6-dihydro-2H-pyran-4-yl)-6-

(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 324 μmol, 97.1 %, 97.58% purity) as a yellow solid. Which confirmed by LCMS. **LC-MS** (ESI^+) m/z: 602.4 $(M+H)^+$.

[1101] ***Step 2.*** A mixture of 7-(3,6-dihydro-2H-pyran-4-yl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 322 μmol), Pd/C (250 mg, 10% wt, 235 μmol) and H_2 (651 μg, 1 Eq, 322 μmol) in ethyl acetate (3 mL)and EtOH (5 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 50 °C for 1 h under H_2 atmosphere(15 psi). The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*3 mm*5um;mobile phase: [water(FA)-ACN];B% 87%-100%,7 min) to give The residue was concentrated under reduced pressure to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(tetrahydro-2H-pyran-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (112 mg, 185 μmol, 57.5 %, 100% purity) as a white solid. **LC-MS** (ESI^+) m/z: 604.3 $(M+H)^+$

[1102] ***Step 3.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(tetrahydro-2H-pyran-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (112 mg, 1 Eq, 185 μmol) in 10% H_2SO_4 (5 mL) and THF (3 mL) was stirred at 70 °C for 40 min. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4, UV) showed a new spot was formed. The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (20 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give 1-(4-(1-fluoro-7-(tetrahydro-2H-pyran-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 90 μmol, 49 % yield, 71.36% Purity), LC-MS (ESI^+) m/z: 492.2 $(M+H_2O)^+$.

[1103] ***Step 4.*** To a solution of 1-(4-(1-fluoro-7-(tetrahydro-2H-pyran-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 1 Eq, 90 μmol) and 1-(2-methyl-4-(2,8-diazaspiro[4.5]decan-8-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (34 mg, 1 Eq, 90 μmol) in DCM (3 mL) and MeOH (3 mL) was added sodium acetate (44 mg, 6 Eq, 0.54 mmol) was stirred at 25 °C for 1 h, Then acetic acid (11 mg, 10 μL, 2 Eq, 0.18 mmol) and sodium triacetoxyhydroborate (38 mg, 2 Eq, 0.18 mmol) was added. The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (30 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and

dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm;mobile phase: [water(FA)-ACN];B% 23%-53%,6min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(tetrahydro-2H-pyran-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (29.4 mg, 37.4 μmol, 41 % yield, 100% purity) was obtained as a white solid.

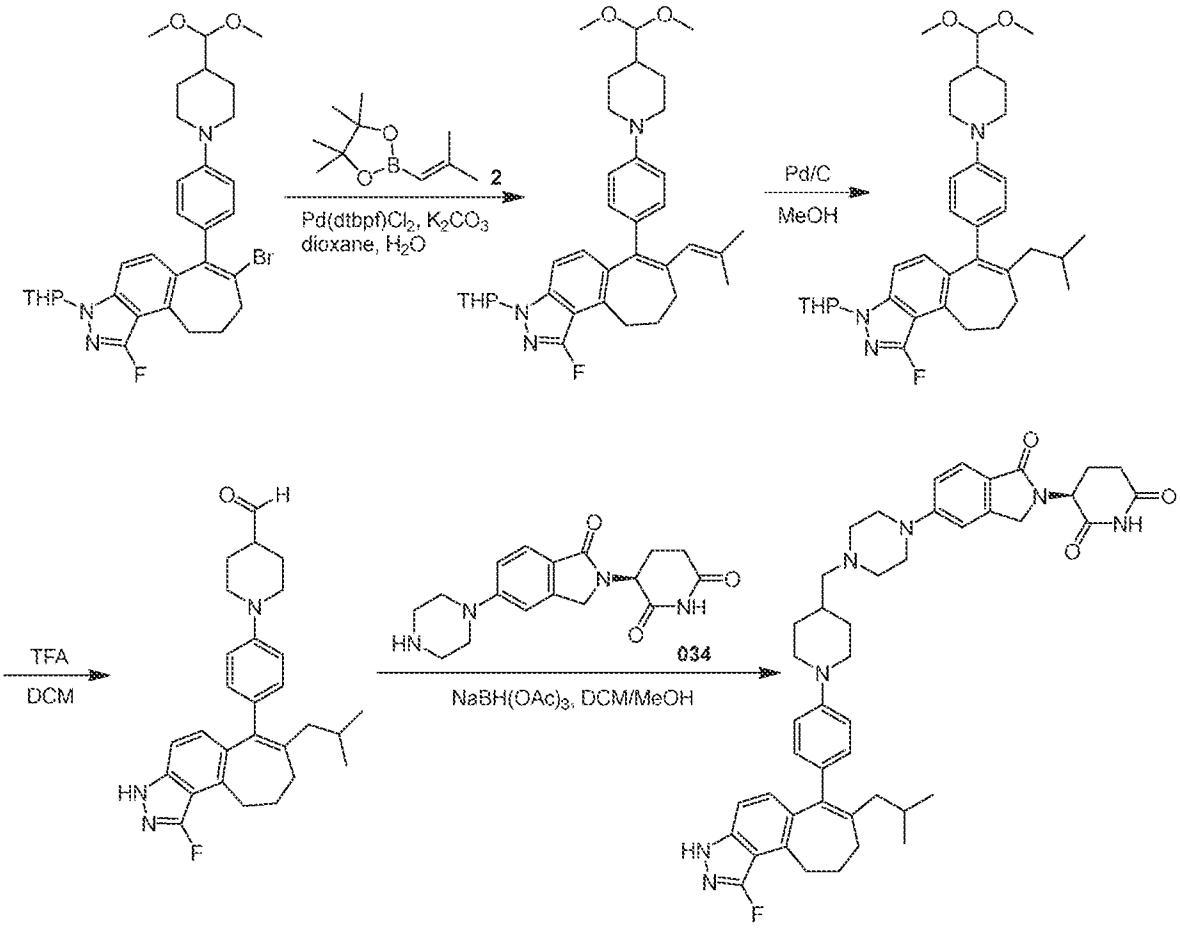
[1104] LCMS: calc. for $C_{46}H_{52}FN_7O_4$: 785.4, found: $[M/2+1]^+$ 393.9.

[1105] HPLC: 98.274% purity at 220 nm.

[1106] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.45 (s, 1H), 10.97 (s, 1H), 8.31 (br s, 0.536H), 7.53 (d, J = 8.6 Hz, 1H), 7.19 - 7.12 (m, 1H), 7.11 - 7.03 (m, 2H),6.89 (s, 4H), 6.71 (d, J = 8.8 Hz, 1H), 5.10 - 5.01 (m, 1H), 4.38 - 4.28 (m, 1H), 4.25 - 4.16 (m, 1H), 3.86 (br d, J = 6.8 Hz, 2H), 3.70 (br d, J = 11.9 Hz, 2H),3.64 - 3.32 (m, 6H), 3.19 (br t, J = 11.3 Hz, 3H), 2.99 - 2.87 (m, 3H), 2.82 - 2.73 (m, 1H), 2.73 - 2.58 (m, 3H), 2.56 (br s, 1H), 2.43 - 2.33 (m, 1H), 2.23 (br d, J = 6.7 Hz, 4H), 2.01 - 1.93 (m, 1H), 1.91 - 1.79 (m, 4H), 1.77 - 1.64 (m, 3H), 1.47 (br d, J = 11.3 Hz, 2H), 1.29 - 1.16 (m, 2H)

[1107] SFC: retention time, 4.175 min; Area, 94.858%; method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

Example 47. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-isobutyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-72



[1108] ***Step 1.*** To a mixture of compound 1 (400 mg, 668 μmol, 1 eq.), compound 2 (183 mg, 1.00 mmol, 1.5 eq.) and $Pd(dtbpf)Cl_2$ (43.6 mg, 66.8 μmol, 0.1 eq.) in dioxane (8 mL) and H_2O (1.6 mL) was added K_2CO_3 (277 mg, 2.00 mmol, 3 eq.) at 25 °C. The mixture was stirred at 25 °C for 1 h. LCMS (RLN-NB-2491-6-R1A) showed the reaction was completed. The mixture was concentrated to give a residue, which was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1) to give compound 3 (300 mg, 78.2% yield) as yellow oil.

[1109] LC-MS (ESI^+) m/z: 574.1 $(M+H)^+$.

[1110] ***Step 2.*** To a mixture of compound 3 (300 mg, 523 μmol, 1 eq.) in MeOH (20 mL) was added Pd/C (556 mg, 523 μmol, 10% purity, 1 eq.) at 25 °C. The mixture was stirred at 25 °C under H_2 (15 psi) for 5 hrs. LCMS (RLN-NB-2491-7-R1B) showed the reaction was completed. The mixture was filtered and concentrated to give a crude, which was purified by prep-HPLC (Column: Boston Green ODS 150 × 30 mm x 5 μm; Condition: water(TFA)-ACN; Begin B: 55;

End B: 85; Gradient Time(min): 12; 100% B Hold Time(min): 2; Flow Rate(mL/min): 25; injections: 5.) to give compound 4 (100 mg, 33.2% yield) as a white solid.

[1111] LC-MS (ESI^+) m/z: 576.5 $(M+H)^+$.

[1112] ***Step 3.*** To a mixture of compound 3 (60 mg, 0.10 mmol, 1 eq.) in DCM (4 mL) was added TFA (2 mL) at 25 °C. The mixture was stirred at 25 °C for 6 hrs. LCMS (RLN-NB-2491-16-R1B) showed the reaction was completed. The mixture was concentrated to give compound 5 (40 mg, 86% yield) as a yellow solid.

[1113] LC-MS (ESI^+) m/z: 446.3 $(M+H)^+$.

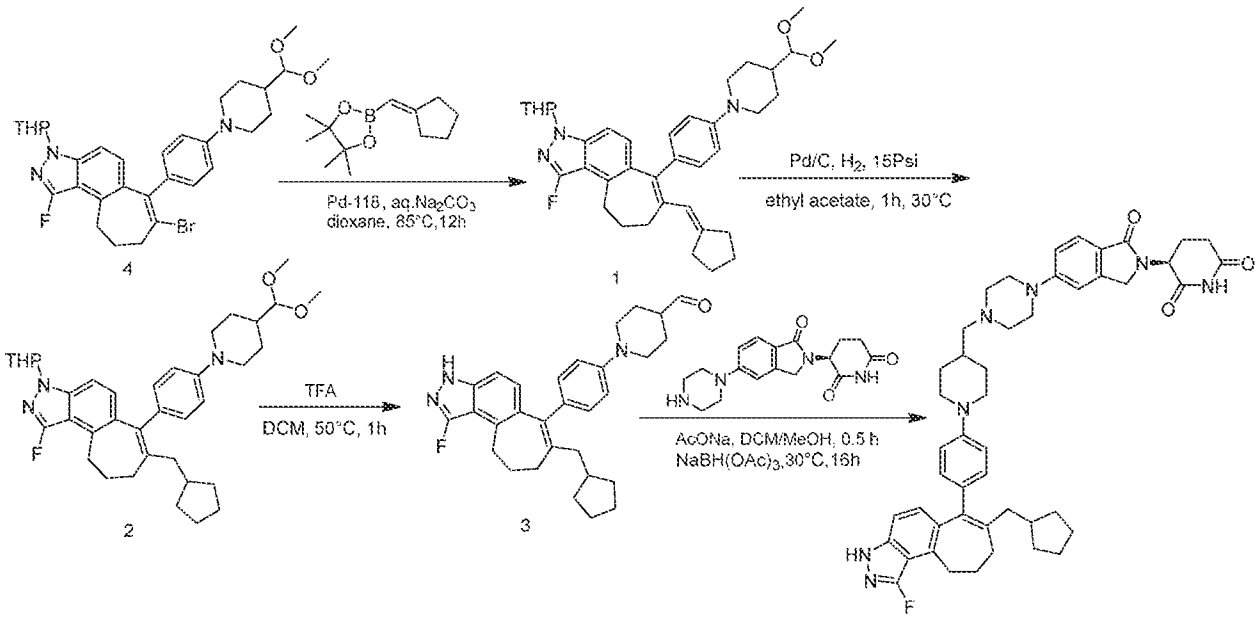
[1114] ***Step 4.*** To a mixture of compound 5 (40 mg, 90 µmol, 1 eq.) in MeOH (4 mL) and DCE (4 mL) was added compound 034 (44 mg, 135 µmol, 1.5 eq.) and $NaBH(OAc)_3$ (57 mg, 270 µmol, 3 eq.) at 25 °C. The mixture was stirred at 25 °C for 1 h. LCMS (RLN-NB-2491-17-R1A) showed the reaction was completed. The reaction mixture was concentrated to give a crude, which was purified by prep-HPLC (Column: Phenomenex Gemini NX 150 × 30 mm x 5 µm; Condition: water(NH_4HCO_3)-ACN; Begin B: 65; End B: 95; Gradient Time(min): 11; 100% B Hold Time(min): 4; Flow Rate(mL/min): 25; injections: 5.) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-isobutyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (8.0 mg, 12% yield) as a white solid. LC-MS (ESI^+) m/z: 758.5 $(M+H)^+$.

[1115] LCMS: calc. for $C_{45}H_{52}FN_7O_3$: 757.96, found: $[M+H]^+$ 758.5.

[1116] HPLC: 96.21% purity at 220 nm.

[1117] ^1H NMR: ^1H NMR (400 MHz, DMSO-d6) δ = 12.40 (s, 1H), 10.95 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.16 - 7.11 (m, 1H), 7.09 - 7.04 (m, 2H), 6.89 (s, 4H), 6.74 (d, J = 8.8 Hz, 1H), 5.08 - 5.01 (m, 1H), 4.37 - 4.29 (m, 1H), 4.24 - 4.17 (m, 1H), 3.73 - 3.66 (m, 2H), 3.31 (br d, J = 6.1 Hz, 5H), 3.04 - 2.85 (m, 3H), 2.68 - 2.59 (m, 3H), 2.31 - 2.14 (m, 6H), 1.97 - 1.79 (m, 6H), 1.75 - 1.65 (m, 1H), 1.27 - 1.07 (m, 6H), 0.84 (d, J = 6.6 Hz, 6H).

Example 48. Synthesis of (S)-3-(5-(4-((1-(4-(7-(cyclopentylmethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-99



[1118] ***Step 1.*** A mixture of 2-(cyclopentylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63 mg, 1.2 Eq, 301 μmol), 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (150 mg, 1 Eq, 251 μmol),1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (16 mg, 0.1 Eq, 25.1 μmol), sodium carbonate (79 mg, 3 Eq, 752 μmol) in dioxane (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 12 h under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=10:1, R_f= 0.5) showed one new spot was observed. The reaction mixture was diluted with H_2O (60 mL) and extracted with ethyl acetate (80 mL * 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) and the organic layer was concentrated in vacuo to give 7-(cyclopentylidenemethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 200 μmol, 79.8 % yield) as a yellow oil. LC-MS (ESI+) m/z: 600.4 $(M+H)^+$.

[1119] ***Step 2.*** A mixture of 7-(cyclopentylidenemethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120

mg, 1 Eq, 200 μmol), Pd/C (120 mg,10% wt, 5.6 Eq, 1.1 mmol) and H_2 (404 μg, 1 Eq, 200 μmol) in ethyl acetate (10 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 30 °C for 1 h with H_2 atmosphere (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to give 7-(cyclopentylmethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 166 μmol, 83.1 % yield) as a colorless oil. LC-MS (ESI+) m/z: 602.2 $(M+H)^+$.

[1120] ***Step 3.*** A mixture of 7-(cyclopentylmethyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 1 Eq, 166 μmol) in DCM (3 mL) and TFA (1 mL), then the mixture was stirred at 50 °C for 1 h. TLC (petroleum ether: ethyl acetate =3:1, R_f =0.5 UV) showed one main new spot was observed. The reaction mixture was slowly added to a large amount of saturated $NaHCO_3$ solution in order to make the pH of solution adjust to 7. Then the solution was diluted with H_2O (40 mL) and extracted with ethyl acetate (60 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(4-(7-(cyclopentylmethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 0.13 mmol, 77 % yield) as a yellow oil. LC-MS (ESI+) m/z: 490.2 $(M+H_2O)^+$.

[1121] ***Step 4.*** A mixture of 1-(4-(7-(cyclopentylmethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (60 mg, 1 Eq, 127.2 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (46.4 mg, 1 Eq, 127.2 μmol), sodium acetate (31.3 mg, 20.5 μL, 3 Eq, 381.7 μmol) and acetic acid (22.9 mg, 21.9 μL, 3 Eq, 381.7 μmol) in DCM (4 mL) and MeOH (4 mL) was stirred at 30 °C for 0.5 h, then sodium triacetoxyborohydride (53.9 mg, 2 Eq, 254.4 μmol) was added in the mixture and stirred at 30 °C for 16 h. LCMS showed 64% desired MS. TLC (DCM/MeOH= 10/1, R_f= 0.4) showed a new spot was detected. The mixture was added H_2O (20 mL), then extracted with ethyl acetate (20 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep-HPLC: Column: Welch Xtimate C18 150*30mm*5um Condition: A: water (FA) B: ACN at the beginning: A (68%) and B (32%) at the end: A: (38%) and B (62%) Gradient Time (min) 7; 100%B Hold Time (min) 1; Flow Rate (ml/min) 25. Then the residue was further purified by prep-HPLC: Column: Phenomenex C18 75*30mm*3um Condition: A:

water(NH_3H_2O+NH_4HCO_3) B: ACN at the beginning: A (15%) and B (85%) at the end: A: (0%) and B (100%) Gradient Time (min) 7; 100%B Hold Time (min) 2; Flow Rate (ml/min) 25.The fractions were lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(7-(cyclopentylmethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (3 mg, 4 μmol, 30 % yield, 100% purity) as a white solid.

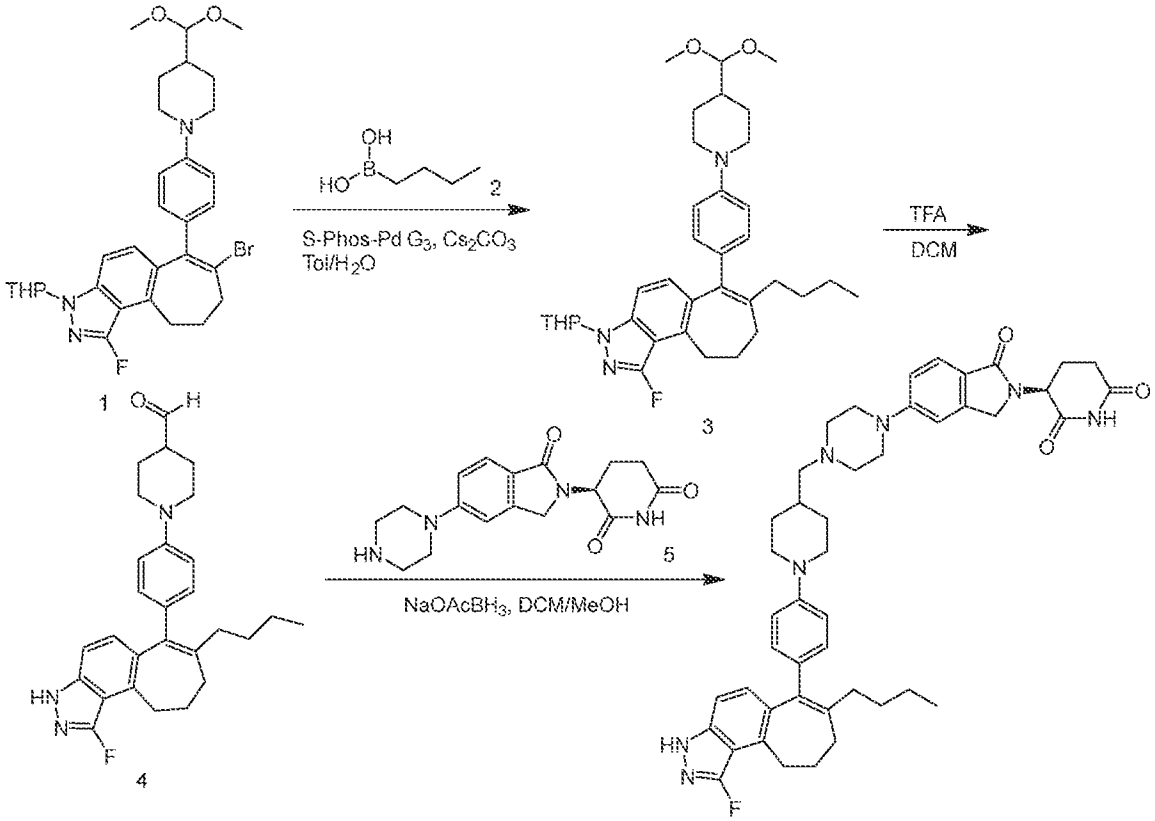
[1122] LC-MS (ESI^+) m/z: 784.5 $(M+H)^+$.

[1123] HPLC: 100%, purity at 220 nm.

[1124] SFC: Rt: 3.836 min; Area, 95.745%; method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[1125] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.41 (s, 1 H) 10.96 (s, 1 H) 7.48 - 7.59 (m, 1 H) 7.01 - 7.16 (m, 3 H) 6.89 (s, 4 H) 6.68 - 6.77 (m, 1 H) 5.01 - 5.11 (m, 1 H) 4.16 - 4.40 (m, 2 H) 3.64 - 3.75 (m, 2 H) 3.30 (br d, J=1.31 Hz, 2 H) 2.87 - 3.02 (m, 3 H) 2.58 - 2.70 (m, 3 H) 2.21 - 2.43 (m, 8 H) 2.06 - 2.12 (m, 1 H) 1.91 - 2.04 (m, 4 H) 1.80 - 1.87 (m, 2 H) 1.68 - 1.77 (m, 3 H) 1.37 - 1.46 (m, 4 H) 1.24 (br s, 5 H) 1.01 - 1.09 (m, 2 H) 0.83 - 0.89 (m, 1 H)

Example 49. Synthesis of (S)-3-(5-(4-((1-(4-(7-butyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-76



[1126] ***Step 1.*** To a solution of compound 1 (200.00 mg, 334.00 μmol, 1 eq.) in toluene (10 mL) and H_2O (1 mL) was added compound 2 (51.10 mg, 501.00 μmol, 1.5 eq.), Cs_2CO_3 (327.00 mg, 1.00 mmol, 3 eq) and S-Phos-Pd G3 (48.20 mg, 66.80 μmol, 0.2 eq). The mixture was stirred at 90°C under N_2 for 16hr. LCMS showed the desired ms was found. The mixture was concentrated to give a residue, which was purified by flash silica gel chromatography eluting with EtOAc in PE from 0% to 75% to give compound 3 (30 mg, 26.00 μmol, 7.70% yield) as a yellow solid. LC-MS (ESI^+) m/z: 576.2 $(M+H)^+$.

[1127] ***Step 2.*** To a solution of compound 3 (30 mg, 52.00 μmol, 1 eq.) in DCM (10 mL) was added HCl/EA (4 M, 10.00 mL, 1 eq.). The reaction was stirred at 20 °C for 2hr. LCMS showed the desired ms was found. The mixture was adjusted to pH 7-8 with aqueous $NaHCO_3$. The mixture was concentrated and then water (20 mL) was added. The mixture was extracted with DCM (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, filtered and concentrated to give compound 4 (20.00 mg, 45.00 μmol, 86.00% yield) as a yellow solid.

[1128] LC-MS (ESI^+) m/z: 446.10 $(M+H_2O)^+$.

[1129] ***Step 3.*** To a solution of compound 4 (30.00 mg, 67.00 µmol, 1 eq.) in DCE (5 mL) and MeOH (3 mL) was added compound 5 (88.00 mg, 0.27 mmol, 4 eq.) and $Na(OAc)_3BH$ (170.00 mg, 0.81 µmol, 12 eq.). The reaction was stirred at 20°C for 3hr. LCMS showed the desired ms was found. The mixture was purified by Prep-HPLC (Phenomenex Gemini NX 150*30mm, 5µm; Condition: water(NH_4HCO_3)-ACN, Begin B 65, End B 95; Gradient Time(min): 11; 100% B Hold Time(min): 2; Flow Rate (ml/min): 25, Injections 1, HPLC 95) to give compound (S)-3-(5-(4-((1-(4-(7-butyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (7.0 mg, 9.20 µmol, 14.00% yield, 100.00% purity) as a white solid. LC-MS (ESI^+) m/z: 758.5 $(M+H)^+$.

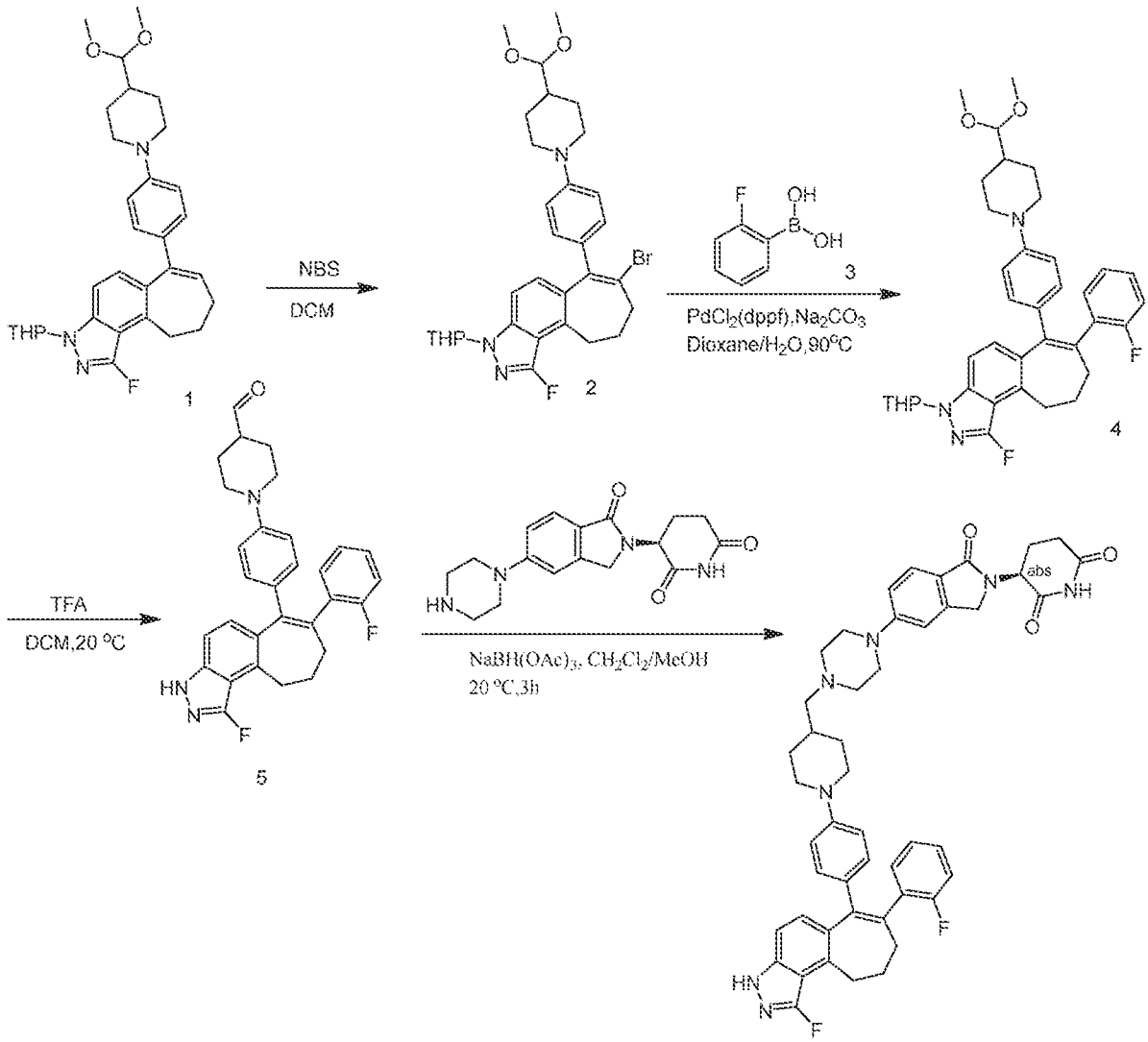
[1130] LCMS: calc. for $C_{45}H_{52}FN_7O_3$: 757.96, found: $[M+H]^+$ 758.5.

[1131] HPLC: 100.00% purity at 220 nm.

[1132] ^1H NMR: ^1H NMR (500 MHz, DMSO-d_6) δ = 12.43 - 12.35 (m, 1H), 11.01 - 10.86 (m, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.15 - 7.13 (m, 1H), 7.07 - 7.05 (m, 2H), 6.89 (s, 4H), 6.74 (d, J =

[1133] 8.9 Hz, 1H), 5.07 - 5.03 (m, 1H), 4.35 - 4.31 (m, 1H), 4.23 - 4.19 (m, 1H), 3.71 - 3.67 (m, 2H), 2.97 - 2.90 (m, 3H), 2.69 - 2.65 (m, 2H), 2.61 - 2.55 (m, 4H), 2.40 (br d, J = 11.0 Hz, 1H), 2.28 - 2.22 (m, 7H), 1.98 - 1.94 (m, 1H), 1.92 - 1.88 (m, 2H), 1.84 - 1.81 (m, 2H), 1.74 - 1.68 (m, 1H), 1.51 - 1.38 (m, 3H), 1.29 - 1.14 (m, 7H), 0.82 (t, J = 7.2 Hz, 3H).

Example 50. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(2-fluorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-104



[1134] ***Step 1.*** To a mixture of compound 1 (500 mg, 1 eq, 962 μmol) in CH_2Cl_2 (10 ml) was added NBS (171 mg, 1 eq, 962 μmol) in one portion. The mixture was stirred at 20 °C for 1 hour hours. LCMS showed the reaction was completed. The mixture was cooled to 20 °C and concentrated in reduced pressure at 20 °C. The residue was poured into ice-water (w/w = 1/1) (200 ml) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (100 ml x 2). The combined organic phase was washed with brine (50 ml*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3/1,) to afford compound 2 (550 mg, 805 μmol, 83.6 %, 87.56% Purity) as yellow solid. LC-MS (ESI+) m/z: 599.7 (M+H)+.

[1135] *Step 2.* A mixture of compound 2 (200.00 mg, 1 eq, 334.14 μmol), compound 3 (51.427 mg, 1.1 eq, 367.55 μmol) ,sodium carbonate (70.830 mg, 2 eq, 668.27 μmol) and $PdCl_2$ (dppf) (24.449 mg, 0.1 eq, 33.414 μmol) in 1,4-Dioxane (5 ml) and H_2O (0.1 ml) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 5 hour under N_2 atmosphere.

[1136] LCMS showed Reactant 6 was consumed completely and one main peak with desired MS was detected. The reaction solution is stirred with an appropriate amount of silica gel powder, and the reaction mixture is concentrated under reduced pressure to remove the solvent.

[1137] The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3/1) Compound 4 (198 mg, 250 μmol, 74.7 %, 77.34% Purity) was obtained as a white solid. LC-MS (ESI^+) m/z: 614.3 $(M+H)^+$.

[1138] *Step 3.* To a solution of compound 4
(180 mg, 1 eq, 293 μmol) in CH_2Cl_2 (15 ml) was added TFA (5ml) . The mixture was stirred at 20 °C for 2 hour。 LCMS showed Reactant 4 was consumed completely and one main peak with desired MS was detected The reaction mixture was quenched by addition Saturated $NaHCO_3$ solution 50 ml at 20 °C, and then extracted with ethyl acetate 50 ml (50 ml * 2). The combined organic layers were washed with dried with anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure to give a crude product compound 9 (200 mg, 153 μmol, 52.2 %, 37.01% Purity). LCMS (ESI^+) m/z: 484.2$(M+H)^+$.

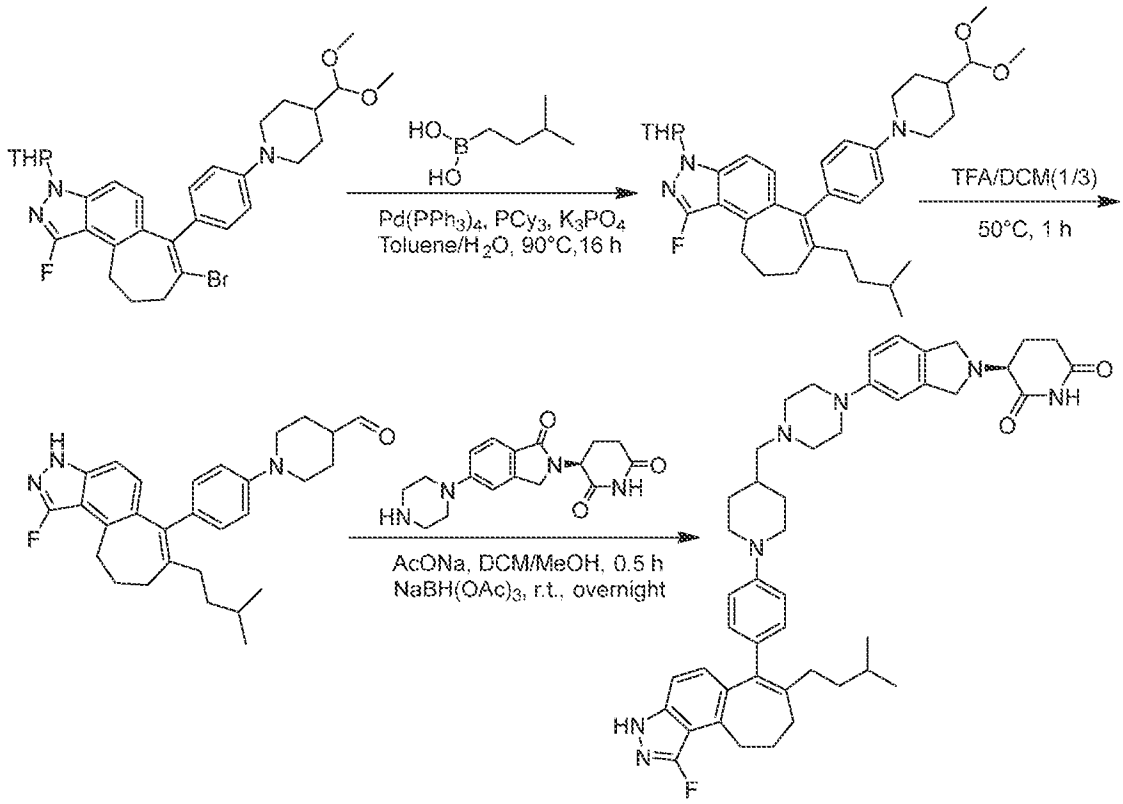
[1139] *Step 4.* To a solution of crude compound 5 (200 mg, 1 eq, 414 μmol) in CH_2Cl_2 (10 ml)and MeOH (2 ml) was added 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (149 mg, 1.1 eq, 455 μmol).The mixture was stirred at 20 °C for 0.5 hour and , than $NaHB(OAc)_3$ (175 mg, 2 eq, 827 μmol) was added to mixture and stirred for 2 hour. LC-MS showed Reactant 9 was consumed completely and one main peak with desired MS was detected. The reaction mixture was quenched by addition Saturated NH_4Cl 50 ml at 20 °C, and then extracted with ethyl acetate 50 ml (50 ml x 2). The combined organic layers were washed with filtered and concentrated under reduced pressure to give a crude product. The crude product was dissolved with DMF. The residue was purified by prep-HPLC to give desired (S)-3-(5-(4-((1-(4-(1-fluoro-7-(2-fluorophenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (22.6 mg, 28.4 μmol, 6.87 %, 100% Purity) as a white solid. LC-MS (ESI^+) m/z: 796.3 $(M+H)^+$.

[1140] LCMS: calc. for C47H47F2N7O3 795.94 found: $[M+H]^+$ 796.3

[1141] HPLC: 100.00% purity at 220 nm.

[1142] 1H NMR (400 MHz, DMSO-d_6) δ ppm 12.50 - 12.56 (m, 1 H) 10.92 - 10.98 (m, 1 H) 7.50 - 7.54 (m, 1 H) 7.17 - 7.26 (m, 3 H) 7.02 - 7.12 (m, 4 H)6.82 - 6.87 (m, 1 H) 6.63 - 6.69 (m, 4 H) 5.01 - 5.09 (m, 1 H) 4.16 - 4.37 (m, 2 H) 3.56 - 3.66 (m, 2 H) 3.26 - 3.31 (m, 8 H) 3.08 - 3.15 (m, 2 H) 2.84 -2.97 (m, 1 H) 2.66 - 2.70 (m, 1 H) 2.31 - 2.40 (m, 2 H) 2.18 - 2.27 (m, 6 H) 1.92 - 1.99 (m, 1 H) 1.74 - 1.82 (m, 2 H) 1.61 - 1.71 (m, 1 H) 1.10 - 1.26(m, 3 H)

Example 51. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-isopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-75



[1143] *Step 1.* A mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 334 μmol), $Pd(PPh_3)_4$(77 mg, 0.2 Eq, 66.8 μmol), isopentylboronic acid (97 mg, 2.5 Eq, 835 μmol), PCy_3(18.7 mg, 0.2 Eq, 66.8 μmol) and potassium phosphate, tribasic (177 mg, 2.5 Eq, 835 μmol) were added in toluene (4 mL) and H_2O (1 mL),then the reaction was heated to 90°C for 16 hours under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=5:1, R_f =0.3) showed one main new spot was observed. The reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl

acetate (100 mL *2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give crude product as a brown oil. The brown oil was purified by flash column (ISCO®; 20 g SepaFlash ® Silica Flash Column, @ 35 mL/min ,petroleum ether/ethyl acetate from 100/0 to 80/20) and the organic layer was concentrated in vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-isopentyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 169 μmol, 50.4% yield, 99.4% purity) as a white solid. LC-MS (ESI+) m/z: 590.4 $(M+H)^+$.

[1144] ***Step 2.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-isopentyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 99.4% purity, 1 Eq, 169 μmol) in DCM (6 mL) was added in TFA (2 mL) at 0°C. The mixture was stirred at 50 °C for 1 hour. The reaction solution was added into saturated aqueous $NaHCO_3$ (10mL) at 0 °C for 10 min. The reaction mixture was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL). The organic layers were washed with 10 mL, dried over anhydrous Na_2SO_4. The organic layers were filtered and concentrated under reduced pressure to give 1-(4-(1-fluoro-7-isopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (70 mg, 0.14 mmol, 81% yield, 89.4% purity) as a colorless oil. LC-MS (ESI^+) m/z: 478.3 $(M+H_2O)^+$.

[1145] ***Step 3.*** A mixture of 1-(4-(1-fluoro-7-isopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (70 mg, 89.4% purity, 1 Eq, 136 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (50 mg, 1 Eq, 136 μmol) and sodium acetate (56 mg, 5 Eq, 680 μmol) were added in DCM (2 mL) and MeOH (2 mL) at 20°C for 0.5 hour, then added acetic acid (25 mg, 3 Eq, 408 μmol) and sodium triacetoxyhydroborate (58 mg, 2 Eq, 272 μmol), then the mixture was stirred at 25 °C for 16 hour. The reaction was dilute with water (50 mL) and extracted with ethyl acetate (50 mL*2). The combined organic layers were concentrated to give crude product as a brown oil. The brown oil was purified by preparative high-performance liquid chromatography. Condition: water (FA)-ACN. Column: Welch Xtimate C18 150*30mm*5um. Begin B: 32%, end B: 62%. Gradient time (min) 7; 100% B hold time (min) 4.7, Flow rate (ml/min) 25. The pure fractions were collected and the solvent was evaporated under vacuum. The aqueous layer was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-isopentyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (26.2 mg, 33.7 μmol, 24.7% yield, 99.19% purity) as a light pink solid.

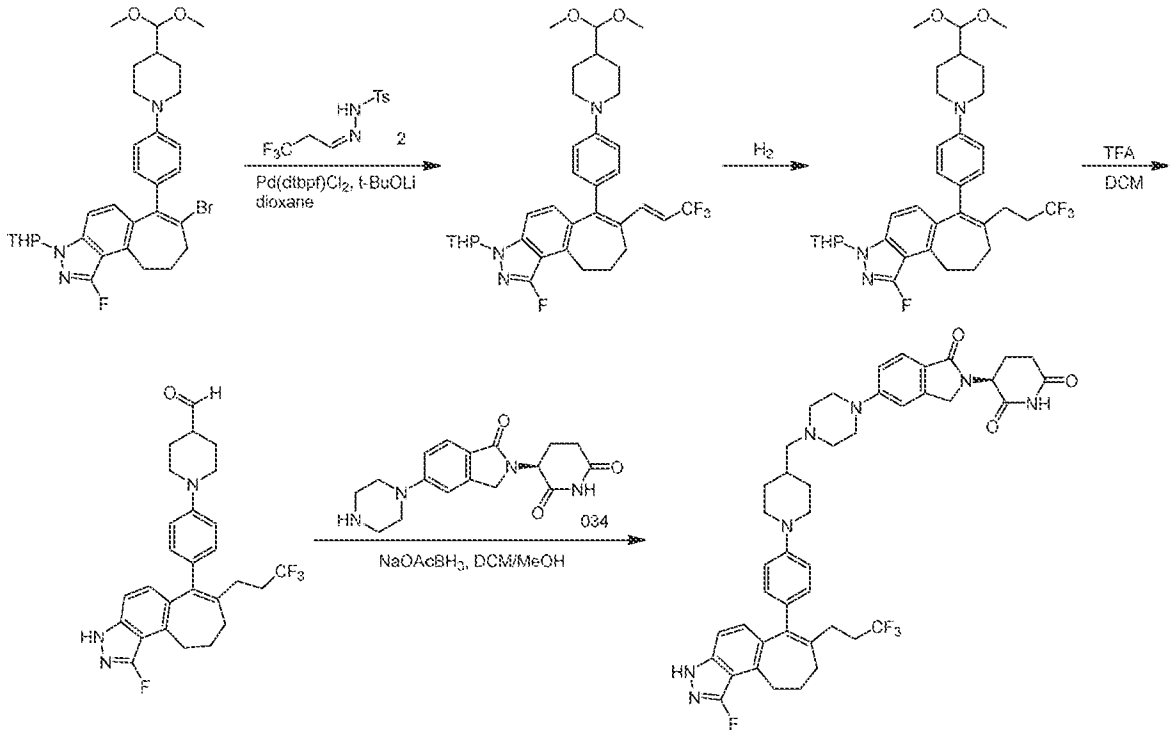
[1146] LCMS: calc. for $C_{46}H_{54}FN_7O_3$: 771.43, found: $[M+H]^+$ 772.3.

[1147] HPLC: 99.19% purity at 220 nm.

[1148] SFC: retention time, 2.725 min; Area, 96.745 %; Method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

[1149] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.39 (s, 1H), 10.93 (s, 1H), 8.22 (s, 0.232H), 7.52 (d, J = 8.8 Hz, 1H), 7.14 (dd, J = 2.4, 8.8 Hz, 1H), 7.09 - 7.04 (m, 2H), 6.89 (s, 4H), 6.74 (d, J = 8.8 Hz, 1H), 5.04 (dd, J = 5.0, 13.4 Hz, 1H), 4.36 - 4.29 (m, 1H), 4.24 - 4.17 (m, 1H), 3.68 (br d, J = 11.9 Hz, 2H), 3.29 - 3.24 (m, 4H), 2.97 - 2.85 (m, 3H), 2.69 - 2.55 (m, 3H), 2.54 - 2.51 (m, 2H), 2.43 - 2.31 (m, 2H), 2.24 (br dd, J = 7.1, 12.1 Hz, 6H), 1.96 (dt, J = 2.9, 4.9 Hz, 1H), 1.89 (br t, J = 6.6 Hz, 2H), 1.82 (br d, J = 13.1 Hz, 2H), 1.75 - 1.66 (m, 1H), 1.59 - 1.44 (m, 2H), 1.41 - 1.35 (m, 2H), 1.27 - 1.19 (m, 2H), 0.79 (d, J = 6.4 Hz, 6H)

Example 52. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(3,3,3-trifluoropropyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-92



[1150] ***Step 1.*** A mixture of Compound 1 (300 mg, 501 μmol, 1 eq.), Compound 2 (169 mg, 601 μmol, 1.2 eq.), $PdCl_2(dppf)$ (36.7 mg, 50.1 μmol, 0.1 eq.) and lithium 2-methylpropan- 2-olate (120 mg, 1.50 mmol, 3 eq.) in Dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hour under N_2 atmosphere. LCMS showed the

reaction was completed. The reaction mixture was quenched by addition EA 10 mL at 20 °C, and then diluted with water 10 mL and extracted with EA 90 mL (30 mL * 3). The combined organic layers were washed with EA 15 mL (5 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 5/1) to give Compound 3 (100 mg, 163 μmol, 32.5 %) as a white solid. LC-MS (ESI^+) m/z: 614.2 $(M+H)^+$.

[1151] ***Step 2.*** To a solution of Compound 3 (150 mg, 244 μmol, 1 eq.) in Ethyl acetate (4 mL) was added Pd/C (10%, 0.1 g) under H_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 3 hour. LCMS showed the reaction was completed. The crude was purified by prep.HPLC together (Welch Xtimate C18 150*25mm*5um, water (FA)-ACN as a mobile phase, from 55% to 85%, Gradient Time (min): 11, Flow Rate (ml/min): 25) to give Compound 4 (20 mg, 32 μmol, 13 %) as a white solid. LC-MS (ESI^+) m/z: 616.2 $(M+H)^+$.

[1152] ***Step 3.*** To a solution of Compound 4 (20 mg, 32 μmol, 1 eq.) in DCM (3 mL) and TFA (1 mL). The mixture was stirred at 20 °C for 3 hour. LCMS showed the reaction was completed. The mixture was concentrated in vacuo to give crude product. No further purification as it is used for the next step directly. LC-MS (ESI^+) m/z: 486.3 $(M+H)^+$.

[1153] ***Step 4.*** To a solution of Compound 5 (12 mg, 25 μmol, 1 eq.) and (S)-3-(1-oxo-5-(piperazin-1- yl)isoindolin-2-yl)piperidine-2,6-dione (9.7 mg, 30 μmol, 1.2 eq.) in DCM (2 mL) and MeOH (2 mL) was added Sodium triacetoxyborohydride (21 mg, 15 μL, 99 μmol, 4 eq.). The mixture was stirred at 20 °C for 2 hour. LCMS showed the reaction was completed. The crude was purified by prep.HPLC together (Phenomenex Gemini NX 150×30mm, 5μm, water (NH_4HCO_3)-ACN as a mobile phase, from 63% to 93%, Gradient Time (min): 11, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(3,3,3-trifluoropropyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (5 mg, 6 μmol, 30 %).

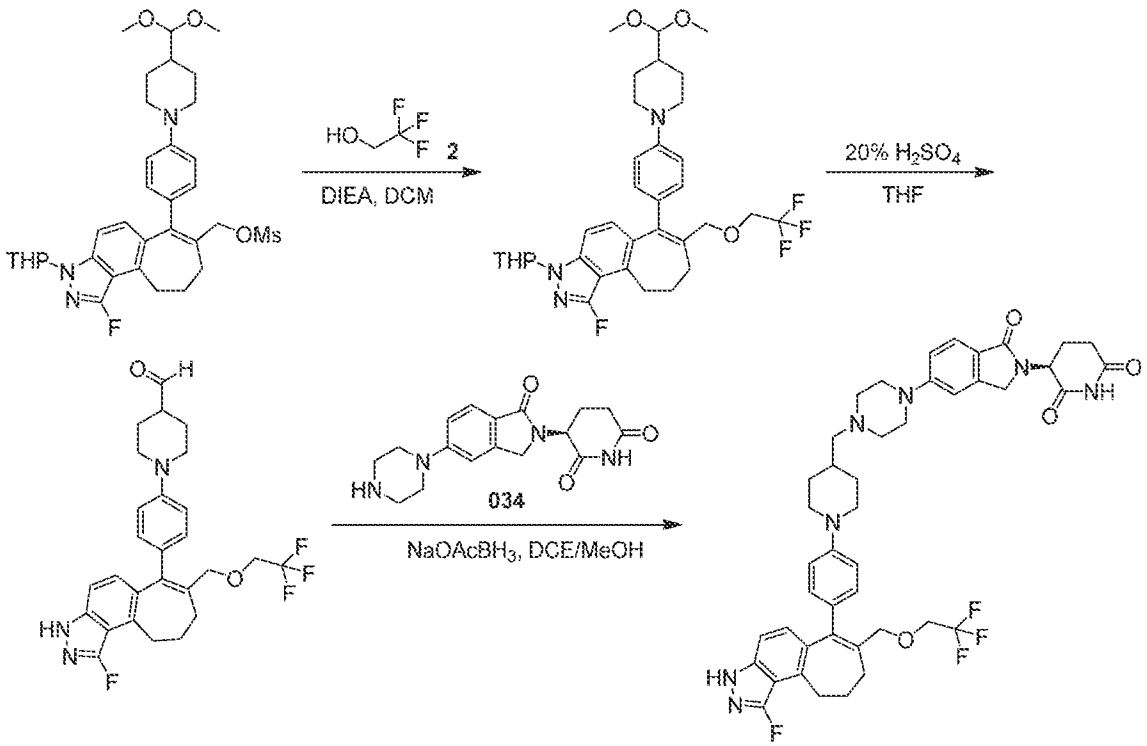
[1154] LCMS: calc. for $C_{44}H_{47}F_4N_7O_3$:797.90, found: $[M+H]^+$ 798.5

[1155] HPLC: 95.76% purity at 220 nm.

[1156] ^1H NMR (400 MHz, METHANOL-d_4) δ : ppm 7.64 (d, J=8.40 Hz, 1 H), 7.06 - 7.13 (m, 3 H), 6.97 - 7.01 (m, 4 H), 6.84 (d, J=8.80 Hz, 1 H), 5.10 (m, 1 H), 4.27 - 4.49 (m, 2 H), 3.70 - 3.76 (m, 2 H), 3.36 - 3.40 (m, 4 H), 3.04 - 3.10 (m, 2 H), 2.84 - 2.96 (m, 1 H), 2.70 - 2.81 (m, 3

H), 2.60 - 2.68 (m, 4 H), 2.53 - 2.58 (m, 2 H), 2.43 - 2.50 (m, 1 H), 2.31 - 2.42 (m, 6 H), 2.12 - 2.19 (m, 1 H), 2.00 - 2.04 (m, 2 H), 1.90 - 1.97 (m, 2 H), 1.71 - 1.83 (m, 1 H), 1.33 - 1.41 (m, 2 H).

Example 53. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-((2,2,2-trifluoroethoxy)methyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-98



[1157] ***Step 1.*** To a solution of compound 1 (60 mg, 96 μmol, 1 eq.) and DIEA (15 mg, 0.11 mmol, 1.2 eq.) in DCM (5 mL) was added compound 2 (19 mg, 0.19 mmol, 2 eq.), which was stirred at 15 °C for 2 hours. LCMS showed the reaction was completed. The mixture was concentrated to get the crude, which was purified on silica gel column chromatography (from PE/EtOAc = 1/1 to 0/1, TLC: PE/EtOAc = 1/1, Rf = 0.6) to yield compound 3 (30 mg, 39 μmol, 41 % yield, 83% purity) as a yellow solid.

[1158] LCMS (ESI^+) m/z: 632.5 ($M+H^+$).

[1159] ***Step 2.*** To a mixture of compound 3 (30 mg, 47 μmol, 1 eq.) and in THF (1 mL) was added H_2SO_4 (0.2 mL, 20% Wt) at 20 °C. The mixture was stirred at 60 °C for 3 hours. LCMS showed desired compound was detected. The mixture neutralized with $NaHCO_3$ to pH = 8 and then was extracted with CH_2Cl_2 (15 mL x 3) and concentrated to get the compound 4 (20 mg, 40 μmol, 84 % yield), which was used for the next step without purification.

[1160] LCMS (ESI$^+$) m/z: 502.3 (M+H$^+$).

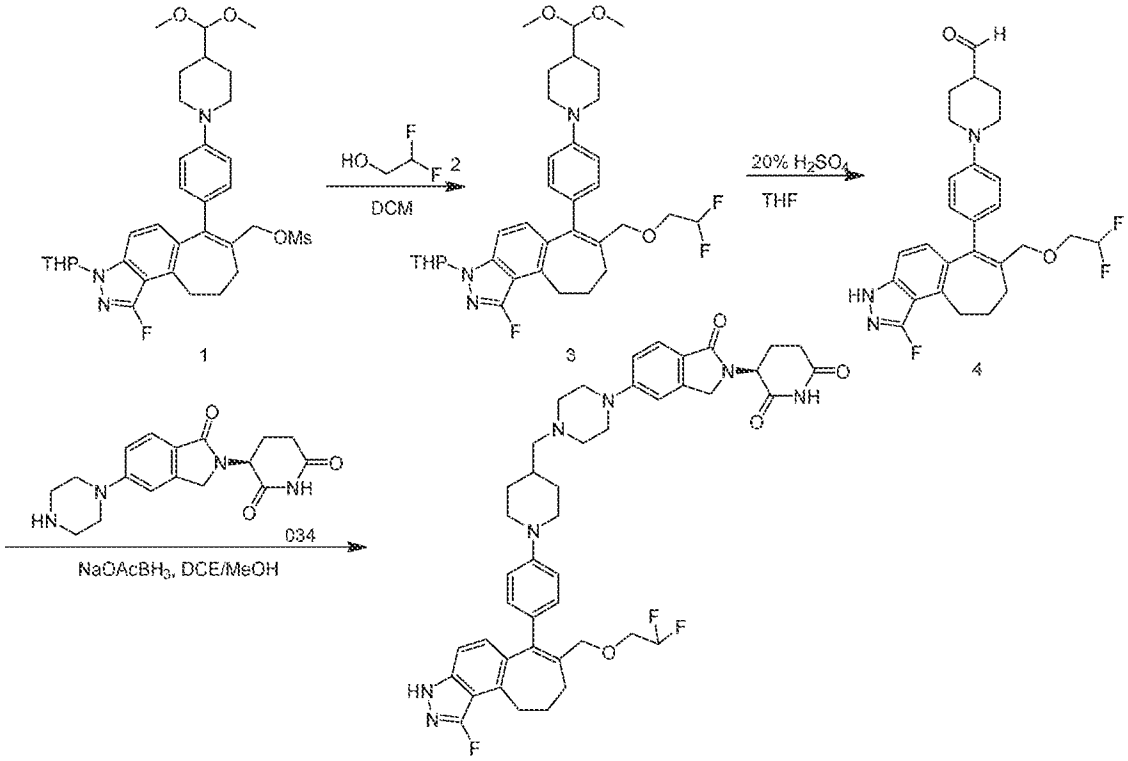
[1161] ***Step 3.*** A mixture of compound 4 (20 mg, 40 µmol, 1 eq.), compound 034 (16 mg, 48 µmol, 1.2 eq.) and $NaBH(OAc)_3$ (25 mg, 0.12 mmol, 3 eq.) was added in DCE (2 mL) and MeOH (2 mL). The reaction mixture was stirred at 25 °C for 16 hour. LCMS showed desired compound was detected. The crude was purified by preparative HPLC (Column: Phenomenex Gemini NX 150 x 30 mm x 5 um, Condition: water (NH_4HCO_3)-ACN, B%: 57%-87%, 11 min.) to give compound (S)-3-(5-(4-((1-(4-(1-fluoro-7-((2,2,2-trifluoroethoxy)methyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (13.3 mg, 16.3 µmol, 41% yield, 100% purity) as a white solid.

[1162] LCMS: calc. for $C_{44}H_{47}F_4N_7O_4$: 813.36, found: [M+H$^+$] 814.5.

[1163] HPLC: 100% purity at 220 nm.

[1164] ^{1}H NMR: ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.66 (d, J=8.34 Hz, 1 H), 7.09 - 7.17 (m, 3 H), 6.97 - 7.02 (m, 4 H), 6.86 (d, J=8.82 Hz, 1 H), 5.12 (dd, J=13.23,5.13 Hz, 1 H), 4.38 - 4.47 (m, 2 H), 4.33 - 4.38 (m, 2 H), 3.89 - 3.96 (m, 2 H), 3.73 - 3.79 (m, 2 H), 3.39 - 3.42 (m, 4 H), 3.04 - 3.11 (m, 2 H), 2.86 - 2.97 (m, 1 H), 2.73 - 2.83 (m, 3 H), 2.62 - 2.70 (m, 4 H), 2.44 - 2.56 (m, 1 H), 2.33 - 2.42 (m, 4 H), 2.14 - 2.22 (m, 1 H), 2.07 - 2.13 (m, 2 H), 1.92 - 1.99 (m, 2 H), 1.74 - 1.88(m, 1 H), 1.35 - 1.43 (m, 2 H).

Example 54. Synthesis of (S)-3-(5-(4-((1-(4-(7-((2,2-difluoroethoxy)methyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-97



[1165] ***Step 1.*** To a solution of compound 1 (30 mg, 48 μmol, 1.0 eq.) in DCM (2 mL) was added compound 2 (3.0 mL). The mixture was stirred at 25 °C for 1 hour. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure to give a product 3 (20 mg, 33 μmol, 68 %).

[1166] LC-MS (ESI+) m/z: 614.4 ($M+H^+$).

[1167] ***Step 2.*** To a solution of compound 3 (20 mg, 33 μmol, 1.0 eq.) in THF (1 mL) was added H_2SO_4 (0.48 g, 0.26 mL, 10% Wt, 0.49 mmol, 15 eq.). The mixture was stirred at 50 °C for 20 min. LCMS showed that the starting material was consumed and the desired product was detected. The residue was poured into $NaHCO_3$ to PH>7. The residue was poured into water (2 mL). The aqueous phase was extracted with ethyl acetate (4 mL*3). The combined organic phase was washed with brine (2 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compound 4 (10 mg, 21 μmol, 63 %) was obtained as oil.

[1168] LC-MS (ESI^+) m/z: 484.3 ($M+H^+$).

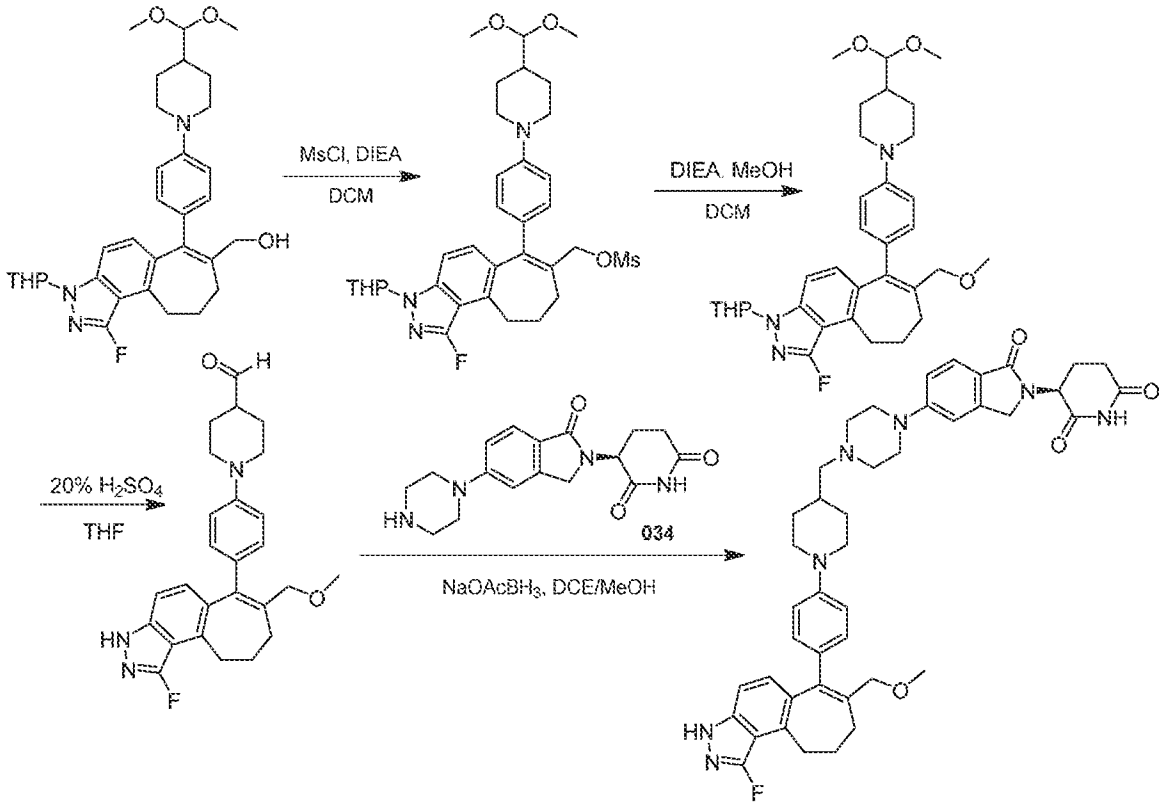
[1169] ***Step 3.*** To a solution of compound 4 (15 mg, 31 μmol, 1.0 eq.) and compound 034 (10 mg, 31 μmol, 1.0 eq.) in DCE (3 mL) and MeOH (2 mL) was added $NaOAcBH_3$ (33 mg, 23 μL, 0.16 mmol, 5.0 eq.). The mixture was stirred at 25 °C for 0.5 hour. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; gradient: 15%-45% B over 18 min) to give product. (S)-3-(5-(4-((1-(4-(7-((2,2-difluoroethoxy)methyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (6 mg, 8 μmol, 20 %) was obtained as a white solid. LC-MS (ESI^+) m/z: 796.4 ($M+H^+$).

[1170] LCMS: calc. for $C_{44}H_{48}F_3N_7O_4$: 795.91, found: [$M+H^+$] 796.4.

[1171] HPLC: 100% purity at 220 nm.

[1172] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.48 (s, 1 H), 10.94 (s, 1 H), 8.29 (s, 1 H), 7.52 (d, J=8.70 Hz, 1 H), 7.19 (dd, J=8.82, 2.62 Hz, 1 H), 7.03 - 7.09 (m, 2 H), 6.89 (s, 4 H), 6.74 (d, J=8.70 Hz, 1 H), 5.95 - 6.38 (m, 1 H), 4.98 - 5.13 (m, 1 H), 4.29 - 4.37 (m, 1 H), 4.18 - 4.24 (m, 3 H), 3.58 - 3.77 (m, 5 H), 2.85 - 2.96 (m, 3 H), 2.53 - 2.74 (m, 6 H), 2.30 - 2.47 (m, 6 H), 2.28 (br d, J=7.15 Hz, 1 H), 2.23 (br d, J=7.39 Hz, 2 H), 1.91 - 2.00 (m, 3 H), 1.68 - 1.85 (m, 3 H), 1.22 (br d, J=10.37 Hz, 2 H).

Example 55. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(methoxymethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-95



[1173] ***Step 1.*** To a solution of compound 1 (160 mg, 291 μmol, 1 eq.) and DIEA (124 mg, 0.52 mmol, 3.3 eq.) in DCM (8 mL) was added MsCl (60 mg, 0.52 mmol, 1.8 eq.) at 0 °C. The mixture was stirred at 0 °C for 2 hours. TLC showed the reaction was completed. The reaction mixture was quenched with 0.2 mL of water, which was concentrated in vacuum to give residue. The residue was poured into 25 mL of water and the aqueous was extracted with DCM (10 mL x 2). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuum to give the compound 2 (120 mg, crude) which was used for the next step without further purification.

[1174] ***Step 2.*** To a solution of compound 2 (100 mg, 159 μmol, 1 eq.) and DIEA (24.7 mg, 33.3 μL, 191 μmol, 1.2 eq.) in DCM (8 mL) was added MeOH (10.2 mg, 12.9 μL, 319 μmol, 2 eq.), which was stirred at 15 °C for 2 hours. LCMS showed the reaction was completed. The mixture was concentrated to get the crude, which was purified on silica gel column chromatography (from PE/EtOAc = 1/1 to 0/1, TLC: PE/EtOAc = 1/1, Rf = 0.6) to yield compound 3 (50 mg, 86 μmol, 54 % yield, 97% purity) as a yellow solid.

[1175] LCMS (ESI^+) m/z: 532.4 ($M+H^+$).

[1176] ***Step 3.*** A mixture of compound 3 (50 mg, 89 μmol, 1 eq.) and H_2SO_4 (0.2 mL, 20% Wt) was added in THF (1 mL). The mixture was stirred at 60 °C for 3 hours. LCMS showed desired compound was detected. The mixture neutralized with $NaHCO_3$ to pH = 8 and then was extracted with CH_2Cl_2 (15 mL x 3) and concentrated to get the compound 4 (20 mg, crude), which was used for the next step without purification.

[1177] LCMS (ESI^+) m/z: 434.4 ($M+H^+$).

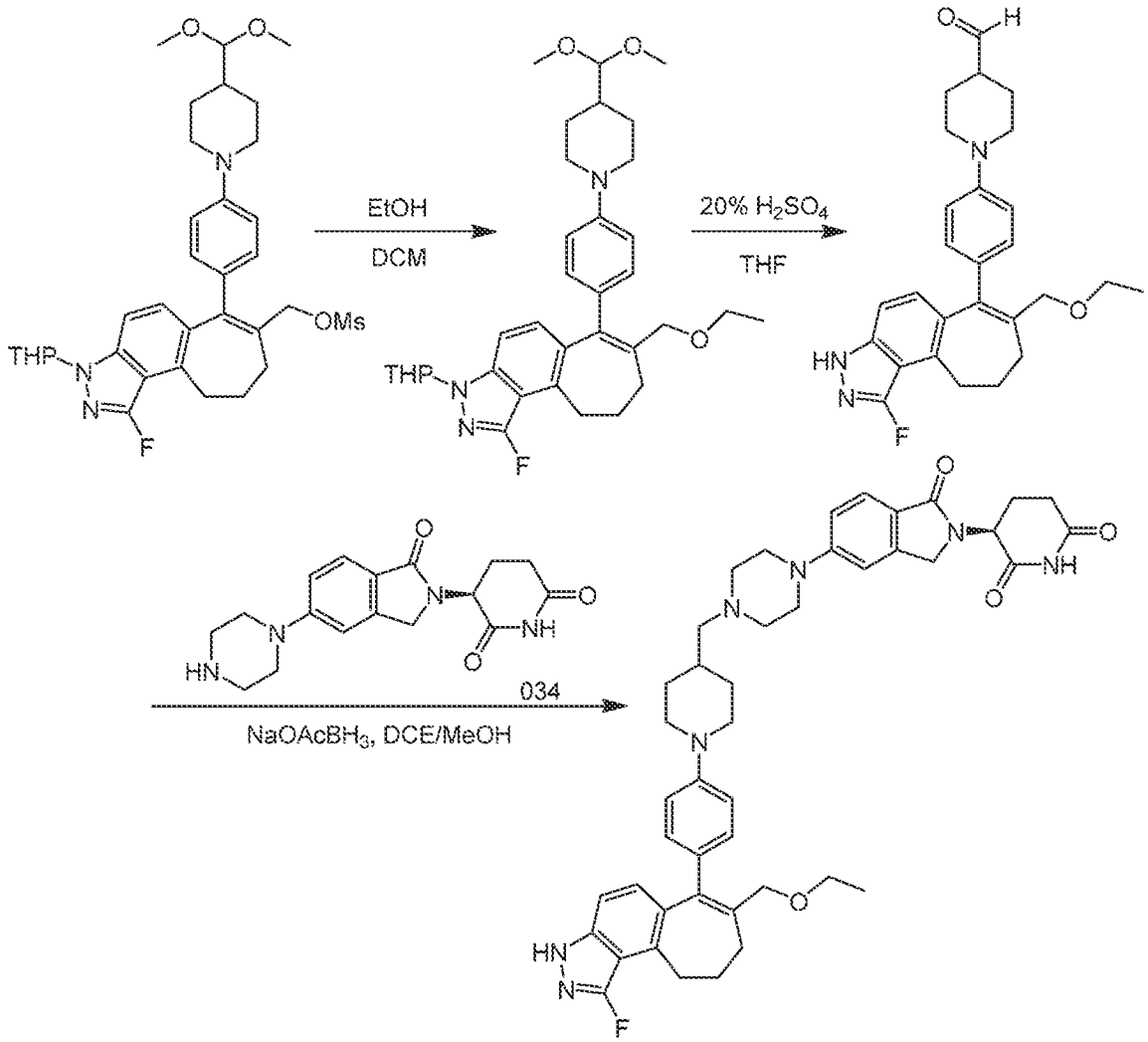
[1178] ***Step 4.*** A mixture of compound 4 (20 mg, 46 μmol, 1 eq.), compound 034 (23 mg, 69 μmol, 1.5 eq.) and $NaBH(OAc)_3$ (29 mg, 0.14 mmol, 3 eq.) was added in DCE (2 mL) and MeOH (2 mL). The reaction mixture was stirred at 25 °C for 1 hour. LCMS showed the reaction was completed. The crude was purified by preparative HPLC (Column: Boston Green ODS 150 * 30 mm * 5 um, Condition water (FA)-ACN as a mobile phase, B%: 22%-32%, 18 min) to give compound (S)-3-(5-(4-((1-(4-(1-fluoro-7-(methoxymethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (5 mg, 6 μmol, 10% yield, 96.93% purity) as a white solid.

[1179] LCMS: calc. for $C_{43}H_{48}FN_7O_4$: 745.38, found: [$M+H^+$] 746.5.

[1180] HPLC: 96.93% purity at 220 nm.

[1181] ^1H NMR: ^1H NMR (500 MHz, DMSO-d6) δ ppm 12.47 (s, 1 H), 10.95 (s, 1 H), 8.45 - 8.49 (m, 1 H), 7.53 (d, J=8.54 Hz, 1 H), 7.19 (dd, J=8.85, 2.44 Hz, 1 H), 7.08 (s, 2H), 6.90 (s, 4 H), 6.75 (d, J=8.85 Hz, 1 H), 5.05 (dd, J=13.35, 4.96 Hz, 1 H), 4.19 - 4.36 (m, 2 H), 4.04 (s, 2 H), 3.73 (br d, J=11.75 Hz, 2 H), 3.25 (s, 3 H), 2.93 -2.97 (m, 2 H), 2.87 - 2.92 (m, 1 H), 2.58 - 2.75 (m, 5 H), 2.57 (br s, 3 H), 2.32 - 2.43 (m, 3 H), 2.26 - 2.31 (m, 2 H), 2.24 (br d, J=7.02 Hz, 2 H), 1.93 - 1.98 (m, 3H), 1.84 (br d, J=11.90 Hz, 2 H), 1.68 - 1.76 (m, 1 H), 1.16 - 1.30 (m, 3 H).

Example 56. Synthesis of (S)-3-(5-(4-((1-(4-(7-(ethoxymethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-96



[1182] ***Step 1.*** To a solution of compound 1 (20 mg, 32 μmol, 1.0 eq.) in DCM (2 mL) was added EtOH (2.0 mL). The mixture was stirred at 25 °C for 1 hour. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure. The residue was poured into water (4 mL). The aqueous phase was extracted with ethyl acetate (8 mL*3). The combined organic phase was washed with brine (4 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The product 2 (8 mg, 0.01 mmol, 40 %).

[1183] LC-MS (ESI+) m/z: 578.4 ($M+H^+$).

[1184] ***Step 2.*** To a solution of compound 3 (20 mg, 35 μmol, 1 eq.) in THF (1 mL) was added H_2SO_4 (0.51 g, 0.28 mL, 10% Wt, 0.52 mmol, 15 eq.). The mixture was stirred at 50 °C for 20

mins. LCMS showed that the starting material was consumed and the desired product was detected. The residue was poured into $NaHCO_3$ to PH>7. The residue was poured into water (2 mL). The aqueous phase was extracted with ethyl acetate (4 mL*3). The combined organic phase was washed with brine (2mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compound 3 (12 mg, 27 μmol, 77 %) was obtained as oil.

[1185] LC-MS (ESI^+) m/z: 448.4($M+H^+$).

[1186] ***Step 3.*** To a solution of compound 3 (10 mg, 22 μmol, 1.0 eq.) and compound 034 (7.3 mg, 22 μmol, 1 eq.) in DCE (3 mL) and MeOH (2 mL) was added $NaOAcBH_3$ (24 mg, 17 μL, 0.11 mmol, 5.0 eq.). The mixture was stirred at 25 °C for 0.5 hour. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; gradient: 15%-45% B over 18 min) to give product. (S)-3-(5-(4-((1-(4-(7-(ethoxymethyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4.3 mg, 5.7 μmol, 25 %) was obtained as a white solid.

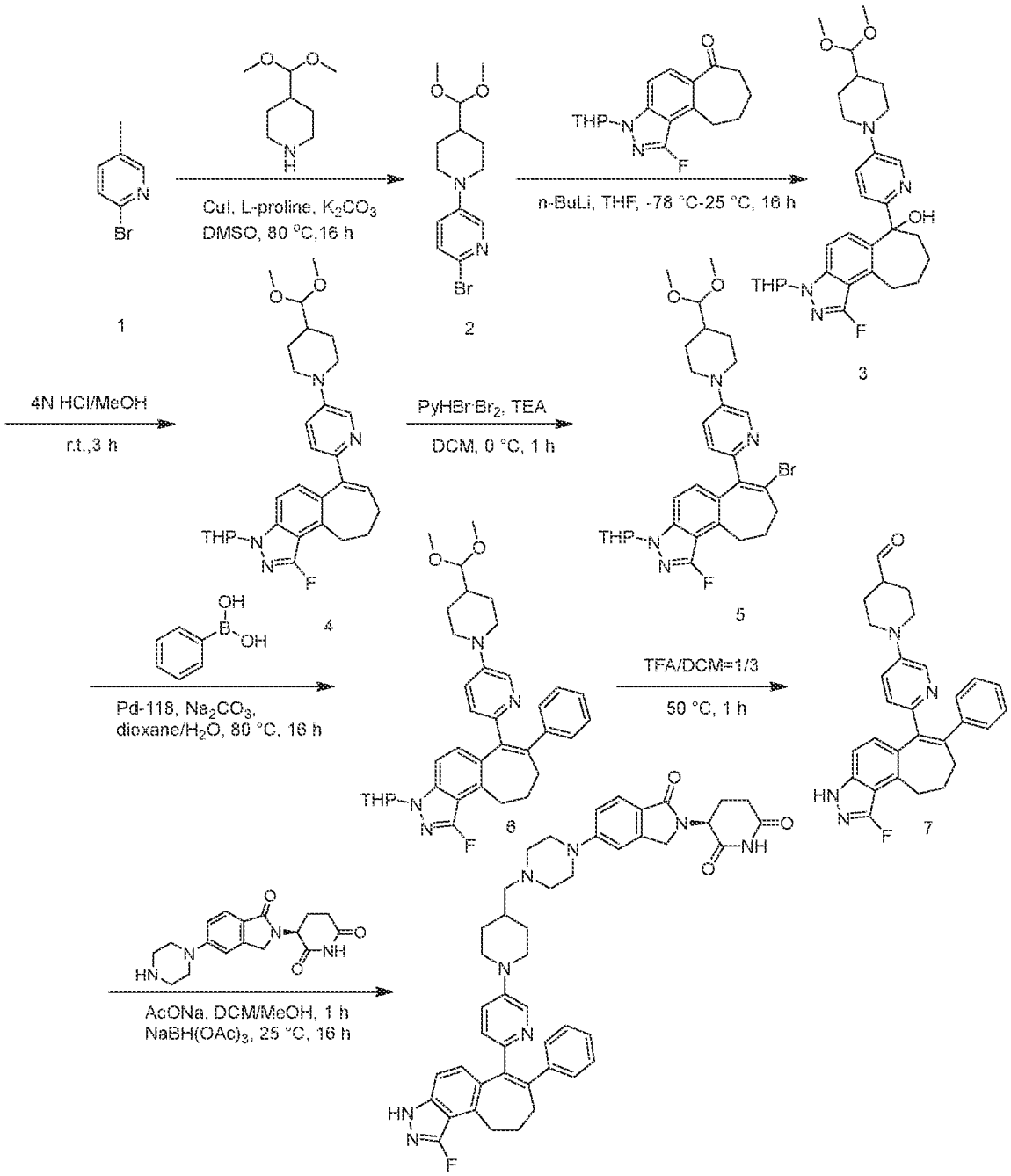
[1187] LC-MS (ESI^+) m/z: 760.4 ($M+H^+$).

[1188] LCMS: calc. for $C_{44}H_{50}FN_7O_4$: 759.93, found: [$M+H^+$] 760.4.

[1189] HPLC: 100% purity at 220 nm.

[1190] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.47 (s, 1 H), 10.91 - 10.99 (m, 1 H), 8.38 (br d, J=3.10 Hz, 1 H), 7.50 - 7.54 (m, 1 H), 7.18 (dd, J=8.46, 2.38 Hz, 1 H), 7.03 – 7.09 (m, 2 H), 6.89 (s, 4 H), 6.74 (d, J=8.82 Hz, 1 H), 5.00 – 5.09 (m, 1 H), 4.29 – 4.37 (m, 1 H), 4.17 – 4.25 (m, 1 H), 4.07 (s, 2 H), 3.68 – 3.76 (m, 2 H), 3.38 – 3.44 (m, 6 H), 2.82 – 3.03 (m, 4 H), 2.53 – 2.71 (m, 5 H), 2.19 – 2.40 (m, 6 H), 1.92 – 1.99 (m, 3 H), 1.70 – 1.87 (m, 3 H), 1.19 – 1.27 (m, 2 H), 1.12 (t, J=6.97 Hz, 3 H).

Example 57. Synthesis of (S)-3-(5-(4-((1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-102



[1191] ***Step 1.*** To a solution of 2-bromo-5-iodopyridine (4 g, 1 Eq, 14.1 mmol) and 4-(dimethoxymethyl)piperidine (2.2 g, 2.4 mL, 1 Eq, 14.1 mmol) in DMSO (100 mL) was added cuprous iodide (537 mg, 96 μL, 0.2 Eq, 2.82 mmol)), (S)-(-)-Proline (649 mg, 481 μL, 0.4 Eq, 5.64 mmol) and potassium carbonate (3.9 g, 1.6 mL, 2 Eq, 28.2 mmol). The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched by addition H_2O (200 mL) at 25°C, and

then diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined organic layers were washed with brine (100 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 50~50% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) and the organic layer was concentrated in vacuo to give 2-bromo-5-(4-(dimethoxymethyl)piperidin-1-yl)pyridine (1 g, 3 mmol, 20 % yield, 100% purity) as a yellow solid. LC-MS (ESI^+) m/z: 317.0 $(M+H)^+$.

[1192] ***Step 2.*** To a mixture of 2-bromo-5-(4-(dimethoxymethyl)piperidin-1-yl)pyridine (584 mg, 3.5 Eq, 1.85 mmol) in THF (8 mL) at r.t., and the mixture was degassed and purged with N_2 for 10 mintues. Then the mixture was stirred until it reached -78 °C. n-Butyllithium in hexane (635 µL, 2.5 molar, 3 Eq, 1.59 mmol) was added to the mixture and stirred at -78 °C for 1 hour, then 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (160 mg, 1 Eq, 529 µmol) was add to the mixture at -78 °C and stirred at 25 °C for 16 h. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.4 UV) showed new spot was formed. The reaction was quenched with saturated NH_4Cl solution (100 mL) and extracted with ethyl acetate (100 mL*2). The combined organic layer were washed with brine (100 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 60% ethyl acetate). The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (180 mg, 334 µmol, 63.1% yield) as a yellow oil. LC-MS (ESI^+) m/z: 539.3 $(M+H)^+$.

[1193] ***Step 3.*** To a solution of 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (180 mg, 1 Eq, 334 µmol) in 4 N HCl/MeOH (10 mL) was stirred at 25 °C for 3 h. TLC (petroleum ether : ethyl acetate=3:1,R_f=0.4UV) showed a new spot was formed. The mixture was added to aq.$NaHCO_3$ (200 mL) and must confirmed pH=8 during this time, then extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazole (160 mg, 0.18 mmol, 55 % yield) as a yellow solid.

[1194] ***Step 4.*** To a mixture of 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazole (155 mg, 1 Eq, 355 μmol) and triethylamine (54 mg, 74 μL, 1.5 Eq, 533 μmol) in DCM (8 mL) at 0 °C, and pyridinium bromide perbromide (114 mg, 1 Eq, 355 μmol) was added to the mixture at 0 °C, then the mixture was stirred at 0 °C for 1 h. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.5 UV) showed a new spot was observed. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL*2). The organic layer was washed with brine (100 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a white solid. The red solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% ethyl acetate). The desired fractions were collected, and concentrated to dryness in vacuo to give 7-bromo-6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazole (180 mg, 349 μmol, 98 % yield) as a yellow solid.

[1195] ***Step 5.*** A mixture of 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (19 mg, 0.1 Eq, 29.1 μmol), benzeneboronic acid (36 mg, 1 Eq, 291 μmol), sodium carbonate (93 mg, 3 Eq, 873 μmol) 7-bromo-6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazole (150 mg, 1 Eq, 291 μmol) in dioxane (8 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=5:1, Rf=0.5 UV) showed new spot was formed. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a black oil. The black oil was subjected to column chromatography over silica gel (gradient elution: 0 – 100% ethyl acetate). The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazole (50 mg, 98 μmol, 34 %yield) as a white solid.

[1196] ***Step 6.*** To a solution of 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazole (50 mg, 1 Eq, 98 μmol) in TFA (1.5 mL) and DCM (4.5 mL) was stirred at 50 °C for 1 hour. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.3, UV) showed new spot was formed. The reaction was adjust to pH=8 with aq.$NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(6-(1-fluoro-7-phenyl-3,8,9,10-

tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidine-4-carbaldehyde (70 mg, 0.15 mmol) as a yellow solid.

[1197] *Step 7.* To a solution of 1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidine-4-carbaldehyde (70 mg, 1 Eq, 0.15 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (55 mg, 1 Eq, 0.15 mmol) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (37 mg, 3 Eq, 0.45 mmol) was stirred at 25 °C for 1 h, Then sodium triacetoxyborohydride (64 mg, 2 Eq, 0.3 mmol) and acetic acid (27 mg, 26 µL, 3 Eq, 0.45 mmol) was added. The mixture was stirred at 25 °C for 16 h. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(0.225%FA)-ACN];B% 18%-48%,7min) to give (S)-3-(5-(4-((1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (9.4 mg, 12 µmol, 8.0 % yield, 100% purity) was obtained as a yellow solid. LC-MS (ESI^+) m/z: 779.5 $(M+H)^+$.

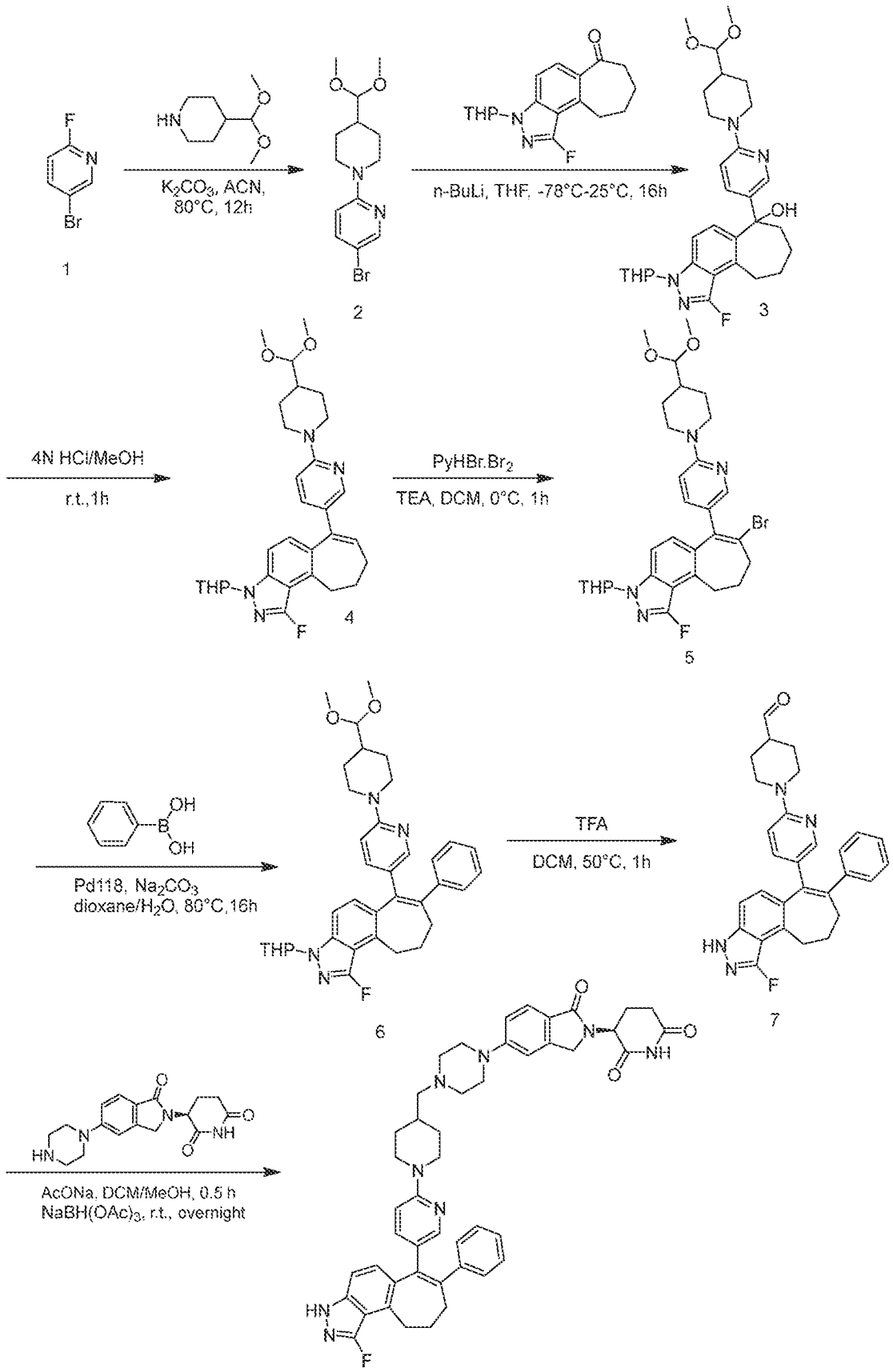
[1198] LCMS: calc. for $C_{46}H_{47}FN_8O_3$: 778.93, found: [M+H] + 779.5.

[1199] HPLC: 100% purity at 220 nm.

[1200] SFC: retention time, 3.749 min; Area, 91.125%;method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

[1201] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.47 (s, 1H), 10.94 (s, 1H), 8.15 (s, 0.383H), 8.10 (d, J = 2.7 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.18 (br d, J = 7.4 Hz,6H), 7.07 (s, 3H), 6.79 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 5.05 (dd, J = 5.1, 13.2 Hz, 1H), 4.40 - 4.27 (m, 1H), 4.26 - 4.13 (m, 1H), 3.68 (br d, J =12.3 Hz, 2H), 3.31 - 3.26 (m, 7H), 3.07 (br s, 2H), 2.99 - 2.82 (m, 1H), 2.63 (br d, J = 12.3 Hz, 3H), 2.31 (br s, 5H), 2.21 (br d, J = 7.0 Hz, 2H), 2.00 - 1.93(m, 1H), 1.79 (br d, J = 12.4 Hz, 2H), 1.70 (br s, 1H), 1.24 (s, 3H).

Example 58. Synthesis of (S)-3-(5-(4-((1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-110


1
K_2CO_3, ACN, 80°C, 12h
2
n-BuLi, THF, -78°C-25°C, 16h
3
4N HCl/MeOH
r.t.,1h
4
$PyHBr.Br_2$
TEA, DCM, 0°C, 1h
5
Pd118, Na_2CO_3 dioxane/H_2O, 80°C,16h
6
TFA
DCM, 50°C, 1h
7
AcONa, DCM/MeOH, 0.5 h
$NaBH(OAc)_3$, r.t., overnight

[1202] ***Step 1.*** A mixture of 5-bromo-2-fluoropyridine (1.5 g, 1 Eq, 8.523 mmol), 4-(dimethoxymethyl)piperidine (1.5 g, 1.1 Eq, 9.376 mmol), K_2CO_3 (2.4 g, 2 Eq, 17.05 mmol) in ACN (20 mL) was stirred at 80 °C for 12 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The yellow oil was purified by silica gel column chromatography (gradient elution: 0 – 10% ethyl acetate in petroleum ether) to yield the desired compound (1.73 g, 100% purity, 64.4% yield) as a off-white solid. LC-MS (ESI^+) m/z: 317.0 $(M+H)^+$.

[1203] ***Step 2.*** A solution of 5-bromo-2-(4-(dimethoxymethyl)piperidin-1-yl)pyridine (730 mg, 3.5 Eq, 2.32 mmol) in THF (8 mL) was bubbled with N_2 for 10 min. Then the mixture was stirred until it reached -78 °C. N-butyllithium in hexane solution (2.5 M, 127 mg, 794 µL, 2.5 molar, 3 Eq, 1.98 mmol) was added to the mixture and stirred at -78 °C for 1 hour, then 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (200 mg, 1 Eq, 661 µmol) was added to the mixture at -78 °C. The mixture was warmed to 25 °C slowly and stirred for 15 hour. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (40 mL*2). The organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 60% ethyl acetate in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuum to give 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (265 mg, 65.4 %, 87.961% purity) as a white foam. LC-MS (ESI^+) m/z: 539.3 $(M+H)^+$.

[1204] ***Step 3.*** A solution of 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (265 mg, 1 Eq, 492 µmol) was added 4N HCl/MeOH (5 mL) at r.t., and the mixture was stirred at 25 °C for 1 hour . The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and was concentrated in vacuum to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 50% ethyl acetate in petroleum ether). The desired fractions were collected concentrated to dryness in vacuum to give 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-

3,8,9,10-tetrahydrocyclohepta[e]indazole (250 mg, 63.842% purity, 62.3% yield) as a white solid. LC-MS (ESI^+) m/z: 521.1 $(M+H)^+$.

[1205] ***Step 4.*** To a mixture of 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (230 mg, 1 Eq, 442 μmol) and TEA (45 mg, 61.6 μL, 1 Eq, 442 μmol) in DCM (10 mL) at 0 °C was added pyridinium bromide perbromide (141 mg, 1 Eq, 442 μmol), then the mixture was stirred at 0 °C for 1 hour. The reaction was added with water (30 mL) and extracted with ethyl acetate (3 mL*2). The organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0 – 30% ethyl acetate in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuum to give 7-bromo-6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (180 mg, 68% yield) as a white solid. LC-MS (ESI^+) m/z: 599.1 $(M+H)^+$.

[1206] ***Step 5.*** To a mixture of Pd-118 (14.1 mg, 0.1 Eq, 21.7 μmol) was added 7-bromo-6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (130 mg, 1 Eq, 217 μmol) benzeneboronic acid (53 mg, 2 Eq, 434 μmol) and sodium carbonate (69 mg, 3 Eq, 650 μmol) in 1,4-dioxane (6 mL) and H_2O (1.5 mL) at r.t. Then the mixture was bubbled with N_2 for 3 min and was stirred at 80 °C for 12 hour. The mixture was diluted with H_2O (20 mL) and was extracted with ethyl acetate (20 mL* 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a yellow oil. The yellow oil was subjected to column chromatography over silica gel (gradient elution: 0 – 30% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuum to give 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-3-yl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (95 mg, 61.486% purity, 45% yield) as a white solid. LC-MS (ESI^+) m/z: 597.2 $(M+H)^+$.

[1207] ***Step 6.*** A mixture of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-7-ethyl-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (95 mg, 1 Eq, 0.17 mmol) in DCM (10 mL) and TFA (2.5 mL) was stirred at 50 °C for 0.5 hour. The mixture was then added slowly into the saturated aqueous $NaHCO_3$ solution (20 mL) and was extracted with ethyl acetate (20 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4,

filtered and concentrated under vacuum to give 1-(4-(7-ethyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (70 mg, crude) as a yellow oil. LC-MS (ESI^+) m/z: 467.2 $(M+H)^+$.

[1208] *Step 7.* A solution of 1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-2-yl)piperidine-4-carbaldehyde (70 mg, 1 Eq, 0.15 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (55 mg, 1 Eq, 0.15 mmol) and sodium acetate (62 mg, 5 Eq, 0.75 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h, Then acetic acid (18 mg, 17 µL, 2 Eq, 0.3 mmol) and sodium triacetoxyhydroborate (64 mg, 2 Eq, 0.30 mmol) were added. The mixture was stirred at 25 °C for 16 hour. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3um; mobile phase: [water(0.05% $NH_3 \cdot H_2O$/10mM NH_4HCO_3)-ACN]; B% 70%-100%, 8 min). The desired fractions were lyophilized under vacuum to give (S)-3-(5-(4-((1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (11.1 mg, 9.0 % yield, 94.353% purity) as a white solid. LC-MS (ESI^+) m/z: 779.7 $(M+H)^+$.

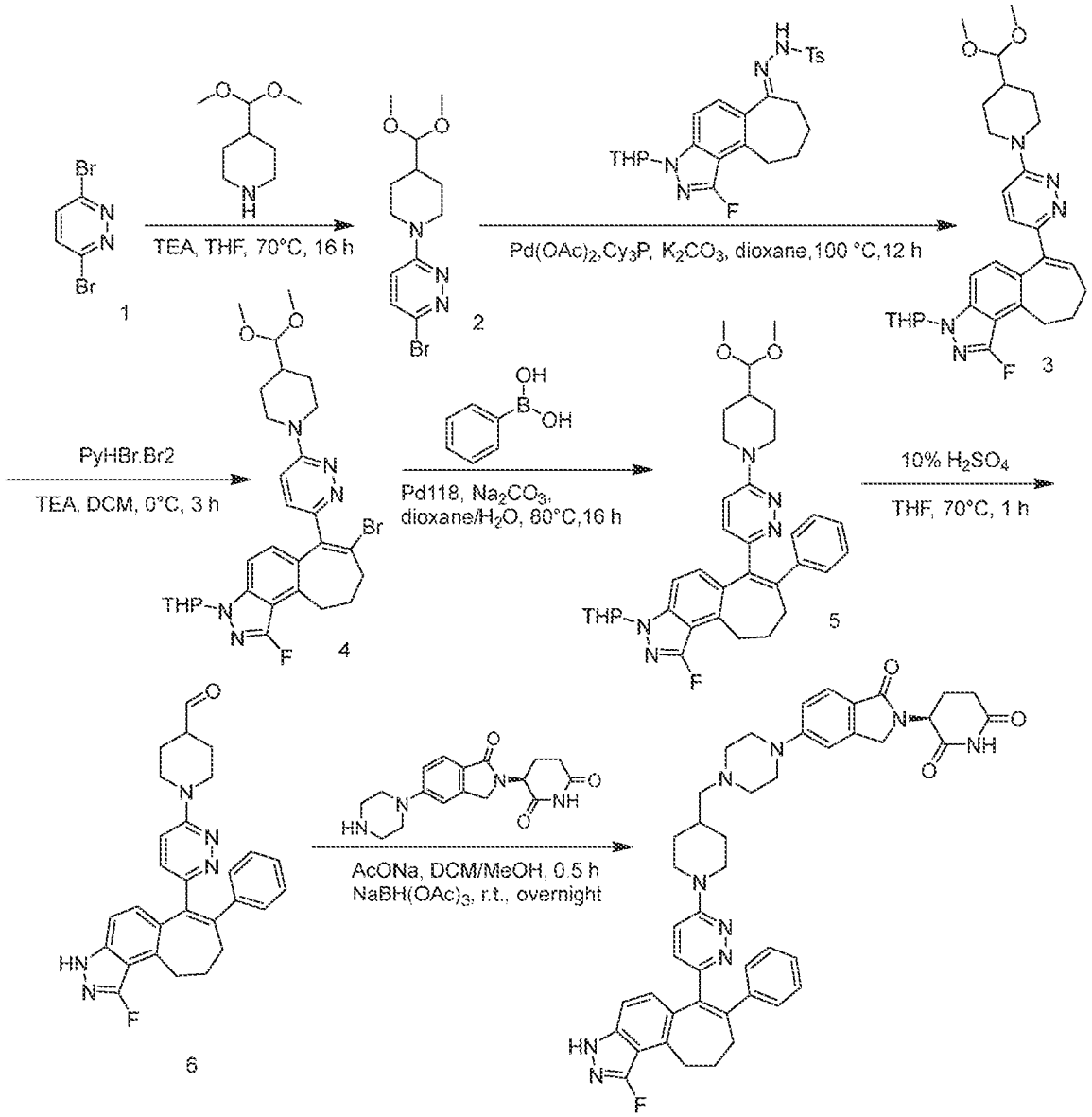
[1209] LCMS: calc. for $C_{46}H_{47}FN_8O_3$: 778.93, found: $[M+H]^+$ 779.7.

[1210] HPLC: 94.353% purity at 220 nm.

[1211] SFC: retention time, 5.512 min; Area, 96.309%; method: IA_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[1212] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.51 (s, 1H), 10.93 (s, 1H), 7.56 (s, 1H), 7.52 (br d, J = 8.6 Hz, 1H), 7.28 - 7.21 (m, 5H), 7.17 (br s, 1H), 7.07 (s, 2H), 6.95 (br d, J = 8.3 Hz, 1H), 6.87 (br d, J = 8.8 Hz, 1H), 6.57 (br d, J = 8.9 Hz, 1H), 5.05 (br dd, J = 5.1, 13.2 Hz, 1H), 4.36 - 4.30 (m, 1H), 4.25 - 4.14 (m, 3H), 3.29 - 3.27 (m, 2H), 3.25 - 3.19 (m, 2H), 3.12 - 3.06 (m, 2H), 2.90 (br s, 1H), 2.71 (br t, J = 12.3 Hz, 2H), 2.59 (br d, J = 18.0 Hz, 2H), 2.42 (br d, J = 4.3 Hz, 2H), 2.36 - 2.23 (m, 6H), 2.20 (br d, J = 6.3 Hz, 2H), 2.01 - 1.93 (m, 1H), 1.76 (br d, J = 10.3 Hz, 3H), 1.06 (br d, J = 11.2 Hz, 2H)

Example 59. Synthesis of (S)-3-(5-(4-((1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-111



[1213] ***Step 1.*** To a mixture of 4-(dimethoxymethyl)piperidine (1.00 g, 6.31 mmol), 3,6-dibromopyridazine (1.0 g, 4.20 mmol), and TEA (851 mg, 1.17 mL, 8.41 mmol) were combined in THF (10 mL) at 25 °C, then the mixture was stirred at 25 °C for 12 h. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.4, UV) showed one main new spot was observed. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layers were washed with brine (50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% ethyl acetate). The desired fractions were collected, and concentrated to dryness in

vacuo to give N-(1-(6-bromopyridazin-3-yl)piperidin-4-yl)-N-methoxy-O-methylhydroxylamine (1.3 g, 4.2 mmol, 97.6% purity, 96.5%yield) as a white solid which confirmed by LC-MS (ESI^+) m/z: 316.1 $(M+H)^+$.

[1214] ***Step 2.*** A mixture of 3-bromo-6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazine (300 mg, 1 Eq, 948.77 µmol) , (E)-N'-(1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-ylidene)-4-methylbenzenesulfonohydrazide (350.0 mg, 0.78 Eq, 743.79 µmol), diacetoxypalladium (21 mg, 0.1 Eq, 94.877 µmol), tricyclohexylphosphane (53 mg, 0.2 Eq, 189.7 µmol)and potassium carbonate (393 mg, 3 Eq, 2.8463 mmol)in dioxane (5 mL was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.6 UV) showed one main new spot was observed. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 50% ethyl acetate). The desired fractions were collected, and concentrated to dryness in vacuo to give t 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (140 mg, 267 µmol, 99.364% purity) as a yellow solid which confirmed by LC-MS (ESI^+) m/z: 522.3 $(M+H)^+$.

[1215] ***Step 3.*** To a mixture of 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 1 Eq, 230 µmol) and diisopropylethylamine (45 mg, 60 µL, 1.5 Eq, 345 µmol) in DCM (5 mL) at 0°C, and pyridinium bromide perbromide (110 mg, 1.5 Eq, 345 µmol) was added to the mixture at 0°C, then the mixture was stirred at 0 °C for 3 h. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.7 UV) showed one main new spot was observed. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (30 mL*2). The organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 30% ethyl acetate in petroleum ether). The desired fractions were collected, and concentrated to dryness in vacuo to give 7-bromo-6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (50 mg, 81 µmol, 35%yield, 97.23% purity) as a yellow solid. LC-MS (ESI^+) m/z: 600.3 $(M+H)^+$.

[1216] ***Step 4.*** Pd-118 (6 mg, 0.1 Eq, 8.326 μmol) was added to the mixture of 7-bromo-6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (50 mg, 1 Eq, 83.26 μmol)BenzeneboronicAcid (15 mg, 1.5 Eq, 124.9 μmol) and sodium carbonate (27 mg, 3 Eq, 249.8 μmol) in dioxane (1.2 mL) and H_2O (0.3 mL) at r.t. Then the mixture was bubbled with N_2 for 3 min and was heated to 80 °C for 12 hour. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.5 UV) showed one main new spot was observed. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (50 mL*2). The organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% ethyl acetate). The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (35 mg, 52 μmol, 89.09% purity) as a yellow solid. LC-MS (ESI^+) m/z: 598.2 $(M+H)^+$.

[1217] ***Step 5.*** To a solution of 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (35 mg, 1 Eq, 59 μmol) in 10% H_2SO_4 (3 mL) and THF (3 mL) was stirred at 70 °C for 1 hour. LCMS showed 64% desired MS The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidine-4-carbaldehyde (20 mg, 28 μmol, 64% purity). as a yellow solid. LC-MS (ESI^+) m/z: 468.1 $(M+H)^+$.

[1218] ***Step 6.*** To a solution of 1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidine-4-carbaldehyde (20. mg, 1 Eq, 42.78 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (16 mg, 1 Eq, 42.78 μmol)and sodium acetate (21 mg, 6 Eq, 256.7 μmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h, Then acetic acid (5 μL, 2 Eq, 85.55 μmol) and sodium triacetoxyhydroborate (18 mg, 2 Eq, 85.55 μmol). The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column:

Welch Xtimate C18 150*30mm;mobile phase: [water(FA)-ACN];B%: 18%-48%,6 min) to give (S)-3-(5-(4-((1-(6-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2.9 mg, 3.7 μmol, 100.00% purity) was obtained as a white solid. LC-MS (ESI^+) m/z: 780.4 $(M+H)^+$.

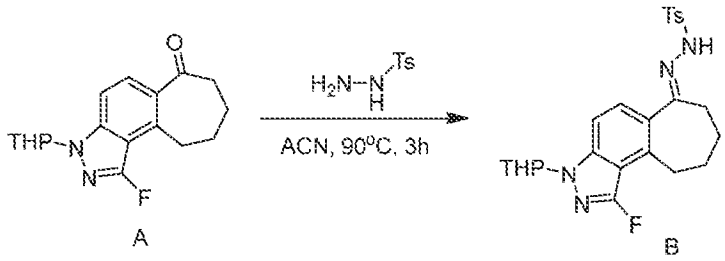
[1219] LCMS: calc. for $C_{45}H_{46}FN_9O_3$: 779.37, found: $[M+H]^+$ 780.4.

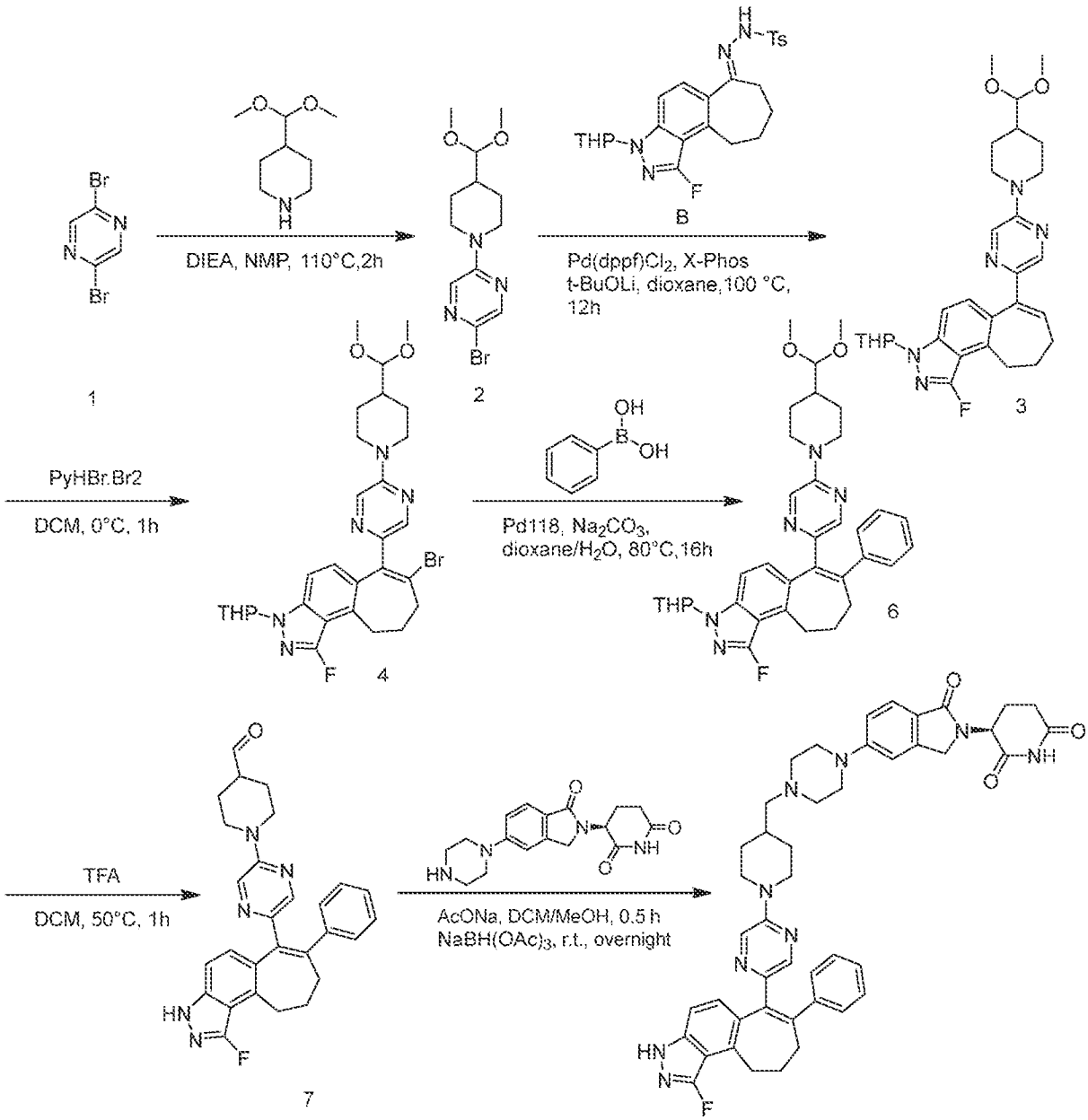
[1220] HPLC: 97.102% purity at 220 nm.

[1221] ^1H NMR (400 MHz, Methanol-d_4) δ = 8.49 - 8.38 (m, 0.626H), 7.64 (d, J = 8.2 Hz, 1H), 7.24 - 7.19 (m, 6H), 7.12 - 7.07 (m, 2H), 6.97 - 6.89 (m, 2H),6.87 (d, J = 8.7 Hz, 1H), 5.14 - 5.08 (m, 1H), 4.40 (d, J = 6.8 Hz, 2H), 4.34 (br d, J = 11.9 Hz, 2H), 3.40 (br s, 5H), 3.24 (br t, J = 6.9 Hz, 2H), 2.95 - 2.86 (m,3H), 2.82 - 2.77 (m, 1H), 2.72 (br s, 4H), 2.51 - 2.45 (m, 3H), 2.44 - 2.39 (m, 4H), 2.19 - 2.12 (m, 1H), 1.89 (br d, J = 12.6 Hz, 2H), 1.27 - 1.17 (m, 2H)

[1222] SFC: retention time, 3.823 min; Area, 95.155%; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 60. Synthesis of (S)-3-(5-(4-((1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyrazin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-112





[1223] *Step 1.* To a solution of 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (300 mg, 1 Eq, 992 μmol) in acetonitrile (10 mL) was added 4-Methylbenzenesulfonic acid hydrazide (222 mg, 1.2 Eq, 1.2 mmol). The mixture was stirred at 90 °C for 3 h . TLC (petroleum ether: ethyl acetate=5:1, R_f =0.4 UV) showed one main new spot was observed. The reaction mixture was diluted with 50 mL H_2O and extracted with 100 mL ethyl acetate. The combined organic layers were washed with 30 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 18 mL/min). Compound (E)-N'-(1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-ylidene)-4-methylbenzenesulfonohydrazide (400 mg, 850 μmol, 85.7 % yield) was obtained as a white solid. LC-MS (ESI+) m/z: 471.2 $(M+H)^+$.

[1224] *Step 2.* A mixture of 2,5-dibromopyrazine(1 g, 1 Eq, 4.2 mmol), diisopropylethylamine (815 mg, 1.1 mL, 1.5 Eq, 6.3 mmol) in NMP (20 mL) was added 4-(dimethoxymethyl)piperidine(669 mg, 1 Eq, 4.2 mmol), and then the mixture was stirred at 110 °C for 2 h. TLC (petroleum ether: ethyl acetate =5:1, R_f =0.4 UV) showed one main new spot was formed. The mixture was added H_2O (20 mL), then extracted with EtOAc (20 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% ethyl acetate/Petroleum ether gradient @ 25 mL/min) and the organic layer was concentrated in vacuo to give 2-bromo-5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazine (1.1 g, 3.5 mmol, 83 % yield) as a yellow solid.

[1225] *Step 3.* A mixture of 2-bromo-5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazine (201 mg, 1 Eq, 637.5 μmol), (E)-N'-(1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-ylidene)-4-methylbenzenesulfonohydrazide (300 mg, 1 Eq, 637.5 μmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)ComplexWithDichloromethane (52 mg, 0.1 Eq, 63.8 μmol), 2-(Dicyclohexylphosphanyl)-2',4',6'-tris(isopropyl)biphenyl (152 mg, 0.5 Eq, 319 μmol) and t-BuOLi (102 mg, 2 Eq, 1.3 mmol) in dioxane (12 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. TLC (petroleum ether: ethyl acetate =1:1, R_f =0.4 UV) showed one main new spot was formed. The reaction mixture was diluted with H_2O 50 mL and extracted with ethyl acetate 200 mL (100

mL * 2). The combined organic layers were washed with brine 50 mL, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 18 mL/min). Compound 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (320 mg, 0.55 mmol, 87 % yield, 90% purity) was obtained as a yellow oil.

[1226] ***Step 4.*** To a mixture of 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 383 μmol) and diisopropylethylamine (74.3 mg, 99 μL, 1.5 Eq, 575 μmol) in DCM (10 mL) was added pyridinium bromide perbromide (123 mg, 1 Eq, 383 μmol) at 0 °C, then the mixture was stirred at 0 °C for 1 h. TLC (petroleum ether: ethyl acetate =1:1, R_f =0.6 UV) showed one main new spot was observed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) and the organic layer was concentrated in vacuum to give 7-bromo-6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (210 mg, 350 μmol, 91.2 % yield) as a white solid. LC-MS (ESI+) m/z: 602.3 $(M+H)^+$.

[1227] ***Step 5.*** A mixture of 7-bromo-6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (210 mg, 1 Eq, 350 μmol), 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (23 mg, 0.1 Eq, 35 μmol), Na_2CO_3 (111 mg, 3 Eq, 1 mmol) and phenylboronic acid (52 mg, 1.2 Eq, 420 μmol) in dioxane (8 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. TLC (petroleum ether: ethyl acetate =5:1, R_f =0.5 UV) showed one main new spot was observed. The reaction mixture was diluted with 50 mL H_2O and extracted with 100 mL ethyl acetate. The combined organic layers were washed with 30 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 18 mL/min). Compound 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazin-2-yl)-1-fluoro-7-

phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 0.30 mmol, 85 % yield, 89% purity) was obtained as a yellow oil. LC-MS (ESI+) m/z: 598.2 $(M+H)^+$.

[1228] ***Step 6.*** A mixture of 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyrazin-2-yl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 335 μmol) in DCM (3 mL) and TFA (1 mL) was stirred at 50 °C for 1 h. The reaction mixture was slowly added to a large amount of saturated $NaHCO_3$ solution in order to make the pH adjust to 7. Then the solution was diluted with 30 mL H_2O and extracted with ethyl acetate 60 mL. The combined organic layers were washed with 20 mL brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyrazin-2-yl)piperidine-4-carbaldehyde (110 mg, 235 μmol, 70 % yield) as a yellow oil. LC-MS (ESI+) m/z: 468.3 $(M+H)^+$.

[1229] ***Step 7.*** A mixture of 1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyrazin-2-yl)piperidine-4-carbaldehyde (110 mg, 1 Eq, 235 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (86 mg, 1 Eq, 235 μmol), sodium acetate (58 mg, 38 μL, 3 Eq, 706 μmol) and acetic acid (43 mg, 41 μL, 3 Eq, 706 μmol) in DCM (4 mL) and MeOH (4 mL) was stirred at 30 °C for 0.5 h, then sodium triacetoxyborohydride (100 mg, 2 Eq, 471 μmol) was added in the mixture and stirred at 30 °C for 16 h. The mixture was added H_2O (20 mL), then extracted with EtOAc (20 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep-HPLC: Column: Welch Xtimate C18 150*30mm*5um Condition: A: water (FA) B: ACN at the beginning: A (71%) and B (29%) at the end: A (41%) and B (59%) Gradient Time (min) 7; 100%B Hold Time (min) 6.7; Flow Rate (ml/min) 25. Then the residue was purified by prep-HPLC: Column: Welch Xtimate C18 150*30mm*5um Condition: A: water (FA) B: ACN at the beginning: A (70%) and B (30%) at the end: A: (40%) and B (60%) Gradient Time (min) 6; 100%B Hold Time (min) 1; Flow Rate (ml/min) 30. The residue was purified by prep-HPLC finally: Column: Phenomenex C18 75*30mm*3um Condition: A: water (NH_3H_2O+NH_4HCO_3) B: ACN at the beginning: A (43%) and B (57%) at the end: A: (13%) and B (87%) Gradient Time (min) 8; 100%B Hold Time (min) 2; Flow Rate (ml/min) 25.The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(5-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyrazin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (3 mg, 4 μmol, 2 %) as a white solid. LCMS, HPLC, SFC and NMR confirmed.

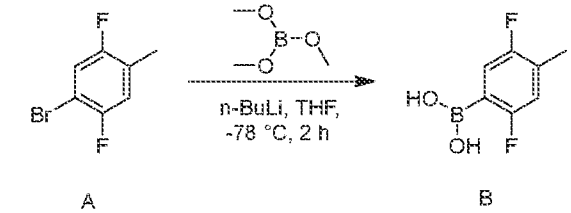
[1230] LC-MS (ESI$^+$) *m/z*: 780.5 $(M+H)^+$.

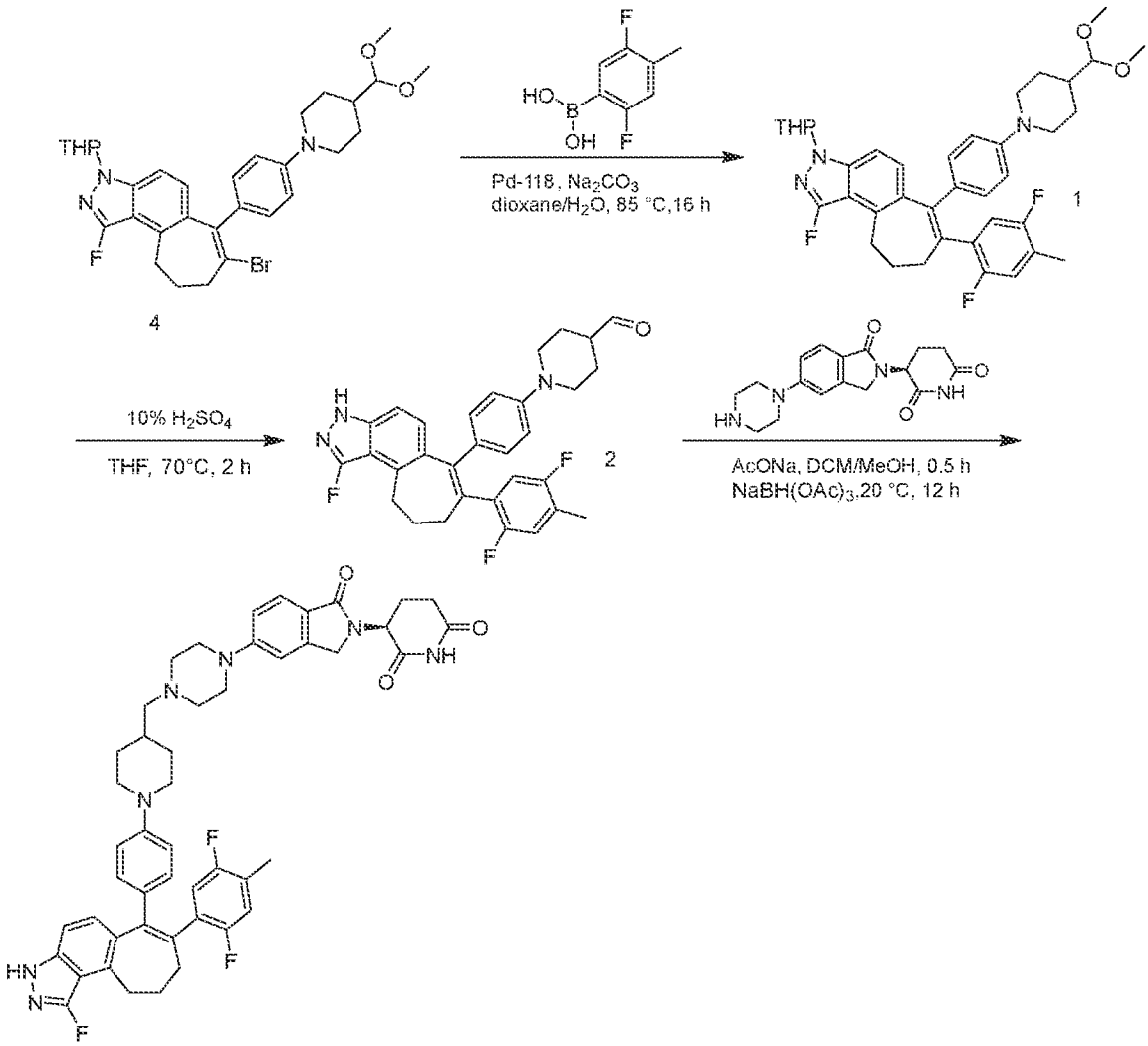
[1231] HPLC: 94.285%, purity at 220 nm.

[1232] SFC: Rt: 3.761 min; Area, 89.859%; method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

[1233] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.91 (s, 1 H) 7.48 - 7.58 (m, 2 H) 7.06 (br s, 6 H) 6.96 - 7.03 (m, 2 H) 6.72 - 6.81 (m, 1 H) 5.00 (dd, *J*=13.41, 5.19 Hz, 1 H) 4.24 - 4.37 (m, 2 H) 4.18 (br d, *J*=13.71 Hz, 2 H) 3.25 - 3.39 (m, 4 H) 3.11 (br t, *J*=6.79 Hz, 2 H) 2.74 - 2.83 (m, 3 H) 2.59 - 2.70 (m, 4 H) 2.23 - 2.43 (m, 7 H) 2.00 - 2.09 (m, 1 H) 1.75 - 1.88 (m, 3 H) 1.04 - 1.27 (m, 3 H)

Example 61. Synthesis of (S)-3-(5-(4-((1-(4-(7-(2,5-difluoro-4-methylphenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-106





[1234] ***Step 1.*** To a solution of 2,5-difluoro-4-bromotoluene (1 g, 1 Eq, 4.8 mmol) in THF (30 mL) at -78° C was added n-butyllithium (371 mg, 2.3 mL, 2.5 molar, 1.2 Eq, 5.80 mmol) dropwise. After addition was complete, stirring was continued for 30 min. Trimethyl borate (753 mg, 826 µL, 1.5 Eq, 7.3 mmol) was added in one portion and stirring was continued for 2 h at -

78° C. TLC(petroleum ether: ethyl acetate=5/1, R_f=0.4 UV) showed new spot was formed. The reaction mixture was slowly warmed to room temperature, quenched with 1.5 M HCl (20 mL), and extracted with ethyl acetate (50 mL*2). The organic extract was washed with water, washed with saturated brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The boronic acid thus obtained were used in the next step without purification.

[1235] ***Step 2.*** A mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 1 Eq, 200 µmol), (2,5-difluoro-4-methylphenyl)boronic acid (40 mg, 1.1 Eq, 221 µmol), Na_2CO_3 (64 mg, 3 Eq, 601 µmol), 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (13 mg, 0.1 Eq, 20 µmol) in 1,4-dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.5 UV) showed one main new spot was observed. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a black solid. The black solid was subjected to column chromatography over silica gel (gradient elution: 0 – 30% EtOAc). The desired fractions were collected, and concentrated to dryness in vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(4-fluorophenyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 196 µmol, 97.5 % yield) as a yellow solid.

[1236] LC-MS (ESI+) m/z: 646.4$(M+H)^+$.

[1237] ***Step 3.*** To a solution of 7-(2,5-difluoro-4-methylphenyl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 1 Eq, 186 µmol) in THF (2 mL) was added 10%H_2SO_4 (4 g, 2 mL, 4 mmol). The mixture was stirred at 70 °C for 2 hr. The reaction was adjust to pH=8 with saturated aq.$NaHCO_3$ (20 mL). Then the mixture was added water (20 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a yellow oil of 1-(4-(7-(2,5-difluoro-4-methylphenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (90 mg, 0.17 mmol, 94 % yield).

[1238] *Step 4.* A solution of 1-(4-(7-(2,5-difluoro-4-methylphenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (90 mg, 1 Eq, 0.2 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (100 mg, 1.2 Eq, 206 μmol, $PhSO_3H$ salt) and sodium acetate (72 mg, 5 Eq, 0.9 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h. Then acetic acid (21 mg, 20 μL, 2 Eq, 0.4 mmol) and sodium triacetoxyhydroborate (74 mg, 2 Eq, 0.4 mmol) was added. The mixture was stirred at 20 °C for 12 hour. The mixture was filtered and the filter cake was washed with ethyl acetate (50 mL). The filtrate was treated with H_2O (50 mL), extracted with ethyl acetate (50 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue.

[1239] The residue was purified by prep-HPLC:

[1240] Column: Phenomenex C18 80*30mm*3um

[1241] Condition:

[1242] A: water (FA)

[1243] B: ACN

[1244] At the beginning: A (68%) and B (32%)

[1245] At the end: A: (38%) and B (62%)

[1246] Gradient Time (min) 7; 100% B Hold Time (min) 4.2; Flow Rate (ml/min) 25.

[1247] The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(7-(2,5-difluoro-4-methylphenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (55 mg, 66 μmol, 38 % yield, 98.9% purity) as a white solid.

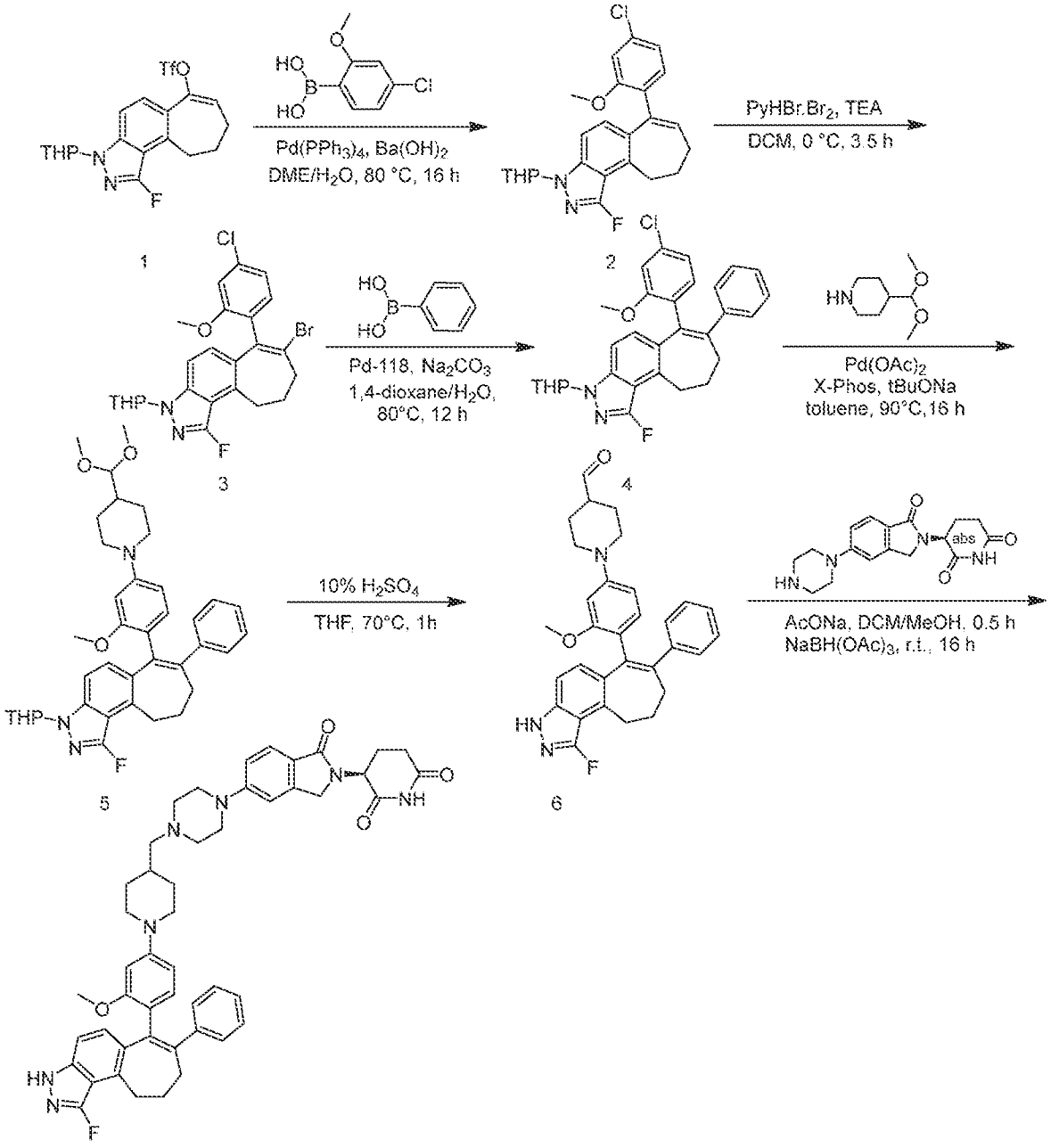
[1248] \LCMS: calc. for $C_{48}H_{48}F_3N_7O_3$: 827.95, found: $[M+H]^+$828.3

[1249] HPLC: 98.919 % purity at 220 nm.

[1250] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.55 (s, 1H), 10.96 (s, 1H), 8.14 (s, 0.212H), 7.55 (br d, J = 6.4 Hz, 1H), 7.24 (dd, J = 2.5, 8.7 Hz, 1H), 7.18 - 6.97 (m, 4H), 6.81 (d, J = 8.8 Hz, 1H), 6.71 (s, 4H), 5.06 (dd, J = 5.1, 13.4 Hz, 1H), 4.42 - 4.14 (m, 2H), 3.66 (br d, J = 11.3 Hz, 2H), 3.34 (s, 8H), 3.09 (br s, 2H), 2.97 - 2.87 (m, 1H), 2.61 (br s, 3H), 2.38 (br dd, J = 4.6, 13.0 Hz, 1H), 2.33 - 2.10 (m, 9H), 2.01 - 1.93 (m, 1H), 1.89 - 1.62 (m, 3H), 1.30 - 1.11 (m, 2H)

[1251] SFC: retention time, 2.998 min; Area, 91.996%; Method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

Example 62. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-109



[1252] ***Step 1.*** $Pd(PPh_3)_4$ (85 mg, 0.1 eq, 73.7 μmol) was added to the mixture of 4-chloro-2-methoxyphenylboronic acid (165 mg, 1.2 eq, 884 μmol), 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yltrifluoromethanesulfonate (320 mg, 1 eq, 737 μmol)

and barium hydroxide (379 mg, 3 eq, 2.21 mmol) in DME (20 mL) and H_2O (10 mL) at r.t. N_2 was bubbled into the mixture for 5 min, then the reaction mixture was stirred at 80 °C for 16 hour. The mixture was added with H_2O (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 70/30). The pure fractions were collected and concentrated to dryness in vacuum to give 6-(4-chloro-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (270 mg, 97.659% purity, 83.8% yield) as a yellow solid. LC-MS (ESI^+) m/z: 427.2 $(M+H)^+$.

[1253] ***Step 2.*** A mixture of 6-(4-chloro-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (240 mg, 1 eq, 562 μmol) and TEA (85 mg, 118 μL, 1.5 eq, 843 μmol) in DCM (10 mL) at 0 °C was added pyridinium bromide perbromide (180 mg, 1 eq, 562 μmol), then the mixture was stirred at 0 °C for 3.5 hour. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 100% ethyl acetate in petroleum ether). The desired fractions were collected and concentrated to dryness in vacuum to give 7-bromo-6-(4-chloro-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (275 mg, 99.5% purity, 96.2% yield) as a white solid. LC-MS (ESI^+) m/z: 507.2 $(M+H)^+$.

[1254] ***Step 3.*** Pd-118 (35 mg, 0.1 eq, 544 μmol) was added to the mixture of 7-bromo-6-(4-chloro-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (275 mg, 1 eq, 544 μmol), benzeneboronic acid (80 mg, 1.2 eq, 652 μmol) and sodium carbonate (173 mg, 3 eq, 1.63 mmol) in 1,4-dioxane (16 mL) and H_2O (4 mL) at r.t. Then the mixture was bubbled with N_2 for 3 min and was heated to 80 °C for 16 hour. The mixture was diluted with H_2O (20 ml) and was extracted with ethyl acetate (20 ml * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a dark oil. The dark oil was purified by silica gel column chromatography (petroleum ether/ethyl acetate from 100/0 to 80/20) to give 6-(4-chloro-2-methoxyphenyl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (230 mg, 77.4% yield, 92.05% purity) as a white solid. LC-MS (ESI^+) m/z: 503.0 $(M+H)^+$.

[1255] ***Step 4.*** A mixture of 6-(4-chloro-2-methoxyphenyl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (210 mg, 1 eq, 417 μmol), X-phos (39 mg, 0.2 eq, 83.5 μmol), palladium diacetate (14 mg, 0.15 eq, 62.6 μmol), 4-(dimethoxymethyl)piperidine (99 mg, 1.5 eq, 626 μmol) and sodium 2-methylpropan-2-olate (60 mg, 1.5 eq, 626 μmol) in toluene (8 mL) was bubbled with N_2 for 3 min and was heated to 90 °C for 16 hour under N_2. The mixture was diluted with H_2O (20 ml) and was extracted with ethyl acetate (20 ml * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a dark oil. The dark oil was purified by silica gel column chromatography (petroleum ether / ethyl acetate from 100/0 to 80/20) to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 85.86% purity, 65.7% yield) as a off-white solid. LC-MS (ESI^+) m/z: 626.2 $(M+H)^+$.

[1256] ***Step 5.*** A solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-1-fluoro-7-phenyl-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 1 Eq, 160 μmol) in THF (1.5 mL) and 10% H_2SO_4 (3 mL) was stirred at 70 °C for 1 hour . The reaction mixture was poured into saturated aqueous. $NaHCO_3$ solution (20 ml), then extracted with ethyl acetate (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (75 mg, crude) as a light red oil. The residue was used for the next step without purification.

[1257] ***Step 6.*** A mixture of 1-(4-(1-fluoro-7-phenyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (75 mg, 1 Eq, 0.15 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (61 mg, 1.1 Eq, 0.17 mmol, HCl salt) and sodium acetate (62 mg, 5 Eq, 0.76 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h, then acetic acid (18 mg, 17 μL, 2 Eq, 0.3 mmol) and sodium triacetoxyhydroborate (64 mg, 2 Eq, 0.3 mmol) was added. The mixture was stirred at 25 °C for 16 hour. The mixture was diluted with H_2O (20 ml) and was extracted with DCM (20 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B% 29%-59%, 7 min). The desired fractions were lyophilized under vacuum to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-phenyl-3,8,9,10-

tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (37.5 mg, 99.218% purity, 30.1% yield) as a white solid. LC-MS (ESI$^+$) m/z: 808.6 (M+H)$^+$.

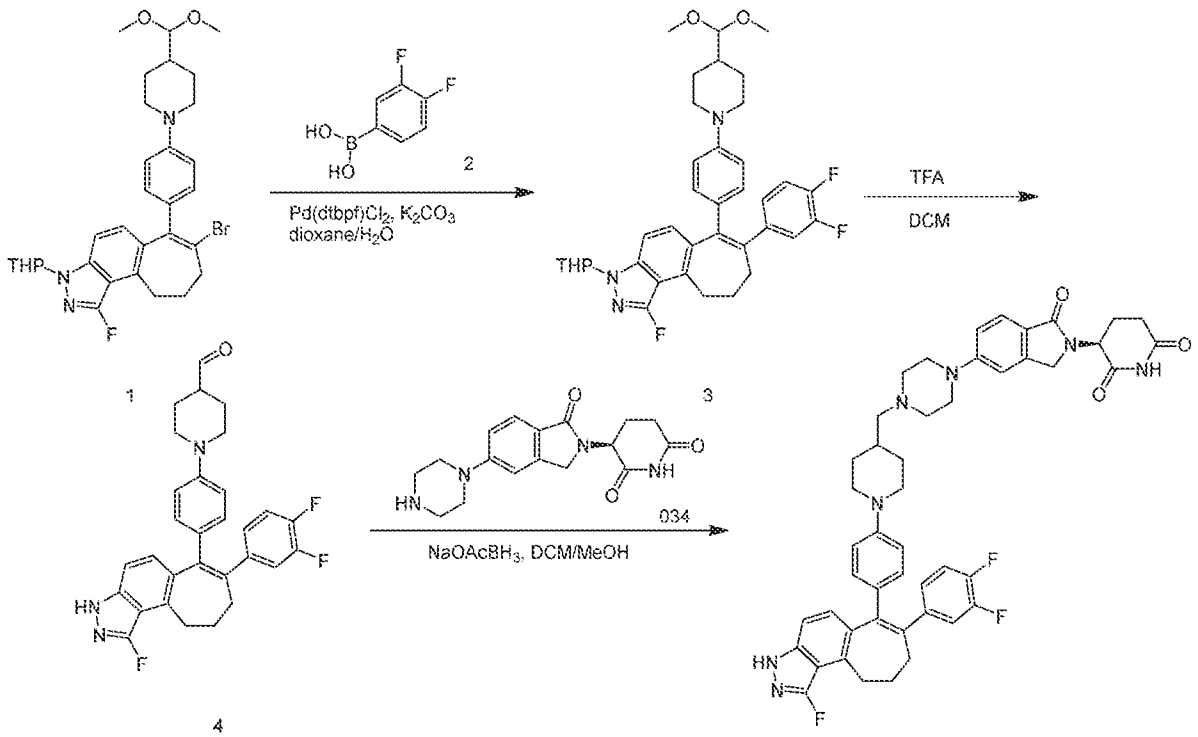
[1258] LCMS: calc. for $C_{48}H_{50}FN_7O_4$: 807.39, found: $[M+H]^+$ 808.6.

[1259] HPLC: 99.218% purity at 220 nm.

[1260] ^{1}H NMR (400 MHz, Methanol-d_4) δ = 8.43 - 8.39 (m, 0.309H), 7.69 - 7.64 (m, 1H), 7.21 - 7.16 (m, 2H), 7.15 - 7.03 (m, 6H), 6.93 (d, J = 8.7 Hz, 1H), 6.75 - 6.70 (m, 1H), 6.47 - 6.43 (m, 1H), 6.38 (dd, J = 2.1, 8.4 Hz, 1H), 5.12 (dd, J = 5.2, 13.3 Hz, 1H), 4.48 - 4.36 (m, 2H), 3.69 - 3.61 (m, 2H), 3.47 - 3.41 (m, 7H), 3.25 (br s, 2H), 2.94 - 2.86 (m, 1H), 2.85 - 2.75 (m, 5H), 2.68 (br t, J = 11.3 Hz, 2H), 2.54 - 2.44 (m, 3H), 2.44 - 2.31 (m, 4H), 2.21 - 2.11 (m, 1H), 1.91 (br d, J = 12.5 Hz, 2H), 1.86 - 1.76 (m, 1H), 1.44 - 1.31 (m, 2H)

[1261] SFC: retention time, 2.806 min; Area, 96.544%; method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 63. Synthesis of (S)-3-(5-(4-((1-(4-(7-(3,4-difluorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-105



[1262] ***Step 1.*** A mixture of Compound 1 (300 mg, 501 μmol, 1 eq.), (3,4-difluorophenyl)boronic acid (95.0 mg, 601 μmol, 1.2 eq.) , $PdCl_2$(dppf) (36.7 mg, 50.1 μmol, 0.1 eq.) and K_2CO_3 (208 mg, 1.50 mmol, 3 eq.) in Dioxane (10 mL) and Water (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hour under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition EA 10 mL at 20 °C, and then diluted with water 10 mL and extracted with EA 90 mL (30 mL * 3). The combined organic layers were washed with EA 15 mL (5 mL * 3), dried over Na_2SO4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 4/1) to give Compound 3 (250 mg, 396 μmol, 79.0 %) as a yellow solid.LC-MS (ESI^+) m/z: 632.2 $(M+H)^+$.

[1263] ^1H NMR (400 MHz, DMSO-d_4) δ : ppm 7.48 (d, J=9.20 Hz, 1 H), 7.16 - 7.33 (m, 2 H), 6.96 - 7.09 (m, 1 H), 6.88 (d, J=8.80 Hz, 1 H), 6.59 - 6.79 (m, 4 H), 5.74 (d, J=10.0 Hz, 1 H), 4.01 - 4.10 (m, 1 H), 3.81 - 3.90 (m, 1 H), 3.59 - 3.72 (m, 3 H), 3.26 (s, 6 H), 2.99 - 3.11 (m, 2 H), 2.64 - 2.72 (m, 1 H), 2.30 - 2.36 (m, 1 H), 2.25 (s, 5 H), 1.92 - 2.04 (m, 2 H), 1.61 - 1.74 (m, 4 H), 1.55 (s, 2 H), 1.21 - 1.31 (m, 2 H).

[1264] ***Step 2.*** To a solution of Compound 3 (250 mg, 396 μmol, 1 eq.) in DCM (6 mL) and TFA (2 mL). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The mixture was concentrated in vacuo to give crude product. No further purification as it is used for the next step directly.

[1265] LC-MS (ESI^+) m/z: 502.3 $(M+H)^+$.

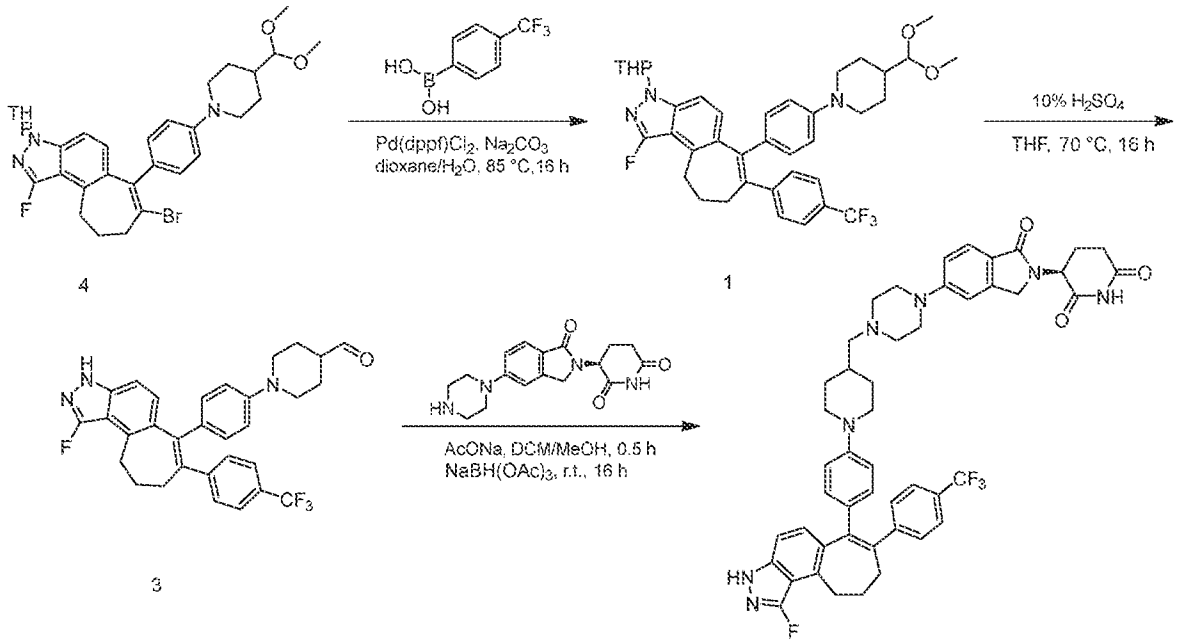
[1266] ***Step 3.*** To a solution of Compound 4 (100 mg, 199 μmol,1 eq.) and (S)-3-(1-oxo-5-(piperazin -1-yl)isoindolin-2-yl)piperidine -2,6-dione (78.5 mg, 239 μmol, 1.2 eq.) in DCE (5 mL) and MeOH (5 mL) was added Sodium triacetoxyborohydride (126.9 mg, 88.8 μL, 597 μmol, 3 eq.). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The crude was purified by prep.HPLC together (Phenomenex Gemini NX 150×30mm, 5μm, water(water(NH_4HCO_3) -ACN) as a mobile phase, from 65% to 95%, Gradient Time (min): 11, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(4-(7-(3,4-difluorophenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (32.2 mg, 39.6 μmol, 19.8 %) as a white solid.

[1267] LCMS: calc. for $C_{47}H_{46}F_3N_7O_3$:813.93, found: $[M+H]^+$ 814.4

[1268] HPLC: 100.00% purity at 220 nm.

[1269] ^1H NMR (400 MHz, METHANOL-d_4) δ : ppm 7.59 - 7.67 (m, 1 H), 7.13 - 7.18 (m, 1 H), 6.98 - 7.10 (m, 5 H), 6.88 - 6.92 (m, 1 H), 6.74 - 6.79 (m, 4 H), 5.05 - 5.14 (m, 1 H), 4.34 - 4.45 (m, 2 H), 3.61 - 3.69 (m, 2 H), 3.34 - 3.38 (m, 4 H), 3.13 - 3.20 (m, 2 H), 2.85 - 2.94 (m, 1 H), 2.74 - 2.80 (m, 1 H), 2.58 - 2.69 (m, 6 H), 2.42 - 2.50 (m, 1 H), 2.28 - 2.38 (m, 6 H), 2.11 - 2.18 (m, 1 H), 1.85 - 1.92 (m, 2 H), 1.70 - 1.79 (m, 1 H), 1.29 - 1.36 (m, 2 H).

Example 64. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(4-(trifluoromethyl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-107



[1270] ***Step 1.*** $Pd(dppf)Cl_2$ (16 mg, 0.1 Eq, 20 μmol) was added to the mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 1 Eq, 200 μmol), (4-(trifluoromethyl)phenyl)boronic acid (46 mg, 1.2 Eq, 241 μmol) and Na_2CO_3 (64 mg, 3 Eq, 601 μmol) in 1,4-Dioxane (5 mL) and H_2O (1 mL) at 25 °C, then the mixture was stirred at 25 °C for 12 hour. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.6, UV) showed one main new spot was observed. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a black solid. The white solid was subjected to column chromatography over silica gel (gradient

elution: 0 – 50% ethyl acetate).The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(4-(trifluoromethyl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (130 mg, 196 μmol, 97.7 % yield, 100% purity) s a white solid. LC-MS (ESI^+) m/z: 664.3 $(M+H)^+$.

[1271] ***Step 2.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2 H-pyran-2-yl)-7-(4-(trifluoromethyl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (125 mg, 1 Eq, 186 μmol) in THF (8 mL) was added 10% H_2SO_4 (4 g, 2 mL, 10% Wt, 4 mmol). And then the mixture was stirred at 70 °C for 40 min. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4, UV) showed a new spot was desired. The reaction was adjust to pH=8 with saturated aq.$NaHCO_3$ (15 mL). Then the mixture was added water (20 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine(20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give 1-(4-(1-fluoro-7-(4-(trifluoromethyl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (81 mg, 47 μmol, 31.28% purity, 26% yield) as a yellow solid.

[1272] ***Step 3.*** To a solution of 1-(4-(1-fluoro-7-(4-(trifluoromethyl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (81 mg, 31.28% purity, 1 Eq, 47.49 μmol) (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione benzene sulfonate (70 mg, 3 Eq, 0.14 mmol) and sodium acetate (19 mg, 5 Eq, 237.4 μmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 hour, Then acetic acid (6 mg, 5 μL, 2 Eq, 94.97 μmol) and sodium triacetoxyhydroborate (20 mg, 2 Eq, 94.97 μmol) was added the mixture and was stirred at 25 °C for 16 h. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*40mm;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B% 78%-100%,12 min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(4-(trifluoromethyl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (21.1 mg, 24.3 μmol, 51.2 % yield, 98.658% purity) as a white solid. LC-MS (ESI+) m/z: 846.2 $(M+H)^+$.

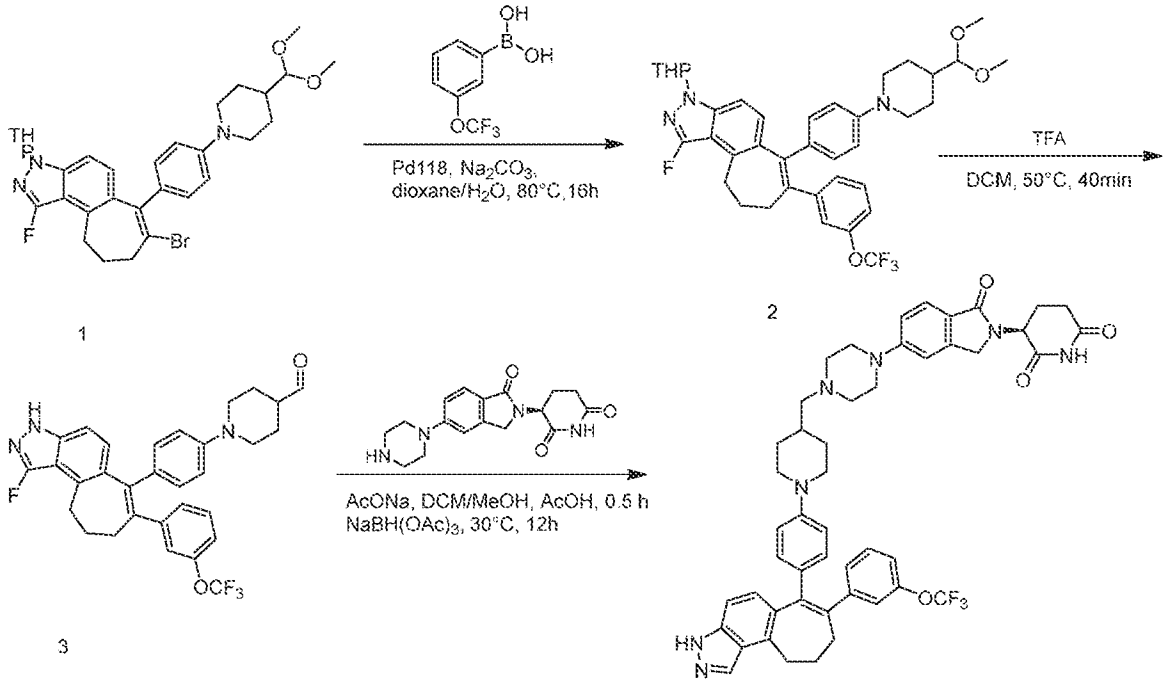
[1273] LCMS: calc. for $C_{48}H_{47}F_4N_7O_3$: 845.94, found: $[M+H]^+$ 846.2.

[1274] HPLC: 98.658% purity at 220 nm.

[1275] SFC: retention time, 3.042 min; Area, 88.651%; method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

[1276] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.53 (s, 1H), 10.94 (s, 1H), 7.58 - 7.49 (m, 3H), 7.41 (br d, J = 7.9 Hz, 2H), 7.27 - 7.20 (m, 1H), 7.09 - 7.01 (m, 2H), 6.82 (d, J = 8.8 Hz, 1H), 6.68 (s, 4H), 5.08 - 5.00 (m, 1H), 4.36 - 4.28 (m, 1H), 4.24 - 4.16 (m, 1H), 3.63 (br d, J = 12.4 Hz, 2H), 3.28 (br s, 6H), 3.08 (br t, J = 6.0 Hz, 2H), 2.96 - 2.84 (m, 1H), 2.64 - 2.54 (m, 3H), 2.38 - 2.26 (m, 4H), 2.25 - 2.13 (m, 4H), 2.00 - 1.91 (m, 1H), 1.77 (br d, J = 11.6 Hz, 2H), 1.72 - 1.62 (m, 1H), 1.26 - 1.08 (m, 3H).

Example 65. Synthesis of (3S)-3-[5-[4-[[1-[4-[1-fluoro-7-[3-(trifluoromethoxy)phenyl]-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-108



[1277] ***Step 1.*** A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (200 mg, 334 μmol, 1 eq), [3-(trifluoromethoxy)phenyl]boronic acid (68 mg, 334 μmol, 1 eq), disodium carbonate (106 mg, 1 mmol, 3 eq), Pd-118 (21 mg, 33 μmol, 0.1 eq) was added in dioxane (4 mL) and H_2O (1 mL) and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. the mixture was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL ×3), the combined organic layers were washed with saturated salt water (50 mL), and were dried with anhydrous Na_2SO_4, filtered, and concentrated to give a residue. the residue was

purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ethergradient @ 40 mL/min) to give 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-7-[3-(trifluoromethoxy)phenyl]-9,10-dihydro-8H-cyclohepta[e]indazole (150 mg, 220 μmol). LC-MS (ESI+) m/z: 680.2 (M+H) +

[1278] ***Step 2.*** A mixture of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-7-[3-(trifluoromethoxy)phenyl]-9,10-dihydro-8H-cyclohepta[e]indazole (150 mg, 220 μmol, 1 eq) was added in DCM (8 mL) and TFA (2 mL) and purged with N_2 for 3 times, the mixture was stirred at 50 °C for 40 min under N_2 atmosphere. the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and was treated with H_2O (50 mL) and was extracted with ethyl acetate (50*2 mL), the combined organic layers were washed with saturated salt water (50 mL), and were dried with anhydrous Na_2SO_4, filtered, and concentrated to give 1-(4-(1-fluoro-7-(3-(trifluoromethoxy)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (130 mg, crude) as a white solid.

[1279] ***Step 3.*** A mixture of 1-[4-[1-fluoro-7-[3-(trifluoromethoxy)phenyl]-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]piperidine-4-carbaldehyde (120 mg, 131 μmol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (57 mg, 157 μmol, 1.2 eq, HCl salt), AcONa (32 mg, 393 μmol, 3 eq) was added in the DCM (2 mL) and MeOH (2 mL), the mixture was stirred at 30 °C for 0.5 h, and then AcOH (23 mg, 393 μmol, 22 μL, 3 eq), $NaBH(OAc)_3$ (55 mg, 262 μmol, 2 eq) was added in the mixture and was stirred at 30 °C for 12 h, the reaction was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. the residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];gradient:32%-62% B over 7 min) to give (3S)-3-[5-[4-[[1-[4-[1-fluoro-7-[3-(trifluoromethoxy)phenyl]-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (43 mg, 49 μmol) was obtained as a white solid.

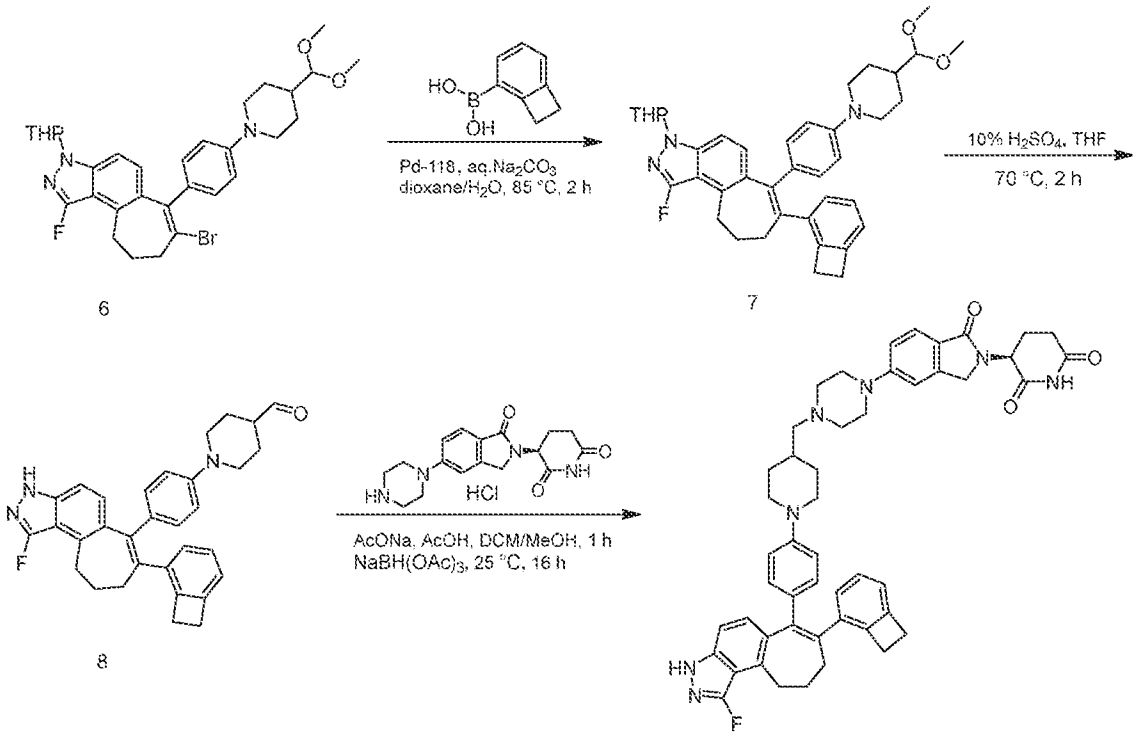
[1280] LC-MS (ESI+) m/z: 862.5 (M+H) +

[1281] HPLC: 95% purity at 220 nm

[1282] SFC: Rt: 2.740 min; Area: 88.865%;Method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

[1283] ^{1}H NMR (400 MHz, DMSO-d_6) δ= 12.60 (s, 1H), 11.02 (s, 1H), 8.20 (s, 0.203H), 7.58 (d, J = 8.7 Hz, 1H), 7.45 - 7.38 (m, 1H), 7.36 - 7.26 (m, 2H), 7.17 (br d, J = 8.3 Hz, 1H), 7.13 (s, 3H), 6.89 (d, J = 8.8 Hz, 1H), 6.79 - 6.67 (m, 4H), 5.11 (dd, J = 5.2, 13.4 Hz, 1H), 4.44 - 4.34 (m, 1H), 4.31 - 4.21 (m, 1H), 3.69(br d, J = 10.6 Hz, 2H), 3.34 (br s, 5H), 3.13 (br s, 2H), 3.04 - 2.89 (m, 1H), 2.78 - 2.61 (m, 4H), 2.52 - 2.22 (m, 9H), 2.08 - 1.97 (m, 1H), 1.91 - 1.71 (m, 3H), 1.31 - 1.12 (m, 2H).

Example 66. Synthesis of (S)-3-(5-(4-((1-(4-(7-(bicyclo[4.2.0]octa-1,3,5-trien-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-113



[1284] ***Step 1.*** A mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 334 µmol), bicyclo[4.2.0]octa-1,3,5-trien-2-ylboronic acid (64 mg, 1.3 Eq, 434 µmol), Na_2CO_3 (106 mg, 3 Eq, 1.00 mmol), Pd-118 (22 mg, 0.1 Eq, 33.4 µmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 85 °C for 2 hour under N_2 atmosphere. Then the reaction was cooled to room temperature. The mixture was treated with H_2O (100 mL), extracted with ethyl acetate (100 mL*2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 95%-100%, 2min). The aqueous

phase was lyophilized to dryness to give 7-(bicyclo[4.2.0]octa-1,3,5-trien-2-yl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (80 mg, 0.12 mmol, 36 % yield, 93.9% purity) as a yellow oil.

[1285] ***Step 2.*** A mixture of 7-(bicyclo[4.2.0]octa-1,3,5-trien-2-yl)-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (80 mg, 1 Eq, 0.12 mmol) in THF (3 mL) and 10% H_2SO_4 (9 mL) was stirred at 70 °C for 2 hour. Then the reaction was cooled to room temperature. The aqueous solution was added $NaHCO_3$ to adjust pH=6. The residue was dissolved in water (50 mL) and extracted by ethyl acetate (50 mL*2). The combined organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 1-(4-(7-(bicyclo[4.2.0]octa-1,3,5-trien-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (50 mg, 0.1 mmol, 84% yield) as a yellow oil. LC-MS (ESI+) m/z: 492.1 $(M+H)^+$

[1286] ***Step 3.*** A mixture of 1-(4-(7-(bicyclo[4.2.0]octa-1,3,5-trien-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (50 mg, 1 Eq, 0.1 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (48 mg, 1.3 Eq, 0.13 mmol), sodium acetate (42 mg, 5 Eq, 0.51 mmol) and acetic acid (18 mg, 18 µL, 3 Eq, 0.31 mmol) was added in DCM (2 mL) and MeOH (2 mL), then stirred at 25 °C for 1 hour, sodium triacetoxyborohydride (43 mg, 2 Eq, 0.20 mmol) was added to the mixture and stirred at 25 °C for 16 hour. The reaction was treated with H_2O (50 mL), extracted with ethyl acetate (50 mL*2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 25%-65%, 9min). The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(7-(bicyclo[4.2.0]octa-1,3,5-trien-2-yl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (9.2 mg, 11 µmol, 11 % yield, 97.567% purity) as a yellow solid.

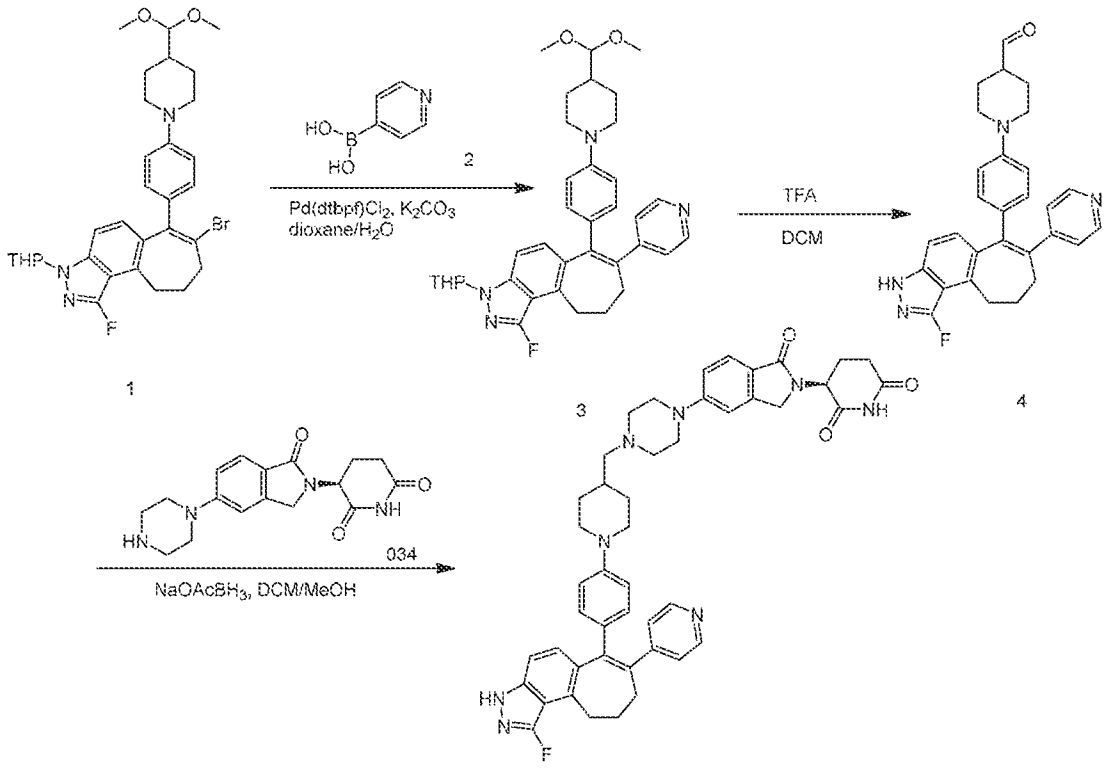
[1287] LC-MS (ESI+) m/z: 804.5 (M+H) +

[1288] HPLC: 97.567%, purity at 220 nm.

[1289] SFC: retention time, 3.687 min; Area, 95.327%; method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[1290] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.52 (s, 1H), 10.94 (s, 1H), 8.30 (br d, J = 16.1 Hz, 0.259H), 7.52 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 2.3, 8.8 Hz, 1H), 7.13 - 7.02 (m, 4H), 6.92 - 6.81 (m, 2H), 6.69 (s, 4H), 5.05 (dd, J = 5.0, 13.4 Hz, 1H), 4.40 - 4.29 (m, 1H), 4.25 - 4.15 (m, 1H), 3.65 (br d, J = 12.6 Hz, 2H), 3.32 - 3.20 (m, 7H), 3.02 (br s, 2H), 2.96 - 2.86 (m, 3H), 2.69 - 2.53 (m, 6H), 2.37 (br dd, J = 4.9, 13.6 Hz, 1H), 2.28 - 2.13 (m, 6H), 2.03 - 1.90 (m, 1H), 1.83 - 1.62 (m, 3H), 1.25 - 1.09 (m, 2H).

Example 67. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(pyridin-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-114



[1291] ***Step 1.*** A mixture of Compound 1 (150 mg, 251 μmol, 1 eq.), pyridin-4-ylboronic acid (33.9 mg, 276 μmol, 1.1 eq.), $PdCl_2$(dppf) (18.3 mg, 25.1 μmol, 0.1 eq.) and K_2CO_3 (104 mg, 752 μmol, 3 eq.) in Dioxane (10 mL) and Water (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hour under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition EA 10 mL at 20 °C, and then diluted with water 10 mL and extracted with EA 90 mL (30 mL * 3). The combined organic layers were washed with EA 15 mL (5 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica

gel column chromatography (from pure PE to PE/EtOAc = 4/1) to give Compound 3 (100 mg, 168 μmol, 66.9 %) as a yellow solid.

[1292] LC-MS (ESI^+) m/z: 597.5 $(M+H)^+$.

[1293] ^1H NMR (400 MHz, DMSO-d_4) δ : ppm 8.37 (d, J=6.00 Hz, 2 H), 7.50 (m, 1 H), 7.16 (d, J=6.00 Hz, 2 H), 6.89 (d, J=8.80 Hz, 1 H), 6.58 - 6.73 (m, 4 H), 5.75 (d, J=9.60 Hz, 1 H), 4.07 (d, J=6.80 Hz, 1 H), 3.83 - 3.92 (m, 1 H), 3.61 - 3.74 (m, 3 H), 3.26 (s, 6 H), 3.06 (t, J=6.40 Hz, 2 H), 2.67 (s, 1 H), 2.31 - 2.34 (m, 1 H), 2.19 - 2.30 (m, 5 H), 1.99 - 2.07 (m, 1 H), 1.89 - 1.97 (m, 1 H), 1.64 - 1.75 (m, 4 H), 1.50 - 1.60 (m, 2 H), 1.21 - 1.32 (m, 2 H).

[1294] *Step 2.* To a solution of Compound 3 (100 mg, 168 μmol, 1 eq.) in DCM (5 mL) and TFA (1.5 mL). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The mixture was concentrated in vacuo to give crude product. No further purification as it is used for the next step directly.

[1295] LC-MS (ESI^+) m/z: 467.3 $(M+H)^+$.

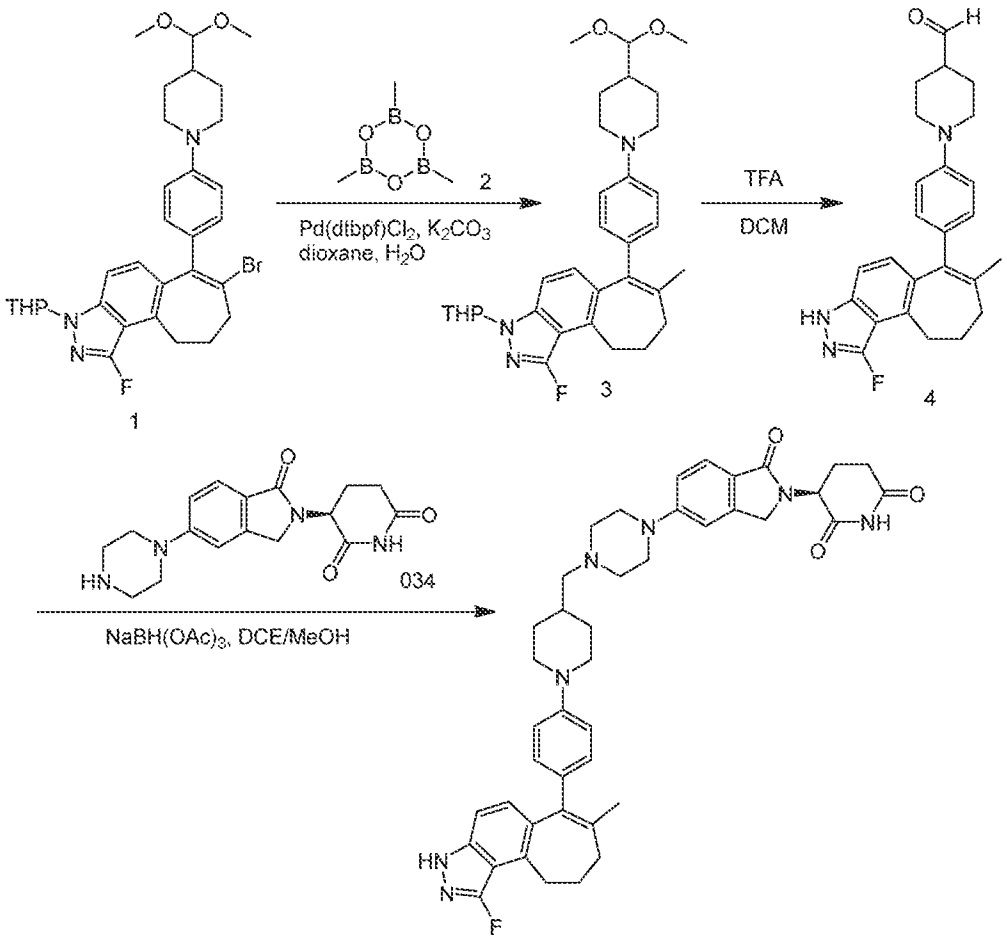
[1296] *Step 3.* To a solution of Compound 4 (45.0 mg, 96.5 μmol, 1 eq.) and (S)-3-(1-oxo-5-(piperazin -1-yl)isoindolin-2-yl)piperidine-2,6-dione (38.0 mg, 116 μmol, 1.2 eq.) in DCE (3 mL) and MeOH (3 mL) was added Sodium triacetoxyborohydride (71.5 mg, 50.0 μL, 338 μmol, 3.5 eq.). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The crude was purified by prep.HPLC together (Phenomenex Gemini NX 150×30mm,5μm, water(water(NH_4HCO_3)-ACN) as a mobile phase, from 50% to 80%, Gradient Time (min): 11, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(pyridin-4-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (12.0 mg, 15.4 μmol, 16.0 %) as a white solid.

[1297] LCMS: calc. for $C_{46}H_{47}FN_8O_3$:778.93, found: $[M+H]^+$ 779.4

[1298] HPLC: 100.00% purity at 220 nm.

[1299] ^1H NMR (400 MHz, METHANOL-d_4) δ : ppm 8.29 (d, J=6.00 Hz, 2 H), 7.56 - 7.68 (m, 1 H), 7.21 - 7.28 (m, 2 H), 7.15 - 7.21 (m, 1 H), 7.04 - 7.12 (m, 2 H), 6.88 - 6.94 (m, 1 H), 6.73 - 6.80 (m, 4 H), 5.09 (m, 1 H), 4.33 - 4.45 (m, 2 H), 3.62 - 3.70 (m, 2 H), 3.34 - 3.39 (m, 4 H), 3.18 (t, J=6.80 Hz, 2 H), 2.84 - 2.94 (m, 1 H), 2.73 - 2.81 (m, 1 H), 2.57 - 2.70 (m, 6 H), 2.39 - 2.51 (m, 3 H), 2.27 - 2.36 (m, 4 H), 2.11 - 2.19 (m, 1 H), 1.84 - 1.92 (m, 2 H), 1.68 - 1.78 (m, 1 H), 1.31 (m, 2 H).

Example 68. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-methyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-74



[1300] ***Step 1.*** A mixture of compound 1 (120.00 mg, 200.48 μmol, 1 eq), compound 2 (50.333 mg, 400.96 μmol, 2 eq), Pd(dppf)Cl2 (14.669 mg, 20.048 μmol, 0.1 eq), K_2CO_3 (55.413 mg, 400.96 μmol, 2 eq) in dioxane (6 mL) and H_2O (1.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hrs under N_2 atmosphere. LCMS showed the reaction was completed. The mixture was concentrated in reduced pressure. The residue was poured into water (8 mL). The aqueous phase was extracted with ethyl acetate (16 mL x 3). The combined organic phase was washed with brine (8 mL), dried with Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate= 3/1) to afford compound 3 (100 mg, 187 μmol, 93.5 %) as oil. LC-MS (ESI+) m/z: 534.8 (M+H)+.

[1301] ***Step 2.*** To a solution of compound 3 (100.0 mg, 187.4 μmol, 1 eq) in DCM (4 mL) was added TFA (64.09 mg, 43.31 μL, 62.1 μmol, 3 eq). The mixture was stirred at 25 °C for 0.5 hr.

LCMS showed the reaction was completed. The mixture was concentrated to give compound 4 (60.2 mg, 149 μmol, 79.6 %) as oil.

[1302] LC-MS (ESI^+) m/z: 404.1 $(M+H)^+$.

[1303] ***Step 3.*** To a solution of compound 4 (60.0 mg, 149 μmol, 1 eq) and compound 034 (48.8 mg, 149 μmol, 1 eq) in MeOH (4 mL) and DCE (6 mL) was added $NaBH(OAc)_3$ (63.0 mg, 44.1 μL, 297 μmol, 2 eq). The mixture was stirred at 25 °C for 0.5 hr. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini NX 150 ×30 mm x 5 μm; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 60%-90% B over 11 min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-methyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (17.3 mg, 24.2 μmol, 16.3 %) as a white solid. LC-MS (ESI^+) m/z: 716.4 $(M+H)^+$.

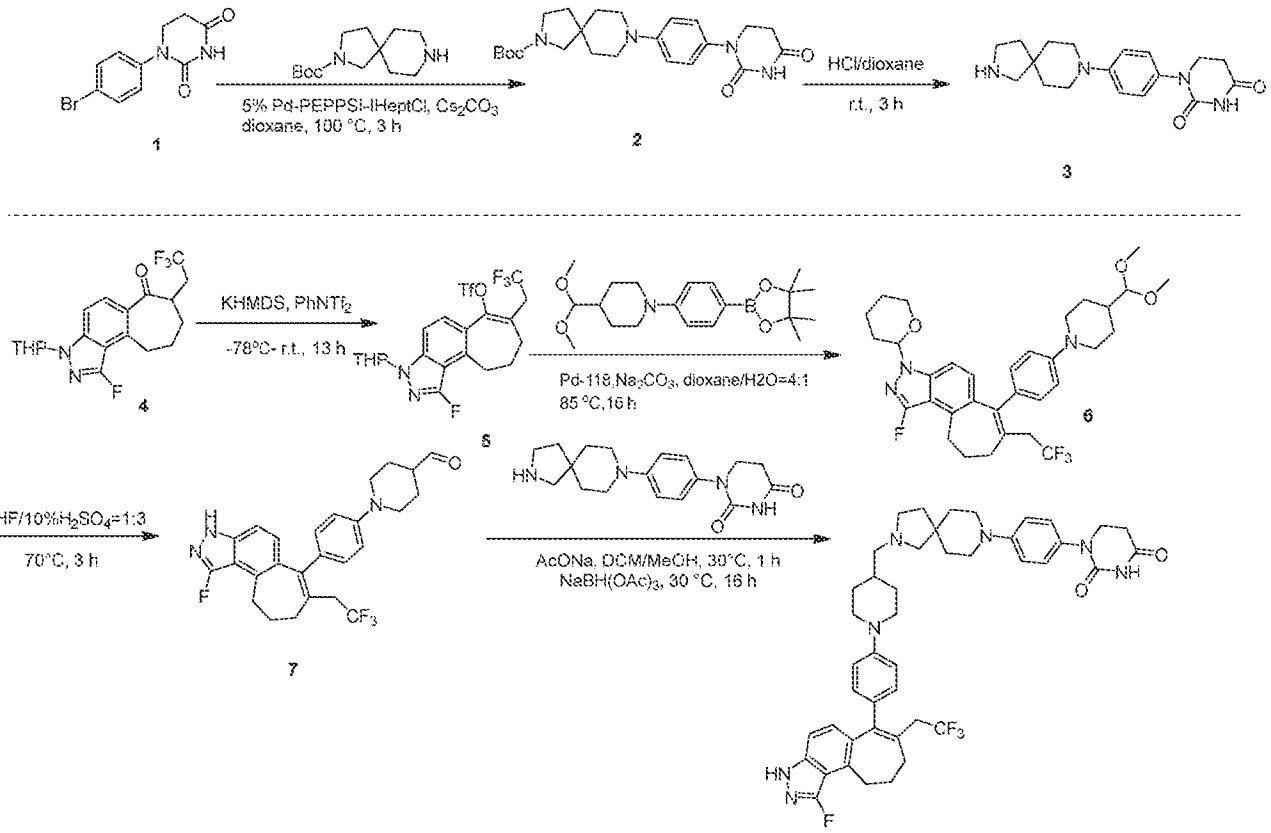
[1304] LCMS: calc. for $C_{42}H_{46}FN_7O_3$: 715.36, found: $[M+H]^+$ 716.4.

[1305] HPLC: 100% purity at 220 nm.

[1306] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.40 (s, 1 H) 10.94 (s, 1 H) 7.52 (d, J=8.46 Hz, 1 H) 7.15 (dd, J=8.88, 2.44 Hz, 1 H) 7.05 - 7.08 (m, 2 H) 6.89 (d, J=1.91 Hz, 4 H) 6.74 (d, J=8.70 Hz, 1 H) 5.05 (dd, J=13.29, 5.07 Hz, 1 H) 4.30 - 4.35 (m, 1 H) 4.18 - 4.23 (m, 1 H) 3.69 (br d, J=12.28 Hz, 2 H) 2.87 - 2.93 (m, 3 H) 2.66 (br s, 6 H) 2.26 - 2.39 (m, 4 H) 2.23 (br d, J=7.27 Hz, 2 H) 1.96 (s, 5 H) 1.64 - 1.92 (m, 7 H) 1.17 - 1.28 (m, 3 H)

Example 69. Synthesis of 1-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-

diazaspiro[4.5]decan-8-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (5.4 mg, 3.2 % yield, 99.4% purity), I-88



[1307] ***Step 1.*** A mixture of 1-(4-bromophenyl)dihydropyrimidine-2,4(1H,3H)-dione (300 mg, 1 Eq, 1.11 mmol), tert-butyl 2,8-diazaspiro[4.5]decane-2-carboxylate (320 mg, 1.2 Eq, 1.34 mmol), Pd-PEPPSI-IHeptCl (108 mg, 0.1 Eq, 111 μmol) and cesium carbonate (1.1 g, 3 Eq, 3.34 mmol) in dioxane (8 mL) was stirred at r.t. N_2 was bubbled into the mixture for 5 min. Then the reaction was heated at 100 °C for 3 h. The mixture was added H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 0/100 and DCM/MeOH from 100/0 to 80/20). The pure fractions were collected and concentrated to dryness in vacuum to give a yellow solid. The yellow solid was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B% 15%-52%, 9 min) to give tert-butyl 8-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-2,8-diazaspiro[4.5]decane-2-carboxylate (120 mg, 20.9 % yield, 83.4 % purity) as a white solid. LCMS (ESI+) m/z: 429.3 $(M+H)^+$.

[1308] *Step 2.* A mixture of tert-butyl 8-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-2,8-diazaspiro[4.5]decane-2-carboxylate (120 mg, 1 Eq, 234 μmol) in HCl/dioxane (10 mL) was stirred at 25 °C for 3 h. The mixture was concentrated to dryness in vacuum to give 1-(4-(2,8-diazaspiro[4.5]decan-8-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (70 mg, 91 % yield) as a grey solid. TLC (DCM/MeOH=10:1, R_f=0.3) confirmed.

[1309] *Step 3.* Hexamethyldisilazane potassium solution (2 mL, 1 molar, 1.5 Eq, 1.95 mmol) in THF (4 mL) was stirred at -78°C under N_2 atmosphere. Then 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (500 mg, 1 Eq, 1.30 mmol) in THF (2 mL) was added to the mixture and stirred at -78°C for 1 h, then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (558 mg, 1.2 Eq, 1.56 mmol) in THF (2 mL) was add to the mixture at -78 °C, then the reaction was warmed to 25°C and stirred for 12 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) at 0°C, then the mixture was added H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 70/30). The pure fractions were collected and concentrated to dryness in vacuum to give 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (800 mg, 60 % yield, 50 % purity) as a yellow oil.

[1310] *Step 4.* A mixture of 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (800 mg, 1 Eq, 775 μmol), 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (560 mg, 2 Eq, 1.55 mmol), sodium carbonate (246 mg, 3 Eq, 2.32 mmol) and 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (51 mg, 0.1 Eq, 77.5 μmol) in dioxane (8 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 85 °C for 16 h under N_2 atmosphere. The reaction mixture was added H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 70/30). The pure fractions were collected and concentrated to dryness in vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-

(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (400 mg, 82.7% yield, 96.4% purity) as a white solid. LC-MS (ESI+) m/z: 602.2 $(M+H)^+$.

[1311] ***Step 5.*** A mixture of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 320 μmol) in THF (2 mL) and 10% H_2SO_4 (6 mL) was stirred at 70 °C for 3 h. The reaction was adjust to pH=8 with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C. Then the mixture was added H_2O (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (180 mg, 96.3 % yield, 80.8% purity) as a yellow solid. LC-MS (ESI+) m/z: 472.1 $(M+H)^+$.

[1312] ***Step 6.*** A mixture of 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (0.16 g, 1.3 Eq, 0.28 mmol) , 1-(4-(2,8-diazaspiro[4.5]decan-8-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (70 mg, 1 Eq, 0.21 mmol), sodium acetate (87 mg, 5 Eq, 1.1 mmol) and acetic acid (38 mg, 37 μL, 3 Eq, 0.64 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 30 °C for 1 h, then sodium triacetoxyborohydride (90 mg, 2 Eq, 0.43 mmol) was added to the mixture and stirred at 30 °C for 16 h. Then the mixture was added H_2O (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The yellow solid was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B% 15%-55%, 9 min) to give 1-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (5.4 mg, 3.2 % yield, 99.4% purity) as a white solid. LC-MS (ESI+) m/z: 784.4 $(M+H)^+$.

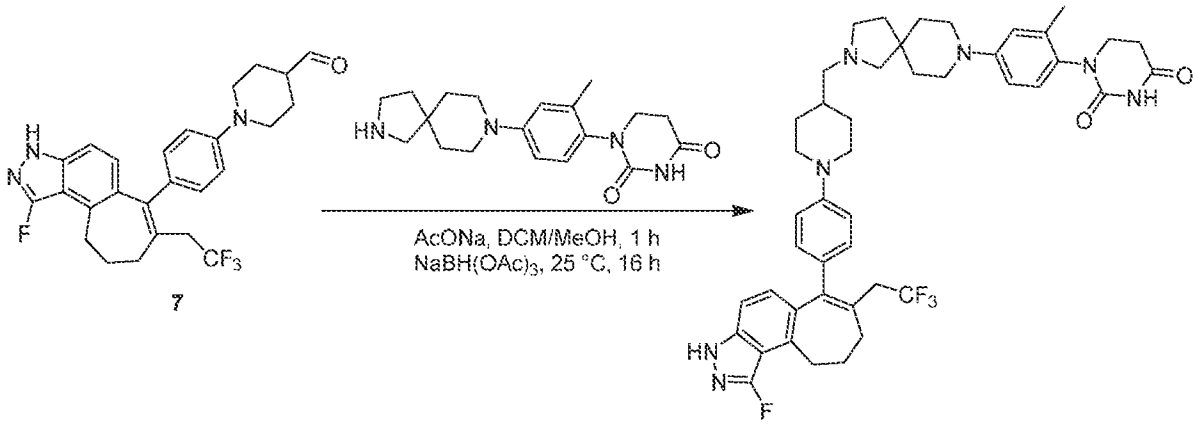
[1313] LCMS: calc. for $C_{44}H_{49}F_4N_7O_2$: 783.39, found: $[M+H]^+$ 784.4.

[1314] HPLC: 99.471 % purity at 220 nm.

[1315] ^{1}HNMR (400MHz, DMSO-d_6) δ = 12.50 (s, 1H), 10.26 (s, 1H), 8.23 (s, 0.504H), 7.19 (dd, J=2.6, 8.8 Hz, 1H), 7.13 (d, J=8.9 Hz, 2H), 6.96 - 6.89 (m, 6H), 6.77 (d, J=8.8 Hz, 1H), 3.69 (br t, J=6.7 Hz, 3H), 3.17 - 3.06 (m, 6H), 2.97 (br s, 2H), 2.71 - 2.65 (m, 3H), 2.54 (br s, 3H), 2.39 - 2.25 (m, 5H), 2.07 - 2.00 (m, 2H), 1.82 (br d, J=11.7 Hz, 2H), 1.61 (br d, J=5.7 Hz, 8H), 1.28 - 1.12 (m, 3H)

[1316] SFC: retention time, 3.504 min; Area, 100 %; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 70. Synthesis of 1-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione, I-89



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[1317] A solution of 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (50 mg, 1 Eq, 0.1 mmol), 1-(2-methyl-4-(2,8-diazaspiro[4.5]decan-8-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (47 mg, 93.3% purity, 1.2 Eq, 0.1 mmol) and sodium acetate (43 mg, 5 Eq, 0.5 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 1 h, Then acetic acid (13 mg, 12 μL, 2 Eq, 0.2 mmol) and sodium triacetoxyhydroborate (45 mg, 2 Eq, 0.2 mmol) was added. The mixture was stirred at 25 °C for 16 h. The reaction was treated with H_2O (50 mL), extracted with ethyl acetate (50 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue.

[1318] The residue was purified by prep-HPLC:

[1319] Column: Welch Xtimate C18 150*30mm*5um

[1320] Condition:

[1321] A: water(FA)

[1322] B: ACN

[1323] at the beginning: A (74%) and B (26%)

[1324] at the end: A: (44%) and B (56%)

[1325] Gradient Time (min) 7; 100%B Hold Time (min) 3.2; Flow Rate (ml/min) 25.

[1326] The aqueous phase was lyophilized to dryness to give 1-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione (17.3 mg, 20.9 μmol, 20 %, 96.404% purity) as a white solid.

[1327] LCMS: calc. for $C_{45}H_{51}F_4N_7O_2$:797.94, found: $[M+H]^+$798.3

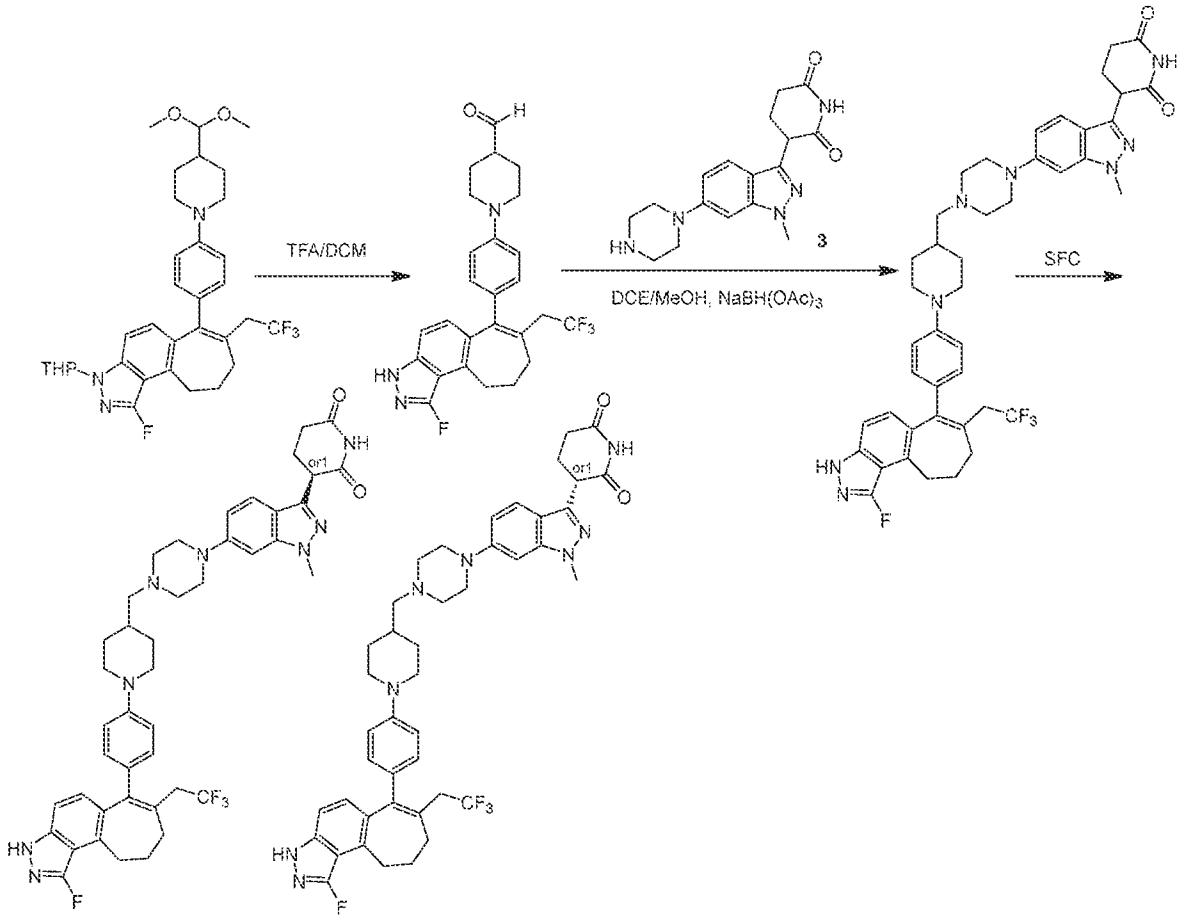
[1328] HPLC: 96.404 % purity at 220 nm.

[1329] SFC: retention time, 3.247 min; Area, 99.52%; Method: AS_ETOH_DEA_40_28ML_10CM

[1330] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.51 (s, 1H), 10.24 (s, 1H), 8.23 (s, 0.541H), 7.19 (dd, J = 2.4, 8.7 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.92 (s, 4H), 6.82 (d, J = 2.3 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 3.71 (br d, J = 12.5 Hz, 4H), 3.22 - 3.05 (m, 6H), 2.97 (br s, 2H), 2.73 - 2.61 (m, 4H), 2.56 (br t, J = 6.8 Hz, 2H), 2.39 (s, 2H), 2.29 (br d, J = 7.0 Hz, 4H), 2.12 (s, 3H), 2.04 (br d, J = 6.3 Hz, 2H), 1.82 (br d, J = 11.8 Hz, 2H), 1.61 (br d, J = 6.0 Hz, 7H), 1.20 (br d, J = 10.3 Hz, 2H)

Example 71. Synthesis of *rel*-(R)-3-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione, I-84, and *rel*-(R)-3-(6-(4-((1-(4-(1-fluoro-7-

(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione, I-85



[1331] ***Step 1.*** To a solution of compound 1 (200 mg, 332 μmol, 1 eq.) in DCM (3 mL) was added TFA (1 mL) at 20 °C. The mixture was stirred at 20 °C for 16 hours. LCMS showed the starting material was consumed completely and a major peak with desired MS was detected. Water (10 mL) and aq. $NaHCO_3$ (20x 2mL) was added and the mixture was extracted with DCM (30 mL x 3). The organics were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give compound 2 (150 mg, 67 % yield) as a white solid.

[1332] LC-MS (ESI^+) m/z: 472.2 $(M+H)^+$.

[1333] ***Step 2.*** To a solution of compound 2 (150 mg, 318 μmol, 1 eq.) and compound 3 (125 mg, 382 μmol, 1.2 eq.) in DCE (3 mL) and MeOH (1 mL) was added $NaBH(OAc)_3$ (337 mg, 236 μL, 1.59 mmol , 5 eq) at 20 °C. Then the mixture was stirred at 20 °C for 2 hours. LCMS showed the starting material was consumed completely and a major peak with desired MS was detected. The mixture was concentrated to get the crude, which was purified by prep-HPLC (column: Phenomenex Gemini NX 150×30mm, 5μm; mobile phase: [water (NH_4HCO_3)-ACN];

gradient: 65%-95% B over 11 min) to give compound 4 (70 mg, 27 % yield) as a white solid. LC-MS (ESI^+) m/z: 783.4 $(M+H)^+$.

[1334] *Step 3.*

[1335] Compound 4 (70 mg, 89 µmol, 1 eq.) was purified by SFC (Column: DAICEL CHIRALPAK ID (250mm*30mm, 10um); mobile phase: [MeOH-ACN]; gradient: 25%-25% B, Flow rate: 80 mL/min) to give rel-(R)-3-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione (16.0 mg, 22 % yield) as a white solid and rel-(R)-3-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione (12.5 mg, 18 % yield) as a white solid.

[1336] rel-(R)-3-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione:

[1337] LC-MS (ESI^+) m/z: 783.5 $(M+H)^+$.

[1338] LCMS: calc. for $C_{43}H_{46}F_4N_8O_2$: 782.89, found $[M+H]^+$ 783.5

[1339] HPLC: 96.59% purity at 220 nm

[1340] ^1H NMR (400 MHz, DMSO-d6) δ = 12.49 (s, 1H), 10.88 (s, 1H), 7.42 - 7.37 (m, 1H), 7.21 - 7.16 (m, 1H), 7.06 - 6.99 (m, 2H), 6.93 (s, 4H), 6.77 (d, J = 8.8 Hz, 1H), 4.39 - 4.29 (m, 1H), 4.24 (s, 3H), 3.73 (br d, J = 12.5 Hz, 2H), 3.29 - 3.23 (m, 2H), 3.18 - 3.05 (m, 2H), 3.01 - 2.80 (m, 6H), 2.71 - 2.61 (m, 4H), 2.34 - 2.25 (m, 6H), 2.20 - 2.14 (m, 1H), 2.03 (br t, J = 6.3 Hz, 2H), 1.87 - 1.69 (m, 3H), 1.28 - 1.13 (m, 3H)

[1341] rel-(R)-3-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione:

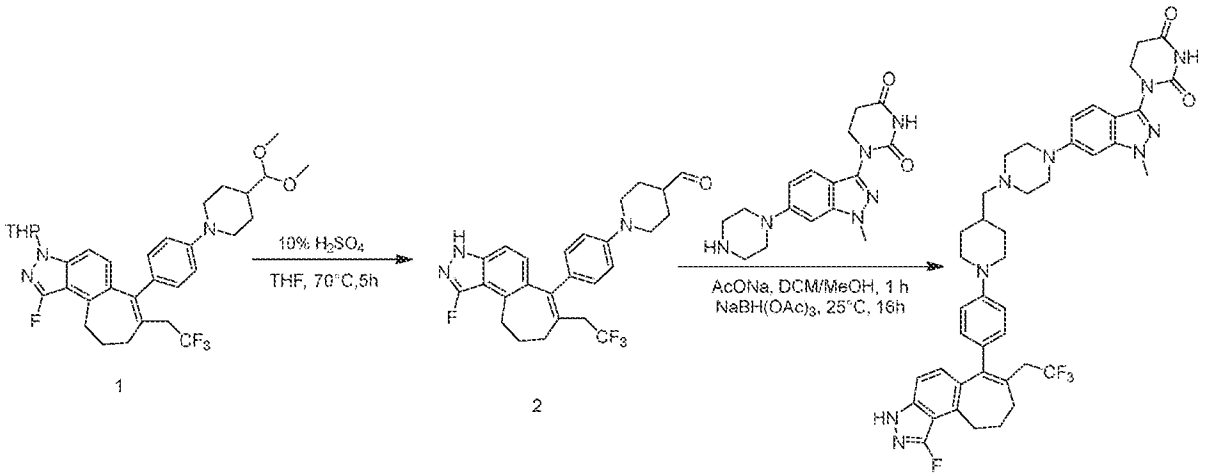
[1342] LC-MS (ESI^+) m/z: 783.4 $[M+H]^+$.

[1343] LCMS: calc. for $C_{43}H_{46}F_4N_8O_2$: 782.89, found $[M+H]^+$ 783.4

[1344] HPLC: 100.00% purity at 220 nm

[1345] ^{1}H NMR (400 MHz, DMSO-d6) δ = 12.49 (s, 1H), 10.88 (s, 1H), 7.42 - 7.36 (m, 1H), 7.22 - 7.16 (m, 1H), 7.09 - 6.99 (m, 2H), 6.92 (s, 4H), 6.77 (d, J = 8.7 Hz, 1H), 4.39 - 4.29 (m, 1H), 4.24 (s, 3H), 3.73 (br d, J = 12.0 Hz, 2H), 3.27 (br d, J = 11.4 Hz, 2H), 3.20 - 3.04 (m, 2H), 3.03 - 2.78 (m, 6H), 2.71 - 2.60 (m, 4H), 2.36 - 2.26 (m, 6H), 2.20 - 2.13 (m, 1H), 2.03 (br t, J = 6.8 Hz, 2H), 1.87 - 1.68 (m, 3H), 1.30 - 1.15 (m, 3H)

Example 72. Synthesis of 1-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, I-93



[1346] ***Step 1.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (70 mg, 1 Eq, 0.12 mmol) in 10% H_2SO_4 (6 mL) and THF (3 mL) was stirred at 70°C for 5 h. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.6, UV) showed a new spot was formed. The reaction was adjust to pH=8 with saturated aqueous $NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine(30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (70 mg, 0.12 mmol, 100 % yield, 79% purity) as a yellow solid.

[1347] ***Step 2.*** To a solution of 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (70 mg, 1 Eq, 0.15 mmol), 1-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (49 mg, 1 Eq, 0.15 mmol) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (37 mg, 3 Eq, 0.45 mmol) was stirred at 25 °C for 1 h, Then sodium triacetoxyborohydride (63 mg, 2 Eq,

0.30 mmol) and acetic acid (27 mg, 26 µL, 3 Eq, 0.45 mmol) was added. The mixture was stirred at 25 °C for 16 h. TLC (dichloromethane: methyl alcohol=10:1, R_f=0.6, UV) showed a new spot was formed. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 25%-55%,7min) to give 1-(6-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (36.2 mg, 45 µmol, 30 % yield, 97.43% purity) was obtained as a white solid. LC-MS (ESI^+) m/z: 784.4 (M+H)

[1348] *Step 3.* LCMS: calc. for $C_{42}H_{45}F_4N_9O_2$: 783.88, found: [M+H] + 784.4.

[1349] HPLC: 97.43% purity at 220 nm.

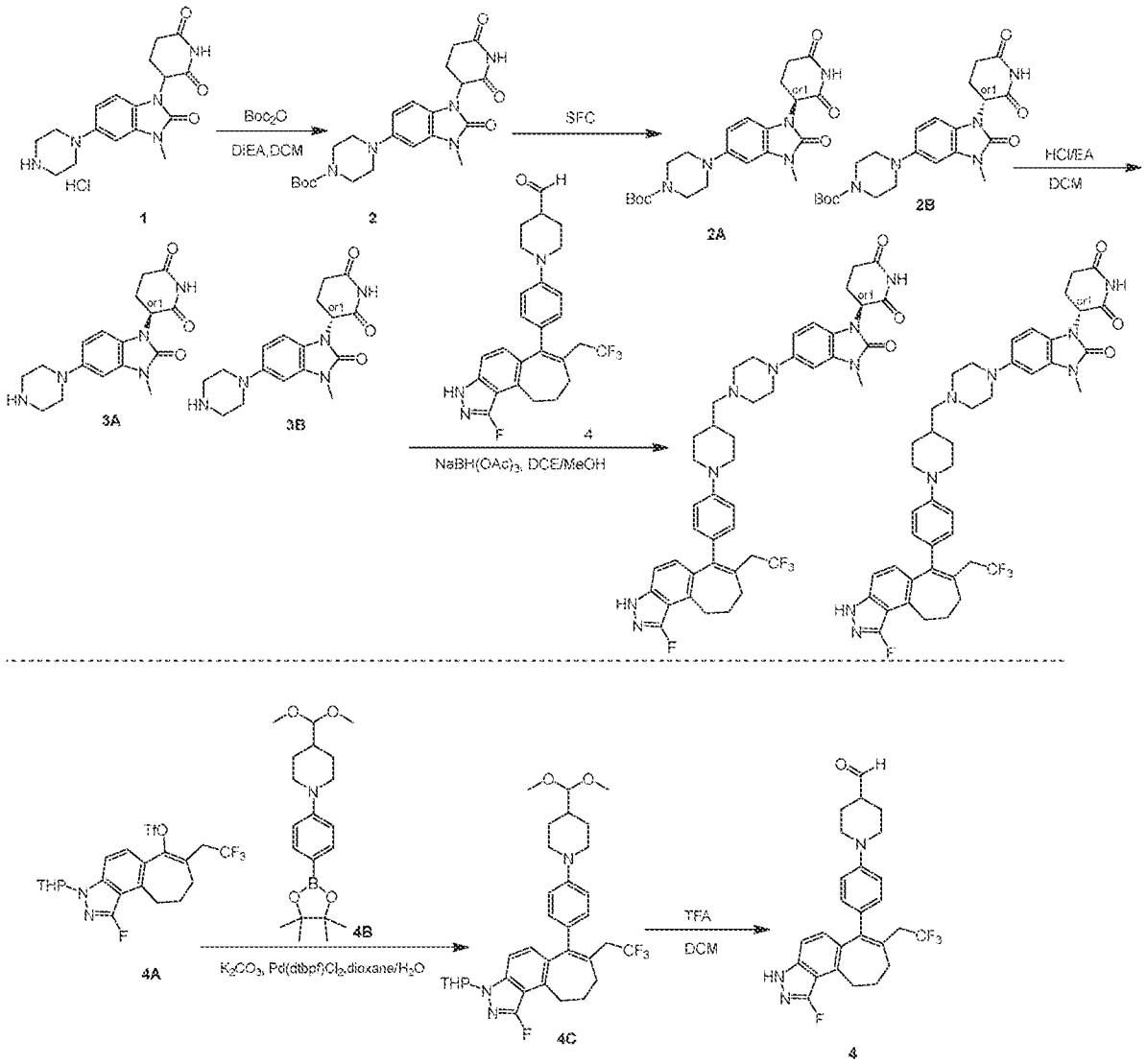
[1350] SFC: retention time, 3.407 min; Area, 98.485%;

[1351] Method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[1352] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.52 (s, 1H), 10.53 (s, 1H), 8.16 (s, 0.310H), 7.46 (d, J = 9.1 Hz, 1H), 7.19 (dd, J = 2.6, 8.8 Hz, 1H), 6.93 (s, 5H), 6.84 (s, 1H), 6.78 (d, J = 8.8 Hz, 1H), 3.89 (s, 5H), 3.73 (br d, J = 12.3 Hz, 2H), 3.30 (br s, 1H), 3.24 (br s, 5H), 2.97 (br s, 2H), 2.77 - 2.64 (m, 4H), 2.55 (br s, 4H), 2.32 (br s, 2H), 2.25 (br d, J = 7.2 Hz, 2H), 2.04 (s, 2H), 1.84 (br d, J = 11.7 Hz, 2H), 1.73 (br s, 1H), 1.24 (br s, 2H)

Example 73. Synthesis of *rel*-(R)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione, I-90, and *rel*-(R)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-

yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione, I-91



[1353] ***Step 1.*** To a solution of compound 1 (500 mg, 1.46 mmol, 1.0 eq.) in DCM (10 mL) were added DIPEA (151 mg, 203 μL, 1.16 mmol, 0.8 eq.) and Boc_2O (477 mg, 2.18 mmol, 1.5 eq.) at 20 °C. The mixture was stirred at 20 °C for 2 hr. LCMS showed the desired MS was detected. The mixture was concentrated to give a residue, which was purified by flash silica gel chromatography eluting with EtOAc in PE from 0% to 100% to give compound 2 (490 mg, 75.9 % yield) as a white solid.

[1354] LC-MS (ESI^+) m/z: 444.2 ($M+H^+$).

[1355] ***Step 2.*** Compound 2 (400 mg, 902 μmol, 1.0 eq.) was purified by SFC (Column: DAICEL CHIRALPAK IG (250mm*30mm, 10um); mobile phase: [CO_2-EtOH]; gradient: 60%-60% B, Flow rate: 80 mL/min) to yield peak 1 and peak 2.

[1356] Peak 1 was concentrated under reduced pressure to yield compound 2A (170 mg, 42.5 % yield) as a white solid. LC-MS (ESI^+) m/z: 443.4 $(M+H)^+$.

[1357] Peak 2 was concentrated under reduced pressure to yield compound 2B (170 mg, 42.5 % yield) as a white solid. LC-MS (ESI^+) m/z: 443.7 $(M+H)^+$.

[1358] ***Step 3.*** To a solution of compound 2A (170 mg, 383 μmol, 1.0 eq.) in DCM (3 mL) was added HCl/Dioxane (1 mL, 4M) at 20 °C. The mixture was stirred at 20 °C for 2 hr. LCMS showed the starting material was consumed completely and the peak with desired MS was detected. The mixture was concentrated to give compound 3A (130 mg, 98.8 % yield) as a white solid. LC-MS (ESI^+) m/z: 344.0 $(M+H)^+$.

[1359] ***Step 4.*** To a solution of compound 2B (170 mg, 383 μmol, 1.0 eq.) in DCM (3 mL)was added HCl/Dioxnae (1 mL, 4M)at 20 °C. The mixture was stirred at 20 °C for 2 hr. LCMS showed the starting material was consumed completely and the peak with desired MS was detected. The mixture was concentrated to give compound 3B (130 mg, 98.8 % yield) as a white solid. LC-MS (ESI^+) m/z: 344.0 $(M+H)^+$.

[1360] ***Step 5.*** To a solution of compound 4A (700 mg, 1.36 mmol, 1.0 eq.), compound 4B (588 mg, 1.63 mmol, 1.2 eq.), $Pd(dtbpf)Cl_2$ (88.3 mg, 136 μmol, 0.1 eq.) and K_2CO_3 (375 mg, 2.71 mmol, 2.0 eq.) in Dioxane (5 mL) and H_2O (1 mL) was bubbled with N_2 for 1 min. Then the mixture was stirred at 90 °C for 1 hr. LCMS showed the starting material was consumed completely and a major peak with desired MS was detected. The reaction mixture was concentrated to get a residue which was purified by column chromagraphy (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 3/1) to give compound 4C (374 mg, 45.9 % yield) as a yellow solid. LC-MS (ESI^+) m/z: 602.8 $(M+H^+)$.

[1361] ***Step 6.*** To a solution of compound 4C (374 mg, 622 μmol, 1.0 eq.) in DCM (3 mL) was added TFA (1 mL) at 20 °C. The mixture was stirred at 20 °C for 16 hr. LCMS showed the starting material was consumed completely and a major peak with desired MS was detected. Water (10 mL) and aq. $NaHCO_3$ (20*2mL) was added and the mixture was extracted with DCM (30 mL* 3). The organics were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give compound 4 (290 mg, 99.0 % yield) as a yellow solid.

[1362] LC-MS (ESI^+) m/z: 472.3 ($M+H^+$).

[1363] ***Step 7.*** To a solution of compound 3A (80 mg, 1 Eq, 0.23 mmol, 1.0 eq.) and compound 4 (77 mg, 0.16 mmol, 0.7 eq.) in DCE (6 mL) and MeOH (2 mL) was added $NaBH(OAc)_3$ (0.25 g, 0.17 mL, 1.2 mmol, 5.0 eq.) at 20 °C. Then the mixture was stirred at 20 °C for 1 hr. LCMS showed the starting material was consumed completely and a major peak with desired MS was detected. The mixture was concentrated to get the crude, which was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; gradient: 19%-49% B over 11 min) to give *rel*-(R)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (16.7 mg, 9.0 % yield) as a white solid.

[1364] LC-MS (ESI^+) m/z: 799.2 $(M+H)^+$.

[1365] LCMS: calc. for $C_{43}H_{46}F_4N_8O_3$: 798.89, found: $[M+H]^+$ 799.2.

[1366] HPLC: 100.00% purity at 220 nm.

[1367] ^1H NMR: (400 MHz, DMSO-d6) δ = 12.51 (s, 1H), 11.07 (s, 1H), 7.21 - 7.16 (m, 1H), 6.95 - 6.90 (m, 5H), 6.84 (d, J = 1.7 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.65 - 6.61 (m, 1H), 5.32 - 5.23 (m, 1H), 3.72 (br d, J = 11.6 Hz, 2H), 3.30 (br s, 3H), 3.26 - 3.20 (m, 4H), 3.10 (br d, J = 0.8 Hz, 4H), 2.96 (br t, J = 6.0 Hz, 2H), 2.90 - 2.84 (m, 1H), 2.71 - 2.61 (m, 4H), 2.59 (br d, J = 2.6 Hz, 2H), 2.33 - 2.28 (m, 2H), 2.23 (br d, J = 7.0 Hz, 2H), 2.05 - 1.97 (m, 3H), 1.85 - 1.71 (m, 3H), 1.25 - 1.17 (m, 2H)

[1368] ***Step 8.*** To a solution of compound 3B (80 mg, 0.23 mmol, 1.0 eq.) and compound 4 (77 mg, 0.16 mmol, 0.7 eq.) in DCE (6 mL) and MeOH (2 mL) was added $NaBH(OAc)_3$ (0.25 g, 0.17 mL, 1.2 mmol, 5.0 eq.) at 20 °C. Then the mixture was stirred at 20 °C for1 hr. LCMS showed the starting material was consumed completely and a major peak with desired MS was detected. The mixture was concentrated to get the crude, which was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; gradient: 19%-49% B over 11 min) to give *rel*-(R)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (16.5 mg, 8.9 % yield) as a white solid.

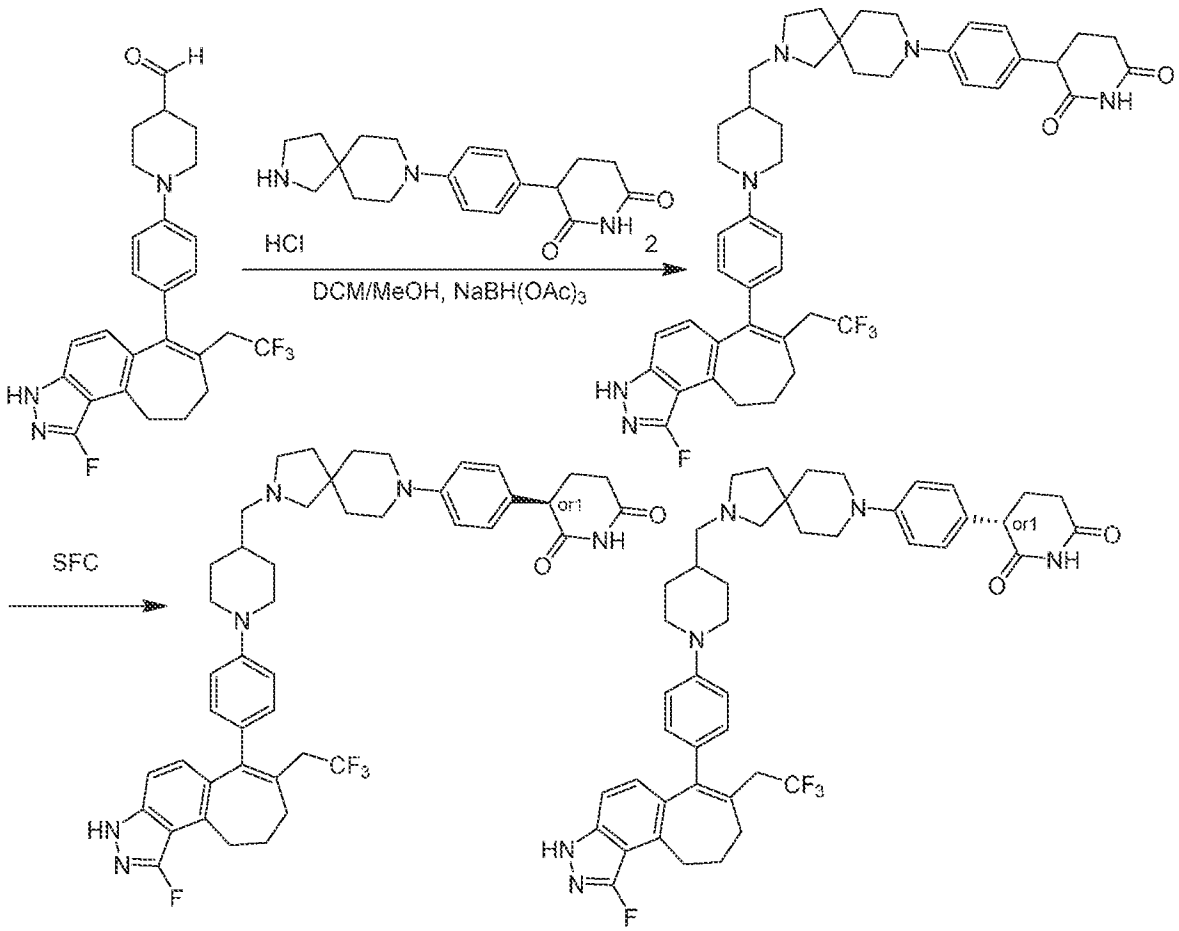
[1369] LC-MS (ESI^+) m/z: 799.3 $(M+H)^+$.

[1370] LCMS: calc. for $C_{43}H_{46}F_4N_8O_3$: 798.89, found: $[M+H]^+$ 799.3.

[1371] HPLC: 100.00% purity at 220 nm.

[1372] ^{1}H NMR: (400 MHz, DMSO-d6) δ = 12.56 - 12.47 (m, 1H), 11.12 - 11.04 (m, 1H), 7.22 - 7.17 (m, 1H), 6.98 - 6.90 (m, 5H), 6.87 - 6.83 (m, 1H), 6.80 - 6.75 (m, 1H), 6.66 - 6.60 (m, 1H), 5.35 (br d, J = 2.5 Hz, 1H), 3.72 (br d, J = 11.6 Hz, 2H), 3.31 (br s, 3H), 3.27 - 3.22 (m, 4H), 3.10 (br s, 4H), 2.99 - 2.94 (m, 2H), 2.91 - 2.85 (m, 1H), 2.74 - 2.62 (m, 4H), 2.61 - 2.54 (m, 2H), 2.35 - 2.29 (m, 2H), 2.24 (br d, J = 6.9 Hz, 2H), 2.06 - 1.97 (m, 3H), 1.86 - 1.71 (m, 3H), 1.27 - 1.18 (m, 2H)

Example 74. Synthesis of *rel*-(R)-3-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione, I-86, and *rel*-(R)-3-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione, I-87



[1373] ***Step 1.*** To a solution of compound 1 (300 mg, 636.28 μmol, 1 eq.) and compound 2 (250.00 mg, 763.54 μmol, 1.2 eq.) in DCE (6 mL) was added $NaBH(OAc)_3$ (404.56 mg, 1.91 mmol, 3 eq.) and MeOH (407.75 mg, 12.73 mmol, 514.97 μl, 20 eq.). The mixture was stirred at 25 °C for 2hr. LCMS showed one peak with desired mass was detected. The reaction mixture was concentrated to dryness. The residue was purified by prep-HPLC (Column YMC-Actus Triart C18 150*30mm*5um; Condition water (TFA)-CAN; Begin B 27, End B 47, Gradient Time (min) 11.5, 100%B Hold Time(min) 1.1, Flow Rate (ml/min) 40, Injections 7, HPLC 98). Compound 3 (150 mg, 30.11% yield) was obtained as a white solid.

[1374] LC-MS (ESI^+) m/z: 783.4$(M+H)^+$.

[1375] ***Step 2.*** Compound 3 (150 mg, 192 μmol, 1.0 eq.) was purified by SFC (Column: DAICEL CHIRALPAK ID (250mm*30mm, 10um); mobile phase: [MeOH-ACN]; gradient: 50%-50% B, Flow rate: 80 mL/min) and then adjusted PH to 6 with formic acid immediately and concentrated to give crude P1 and crude P2.

[1376] The crude P1 was purified by prep-HPLC (Column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; gradient: 30%-60% B over 11 min) to *rel*-(R)-3-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione (16.6 mg, 11.1 % yield) as a white solid. LC-MS (ESI^+) m/z: 783.3 $(M+H)^+$.

[1377] The crude P2 was purified by prep-HPLC (Column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; gradient: 30%-60% B over 11 min) to *rel*-(R)-3-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione (16.5 mg, 11.0 % yield) as a white solid. LC-MS (ESI^+) m/z: 783.3 $(M+H)^+$.

[1378] *rel*-(R)-3-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione:

[1379] LCMS: calc. for $C_{45}H_{50}F_4N_6O_2$: 782.93, found: $[M+H]^+$ 783.3.

[1380] HPLC: 100.00% purity at 220 nm.

[1381] ^1H NMR: (400 MHz, DMSO-d6) δ = 12.49 (s, 1H), 10.77 (s, 1H), 7.20 - 7.16 (m, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.92 - 6.86 (m, 6H), 6.77 (d, J = 8.8 Hz, 1H), 3.73 - 3.67 (m, 3H), 3.22 - 3.05 (m, 6H), 2.96 (br t, J = 6.9 Hz, 2H), 2.67 - 2.62 (m, 2H), 2.58 - 2.54 (m, 2H), 2.48 - 2.34 (m,

4H), 2.33 - 2.26 (m, 4H), 2.13 - 1.99 (m, 4H), 1.84 - 1.78 (m, 2H), 1.65 - 1.55 (m, 7H), 1.25 - 1.16 (m, 2H)

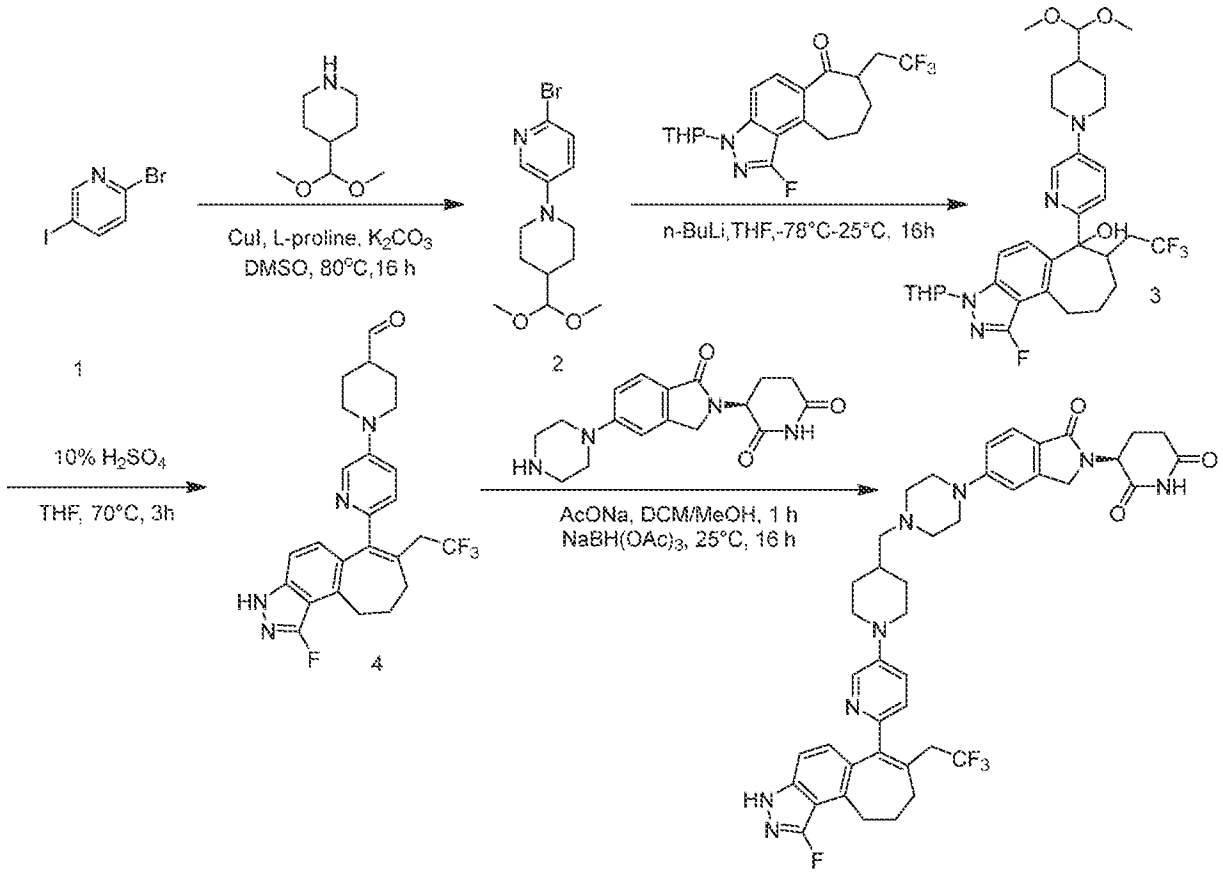
[1382] *rel*-(R)-3-(4-(2-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)-2,8-diazaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione

[1383] LCMS: calc. for $C_{45}H_{50}F_4N_6O_2$: 782.93, found: $[M+H]^+$ 783.3.

[1384] HPLC: 100.00% purity at 220 nm.

[1385] ^{1}H NMR: (400 MHz, DMSO-d6) δ = 12.49 (s, 1H), 10.77 (s, 1H), 7.21 - 7.16 (m, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.92 - 6.87 (m, 6H), 6.77 (d, J = 8.8 Hz, 1H), 3.74 - 3.68 (m, 3H), 3.23 - 3.05 (m, 6H), 2.96 (br t, J = 6.8 Hz, 2H), 2.67 - 2.62 (m, 2H), 2.57 - 2.53 (m, 2H), 2.39 (s, 4H), 2.33 - 2.26 (m, 4H), 2.13 - 1.98 (m, 4H), 1.81 (br d, J = 12.2 Hz, 2H), 1.65 - 1.56 (m, 7H), 1.24 - 1.15 (m, 2H)

Example 75. Synthesis of (S)-3-(5-(4-((1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-82



[1386] ***Step 1.*** To a solution of 2-bromo-5-iodopyridine (4 g, 1 Eq, 14.1 mmol) and 4-(dimethoxymethyl)piperidine (2.2 g, 2.4 mL, 1 Eq, 14.1 mmol) in DMSO (100 mL) was added cuprous iodide (537 mg, 0.2 Eq, 2.82 mmol)), (S)-(-)-Proline (649 mg, 0.4 Eq, 5.64 mmol) and potassium carbonate (3.9 g, 1.6 mL, 2 Eq, 28.2 mmol).The mixture was stirred at 80°C for 16 h. TLC (petroleum ether: ethyl acetate=5:1, R_f=0.4) showed a new spot was formed. The reaction mixture was quenched by addition H_2O (200 mL) at 20°C, and then diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 50~50% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) and the organic layer was concentrated in vacuum to give 2-bromo-5-(4-(dimethoxymethyl)piperidin-1-yl)pyridine (1.76 g, 5.3 mmol, 38% yield, 95% purity) as a white solid. LC-MS (ESI^+) m/z: 317.1 $(M+H)^+$.

[1387] ***Step 2.*** To a mixture of 2-bromo-5-(4-(dimethoxymethyl)piperidin-1-yl)pyridine (1.8 g, 3 Eq, 5.58 mmol) in THF (40 mL) at r.t., and the mixture was degassed and purged with N_2 for 10 minutes. Then the mixture was stirred until it reached -78°C. N-butyllithium(1.9 mL, 2.5 M in hexane, 2.5 Eq, 4.65 mmol) was added to the mixture and stirred at -78 °C for 1 h, then 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (715 mg, 1 Eq, 1.86 mmol) was added to the mixture at -78°C-25°C for 16 h. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.4 UV) showed a new spot was formed. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with H_2O (100mL) and ethyl acetate (100 mL*2). The organic layer was washed with brine (100 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 100*40mm*3um;mobile phase: [water(FA)-ACN]; 10min) to give 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-7-(2,2,2-trifluoroethyl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (230 mg, 429 μmol, 23.0% yield, 100% purity) was obtained as a yellow solid. LC-MS (ESI^+) m/z: 621.4 $(M+H)^+$.

[1388] ***Step 3.*** To a solution of 6-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,6,7,8,9,10-hexahydrocyclohepta[e]indazol-6-ol (230 mg, 1 Eq, 371 μmol) in 10% H_2SO_4 (12 mL) and THF (8 mL) was stirred at 70°C for 3 h. The reaction was adjust to pH=8 with saturated aqueous $NaHCO_3$ (50 mL). Then the mixture was added water (50 mL) and extracted with ethyl acetate

(2×50 mL). The combined organic layers were washed with brine (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the compound 1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidine-4-carbaldehyde (200 mg, 0.34 mmol, 91% yield, 80% purity) as a yellow solid. LC-MS (ESI^+) m/z: 491.1 $(M+H_2O)^+$.

[1389] *Step 4.* To a solution of 1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidine-4-carbaldehyde (100 mg, 1 Eq, 212 μmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (77.2 mg, 1 Eq, 212 μmol, HCl salt) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (52 mg, 3 Eq, 635 μmol) was stirred at 25°C for 1 h, Then sodium triacetoxyborohydride (90 mg, 2 Eq, 423 μmol) and acetic acid (38 mg, 37 μL, 3 Eq, 635 μmol) was added. The mixture was stirred at 25 °C for 16 h. The reaction was quenched with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 19%-49%,7min) to give (S)-3-(5-(4-((1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (8 mg, 0.01 mmol, 5% yield, 98.693% purity) was obtained as a white solid. LC-MS (ESI^+) m/z: 785.4 $(M+H)^+$.

[1390] LCMS: calc. for $C_{42}H_{44}F_4N_8O_3$: 784.86, found: [M+H] + 785.4.

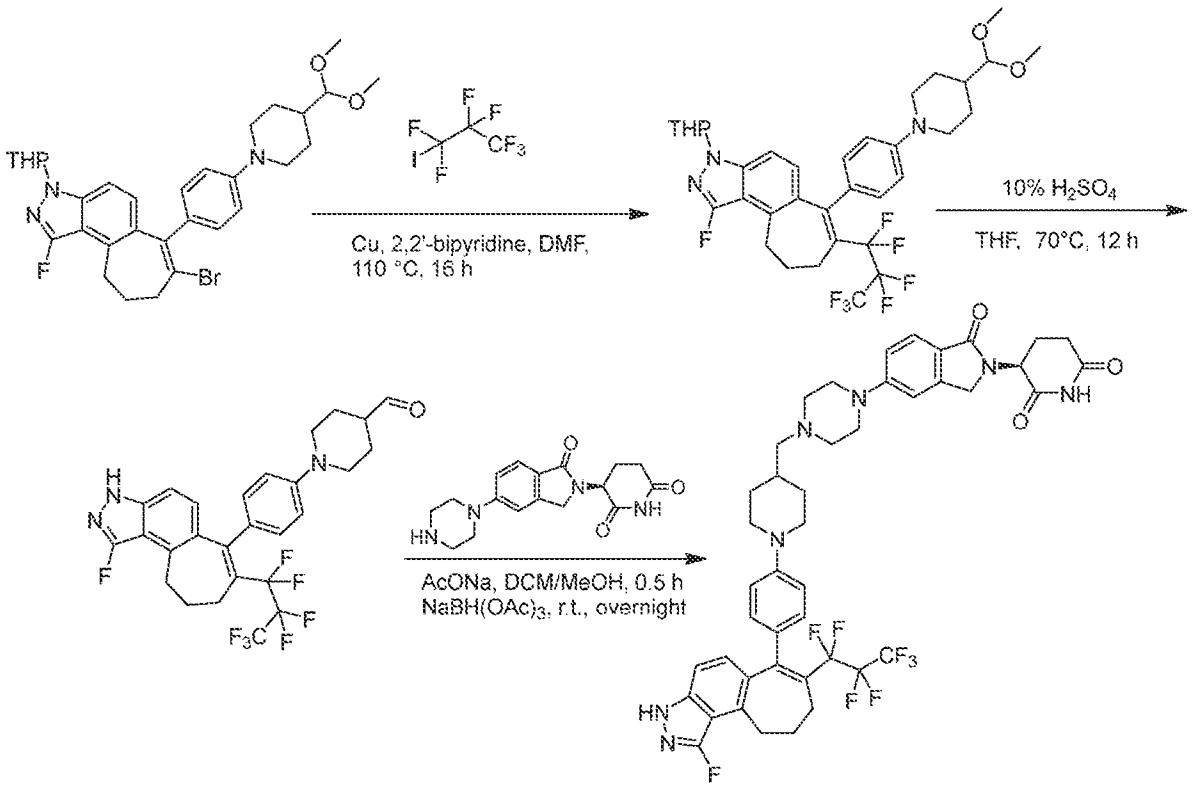
[1391] HPLC: 98.693% purity at 220 nm.

[1392] SFC: retention time, 2.608 min; Area, 92.498%;

[1393] Method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

[1394] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.54 (s, 1H), 10.96 (s, 1H), 8.32 (d, J = 2.6 Hz, 1H), 8.19 (s, 0.204H), 7.53 (d, J = 8.6 Hz, 1H), 7.34 - 7.15 (m, 2H),7.08 (s, 2H), 6.88 - 6.71 (m, 2H), 5.06 (dd, J = 5.1, 13.3 Hz, 1H), 4.40 - 4.29 (m, 1H), 4.27 - 4.16 (m, 1H), 3.80 (br d, J = 12.0 Hz, 2H), 3.54 (br d, J = 12.0Hz, 2H), 3.35 (br s, 8H), 2.96 (br s, 2H), 2.91 (br s, 1H), 2.75 (br s, 2H), 2.59 (br d, J = 17.5 Hz, 1H), 2.39 (br d, J = 4.3 Hz, 1H), 2.32 (br s, 2H), 2.24 (br d, J= 7.0 Hz, 2H), 2.04 (br s, 2H), 1.97 (br d, J = 5.7 Hz, 1H), 1.84 (br d, J = 11.7 Hz, 2H), 1.79 - 1.69 (m, 1H), 1.23 (br d, J = 9.7 Hz, 2H)

Example 76. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-94



[1395] ***Step 1.*** 2,2'-Bipyridine (26 mg, 1 Eq, 167.07 µmol), perfluoropropyliodide (36 µL, 1.5 Eq, 250.60 µmol), 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 1 Eq, 167.07 µmol) and copper (53.09 mg, 5 Eq, 835.34 µmol) in DMF (3 mL) was stirred at 110 °C for 16 hour under N_2. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.6, UV) showed one main new spot was observed. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layers were washed with brine (50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 70% ethyl acetate).The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(perfluoropropyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (80 mg, 167.07 µmol, 31.72% purity) as a white solid which confirmed by LC-MS (ESI$^+$) m/z: 688.1 $(M+H)^+$.

[1396] ***Step 2.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(perfluoropropyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (80

mg, 1 Eq, 0.12 mmol) in 10% H_2SO_4 (3 mL) and THF (3 mL) was stirred at 70 °C for 12 hour. LCMS showed 19 % desired MS. The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-(1-fluoro-7-(perfluoropropyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (45 mg, 16 μmol, 19.56% purity), as a yellow solid. LC-MS (ESI^+) m/z: 588.1 $(M+H)^+$.

[1397] ***Step 3.*** To a solution of 1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (45 mg, 1 Eq, 98 μmol) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (32 mg, 1 Eq, 98 μmol, HCl salt)and sodium acetate (48 mg, 6 Eq, 0.59 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h, Then acetic acid (11 μL, 2 Eq, 0.20 mmol) and sodium triacetoxyhydroborate (42 mg, 2 Eq, 0.20 mmol) was added. The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*3um;mobile phase: [water(FA)-ACN];B%: 31%-61%, 6 min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (5.6 mg, 7.3 μmol, 100% purity) was obtained as a white solid. LC-MS (ESI^+) m/z: 870.1 $(M+H)^+$.

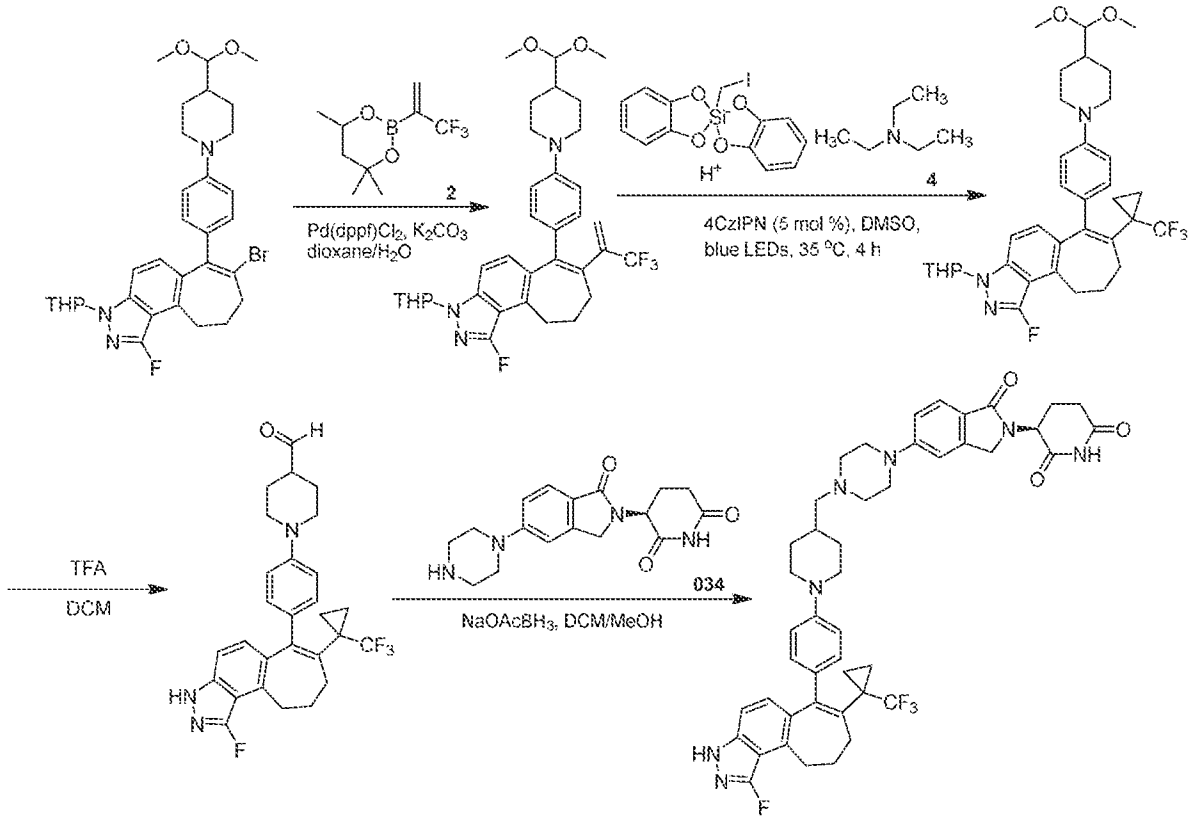
[1398] LCMS: calc. for $C_{44}H_{43}F_8N_7O_3$: 869.33, found: $[M+H]^+$ 870.1.

[1399] HPLC: 100% purity at 220 nm.

[1400] ^1H NMR (400 MHz, DMSO-d_6) δ= 12.64 (s, 1H), 10.95 (s, 1H), 8.31 - 8.29 (m, 0.283H), 7.52 (d, J = 8.6 Hz, 1H), 7.28 - 7.21 (m, 1H), 7.09 - 7.04 (m, 2H),6.96 - 6.89 (m, 2H), 6.89 - 6.84 (m, 2H), 6.80 (d, J = 8.8 Hz, 1H), 5.08 - 5.01 (m, 1H), 4.36 - 4.29 (m, 1H), 4.23 - 4.17 (m, 1H), 3.71 (br d, J = 12.3 Hz, 2H),3.29 - 3.22 (m, 6H), 3.05 (br s, 2H), 2.93 - 2.85 (m, 1H), 2.70 - 2.63 (m, 2H), 2.62 - 2.52 (m, 2H), 2.43 - 2.29 (m, 4H), 2.22 (br d, J = 6.8 Hz, 2H), 2.12 - 2.02(m, 2H), 1.99 - 1.93 (m, 1H), 1.86 - 1.79 (m, 2H), 1.77 - 1.67 (m, 1H), 1.25 - 1.15 (m, 2H)

[1401] SFC: retention time, 2.579 min; Area, 94.075%; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 77. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(1-(trifluoromethyl)cyclopropyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-118



[1402] ***Step 1.*** To a solution of compound 1 (400 mg, 668 μmol, 1 eq.), compound 2 (223 mg, 1 mmol, 1.5 eq.), $Pd(dppf)Cl_2$ (48.9 mg, 66.8 μmol, 0.01 eq.) and K_2CO_3 (227 mg, 2 mmol, 3 eq.) was added in dioxane (5 mL) and H_2O (1 mL). The mixture was stirred at 90 °C for 2 hours. LCMS showed the reaction was completed. The mixture was concentrated to get the crude, which was purified on silica gel column chromatography (from PE/EtOAc = 3/1 to 1/1, TLC: PE/EtOAc = 3/1, Rf = 0.6) to yield compound 3 (330 mg, 0.49 mmol, 74% yield, 92% purity) as a yellow solid.

[1403] LCMS (ESI^+) m/z: 614.5 ($M+H^+$).

[1404] ***Step 2.*** A mixture of compound 3 (100 mg, 163 μmol, 1 eq.), compound 4 (119 mg, 244 μmol, 1.5 eq.) and 4CzIPN (6.43 mg, 8.15 μmol, 0.05 eq.) was added in DMSO (3 mL) under N_2. The mixture was stirred at 35 °C for 4 hours with blue LEDs. LCMS showed desired compound was detected. The mixture was diluted with EtOAc (20 mL) and 2 M aq NaOH (10 mL). The layers were separated, and the organic layer was washed with additional 2 M aq NaOH (2 × 10 mL). The organic layer was then washed with brine (10 mL). The combined

organic layers were dried with Na_2SO_4 and concentrated to get the crude, which was purified on silica gel column chromatography (from PE/EtOAc = 3/1 to 1/1, TLC: PE/EtOAc = 3/1, Rf = 0.65) to yield to afford the compound 5 (60 mg, 64 μmol, 39% yield, 67% purity).

[1405] LCMS (ESI^+) m/z: 628.2 ($M+H^+$)

[1406] ***Step 3.*** To a solution of compound 5 (60 mg, 96 μmol, 1 eq.) and TFA (1 mL) was added in DCM (3 mL). The mixture was stirred at 15 °C for 4 hours. LCMS showed desired compound was detected. The mixture neutralized with $NaHCO_3$ to pH = 8 and then was extracted with EtOAc (10 mL x 3), dried over Na_2SO_4, filtered and concentrated to get the compound 6 (30 mg, crude), which was used for the next step without purification. LCMS (ESI^+) m/z: 498.2 ($M+H^+$).

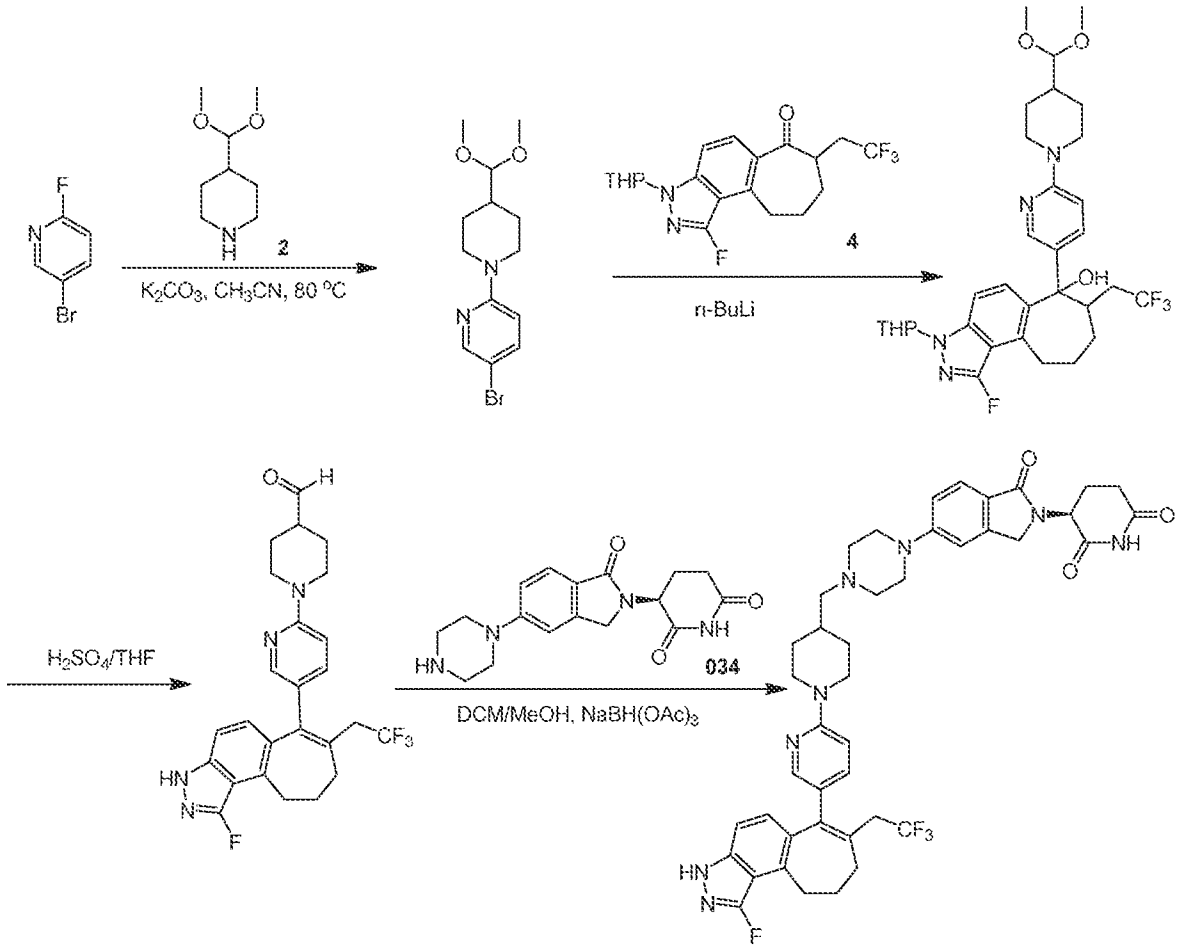
[1407] ***Step 4.*** A mixture of compound 6 (30 mg, 60 μmol, 1 eq.), compound 034 (24 mg, 72 μmol, 1.2 eq.) and $NaBH(OAc)_3$ (38 mg, 0.18 mmol, 3 eq.) was added in DCE (2 mL) and MeOH (2 mL). The reaction mixture was stirred at 25 °C for 16 hours. LCMS showed desired compound was detected. The crude was purified by preparative HPLC (Column: Phenomenex Gemini NX 150 * 30 mm * 5 um, Condition water (NH_4HCO_3)-ACN as a mobile phase, B%: 65%-95%, 11 min) to give compound (S)-3-(5-(4-((1-(4-(1-fluoro-7-(1-(trifluoromethyl)cyclopropyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (8.1 mg, 9.9 μmol, 16% yield, 98.57% purity) as a white solid.

[1408] LCMS: calc. for $C_{45}H_{47}F_4N_7O_3$: 809.37, found: [$M+H^+$] 810.5.

[1409] HPLC: 98.57% purity at 220 nm.

[1410] ^1H NMR: ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.63 - 7.69 (m, 1 H), 7.16 (s, 3 H), 7.03 - 7.08 (m, 2 H), 6.94 - 7.00 (m, 2 H), 6.82 - 6.91 (m, 1 H), 5.11 - 5.15 (m, 1 H), 4.38 - 4.47 (m, 2 H), 3.76 (br d, J=12.04 Hz, 2 H), 3.37 - 3.43 (m, 5 H), 2.96 - 3.05 (m, 2 H), 2.87 - 2.94 (m, 1 H), 2.70 - 2.83 (m, 4 H), 2.65 (br d, J=7.03 Hz, 3 H), 2.45 - 2.51 (m, 1 H), 2.38 - 2.40 (m, 1 H), 2.34 - 2.37 (m, 2 H), 2.30 - 2.33 (m, 1 H), 2.13 - 2.20 (m, 1 H), 1.92 - 1.99 (m, 2 H), 1.76 - 1.85 (m, 1 H), 1.31 (s, 3 H), 1.00 - 1.08 (m, 2 H), 0.74 - 0.85 (m, 2 H).

Example 78. Synthesis of (S)-3-(5-(4-((1-(5-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-81



[1411] ***Step 1.*** To a solution of compound 1 (2.0 g, 11 mmol, 1 eq.) and compound 2 (2.2 g, 14 mmol, 1.2 eq.) in MeCN (25 mL) was added K_2CO_3 (4.7 g, 34 mmol, 3 eq.). The mixture was stirred at 80 °C for 3 hr. The mixture was concentrated in reduced pressure. The residue was poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (50 mL*3). The combined organic phase was washed with brine (25 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3:1) to afford compound 3 (2.34 g, 7.42 mmol, 65 %) as yellow oil.

[1412] LC-MS (ESI+) m/z: 317.0 $(M+H)^+$.

[1413] ***Step 2.*** A mixture of compound 3 (169.0 mg, 536.2 μmol, 1 eq.), n-BuLi (41.21 mg, 257.4 μL, 2.5 molar, 643.4 μmol, 1.2 eq.) in THF (33 mL) was degassed and purged with N_2 for

3 times, and then the mixture was added compound 4 (206.1 mg, 536.2 μmol, 1 eq.). Then the mixture was stirred at -78 °C for 3 hours under N_2 atmosphere. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure to get a residue. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic phase was washed with brine (5 mL*3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=3:1) to afford compound 5 (120 mg, 193 μmol, 36.1 %) as oil. The reaction mixture was filtered under reduced pressure to give a compound. LC-MS (ESI+) m/z: 621.7 $(M+H)^+$.

[1414] ***Step 3.*** To a solution of compound 5 (40 mg, 64 μmol, 1 eq.) in THF (2 mL) was added H_2SO_4 (0.95 g, 0.52 mL, 10% Wt, 0.97 mmol, 15 eq.). The mixture was stirred at 50 °C for 0.5 hour. LCMS showed that the starting material was consumed and the desired product was detected. The reaction liquid is dried with N_2 at 0 °C to give a residue. Compound 6 (25 mg, 53 μmol, 82 %) was obtained as oil.

[1415] LC-MS (ESI+) m/z: 473.2$(M+H)^+$.

[1416] ***Step 4.*** To a solution of compound 6 (50 mg, 0.11 mmol, 1 eq.) and compound 034 (35 mg, 0.11 mmol, 1 eq.) in DCE (3 mL) and MeOH (2 mL) was added $NaBH(OAc)_3$ (0.11 g, 78 μL, 0.53 mmol, 5 eq.). The mixture was stirred at 25 °C for 0.5 hour. LCMS showed that the starting material was consumed and the desired product was detected. The reaction mixture was filtered under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; gradient: 10%-40% B over 11 min) to give (S)-3-(5-(4-((1-(5-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (21 mg, 27 μmol, 25 %) was obtained as a white solid.

[1417] LC-MS (ESI+) m/z: 785.3 $(M+H)^+$.

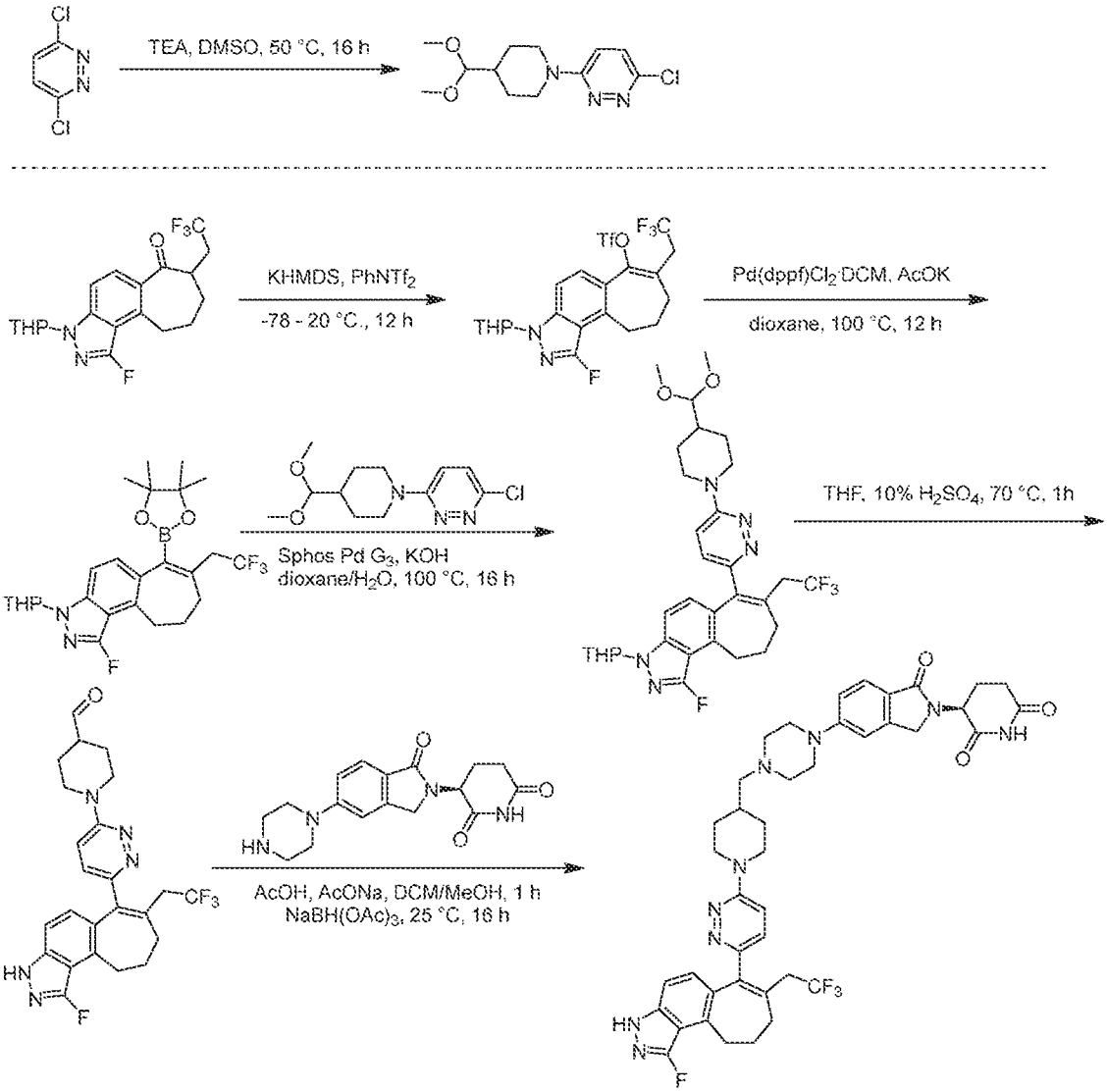
[1418] LCMS: calc. for $C_{42}H_{44}F_4N_8O_3$: 784.86, found: $[M+H]^+$ 785.3.

[1419] HPLC: 100% purity at 220 nm

[1420] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.52 (s, 1 H), 10.95 (s, 1 H), 8.13 (s, 1 H), 7.89 (d, J=2.03 Hz, 1 H), 7.51 - 7.60 (m, 1 H), 7.12 - 7.34 (m, 3 H), 7.07 (br s, 1 H), 6.78 - 6.83 (m, 2 H), 5.05 (dd, J=12.87, 4.77 Hz, 1 H), 4.35 (s, 3 H), 4.18 - 4.24 (m, 1 H), 3.24 - 3.30 (m, 6 H),

2.75 - 2.99 (m, 6 H), 2.55 - 2.68 (m, 2 H), 2.29 - 2.43 (m, 4 H), 2.17 - 2.27 (m, 2 H), 1.89 - 2.13 (m, 4 H), 1.82 (br d, J=11.32 Hz, 3 H), 1.06 - 1.17 (m, 2 H).

Example 79. Synthesis of (S)-3-(5-(4-((1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-83



[1421] ***Step 1.*** A mixture of 4-(dimethoxymethyl)piperidine (1 g, 1 Eq, 6.7 mmol), 3,6-dichloropyridazine (1 g, 1 Eq, 6.7 mmol), and TEA (1.4 g, 2 Eq, 13.4 mmol) were added in DMSO (10 mL) at 20 °C. The solution was heated at 50 °C for 16 h. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.4 UV) showed a new spot was desired. The reaction mixture was treated with H_2O (50 mL), extracted with ethyl acetate (150 mL). The extract was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The crude product was purified on silica gel column chromatography (from petroleum ether/ethyl acetate = 1/0 to 0/1) to

yield desired compound as a white solid. Compound N-(1-(6-bromopyridazin-3-yl)piperidin-4-yl)-N-methoxy-O-methylhydroxylamine (1.3 g, 4.2 mmol, 97.7% yield, 96.5% purity) was obtained as a white solid.

[1422] LC-MS (ESI+) m/z: 272.1(M+H) $^+$.

[1423] *Step 2.* To a mixture of Hexamethyldisilazane potassium salt solution (3.9 mL, 1 molar, 1.5 Eq, 3.9 mmol) in THF (8 mL) at 20 °C, and the mixture was degassed and purged with N_2 for 10 minutes. Then the mixture was stirred until it reached -78 °C. 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (1 g, 1 Eq, 2.6 mmol) was added to the mixture and stirred at -78 °C for 1 hour, then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.1 g, 1.2 Eq, 3.1 mmol) was add to the mixture at -78 °C and stirred at 20 °C for 12 h. TLC (petroleum ether: ethyl acetate=10:1, R_f=0.3 UV) showed a new spot was observed. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL), extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100%~20% Petroleum ether/Ethyl acetate gradient @ 30 mL/min) Compound 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (1.44 g, 1.39 mmol, 53.5 % yield, 49.9% purity) was obtained as a yellow solid.

[1424] *Step 3.* To a stirred solution of 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (500 mg, 49.9% Wt, 1 Eq, 483 μmol) in Dioxane (3 mL), bis(pinacolato)diborane (245 mg, 2 Eq, 966 μmol) was added with N_2. Potassium acetate (142 mg, 3 Eq, 1.5 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)Complex with dichloromethane (39 mg, 0.1 Eq, 48.3 μmol) were added there to and again deoxygenated. The reaction mixture was heated to 100 °C for 12 h. TLC (petroleum ether: ethyl acetate=5:1,R_f=0.5 UV) showed one main new spot was observed. The reaction mixture was quenched by addition of water (30 mL), extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100%~15% Petroleum ether/Ethylacetate gradient @

30 mL/min) Compound 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (180 mg, 364 μmol, 75.4 % yield) was obtained as colorless oil.

[1425] ***Step 4.*** To a stirred solution of 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (230 mg, 1 Eq, 465 μmol) in 1,4-Dioxane (5 mL) and H_2O (1 mL), 3-chloro-6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazine (139 mg, 1.1 Eq, 512 μmol) was added with N_2. (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methane sulfonate (41 mg, 0.1 Eq, 46.5 μmol) and KOH (52 mg, 2 Eq, 931 μmol) were added there to and again deoxygenated. The reaction mixture was heated to 100 °C for 16 h. TLC (petroleum ether: ethyl acetate=2:1,R_f=0.4UV) showed a new spot was desired. The reaction mixture was quenched by addition of water (50 mL), extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100%~50% Petroleum ether/Ethyl acetate gradient @ 30 mL/min) Compound 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (110 mg, 176 μmol, 37.9 % yield, 96.8% purity) was obtained as a yellow solid.

[1426] ***Step 5.*** To a solution of 6-(6-(4-(dimethoxymethyl)piperidin-1-yl)pyridazin-3-yl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (110 mg, 1 Eq, 182 μmol) in THF (2 mL) was added H_2SO_4 (4 mL, 10% V/V, 8 mmol).The mixture was stirred at 70 °C for 1 h. The reaction was adjust to pH=8 with saturated aqueous $NaHCO_3$.Then the mixture was added water (20 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a yellow oil of 1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidine-4-carbaldehyde (80 mg, 0.17 mmol, 93 % yield).

[1427] ***Step 6.*** A solution of 1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidine-4-carbaldehyde (80 mg, 1 Eq, 0.2 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (74 mg, 1.2 Eq, 0.2 mmol, HCl salt) and sodium acetate (69 mg, 5 Eq, 0.8 mmol) in DCM (3 mL) and MeOH (3 mL)

was stirred at 25 °C for 1 h, Then acetic acid (20 mg, 19 µL, 2 Eq, 0.3 mmol) and sodium triacetoxyhydroborate (72 mg, 2 Eq, 0.3 mmol) was added. The mixture was stirred at 25 °C for 16 h. The filtrate was treated with H_2O (50 mL), extracted with ethyl acetate (50 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue.

[1428] The residue was purified by prep-HPLC:

[1429] Column: Welch Xtimate C18 150*30mm*5um

[1430] Condition:

[1431] A: water(FA)

[1432] B:ACN

[1433] at the beginning: A (81%) and B (19%)

[1434] at the end: A: (51%) and B (49%)

[1435] Gradient Time (min) 7; 100%B Hold Time (min) 2.2; Flow Rate (ml/min) 25.

[1436] The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(6-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (24.3 mg, 29.6 µmol, 18 % yield, 95.6% purity) as a white solid.

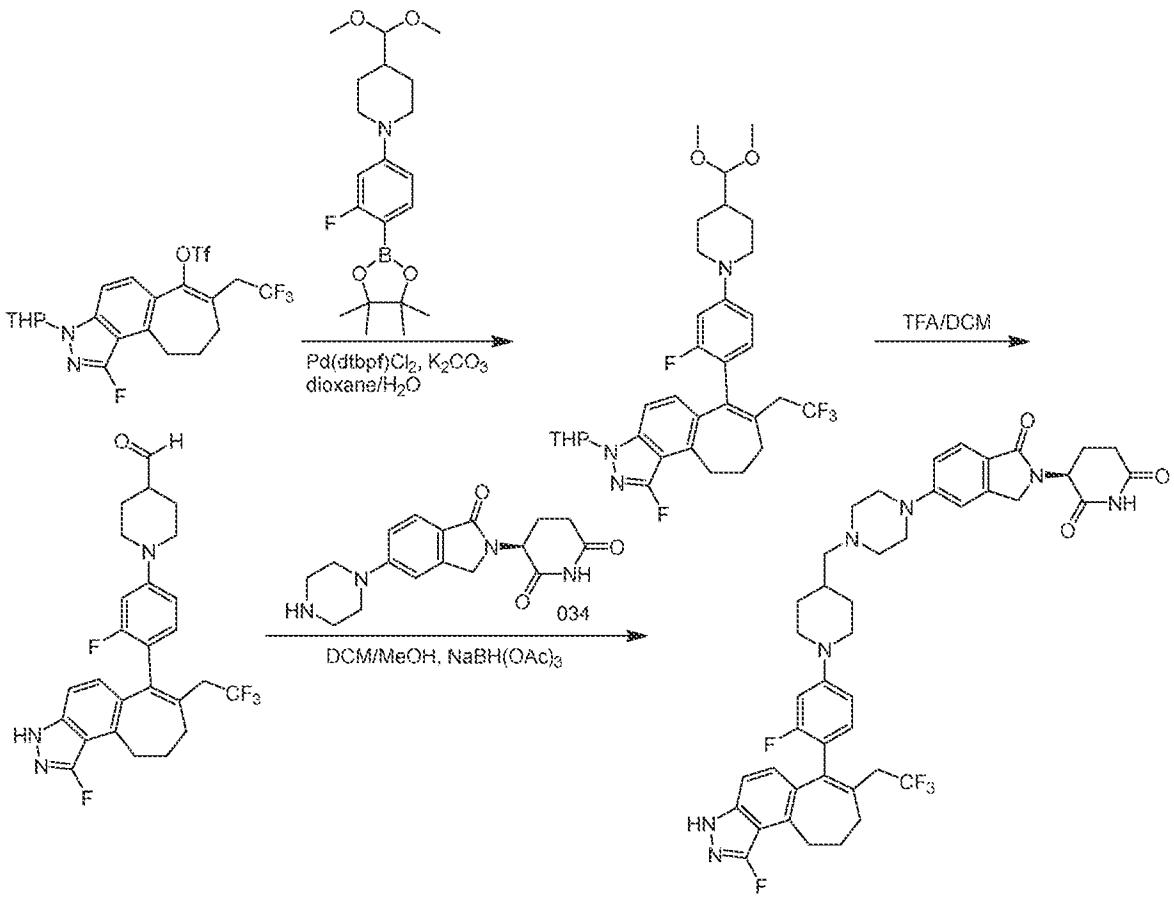
[1437] LCMS: calc. for $C_{41}H_{43}F_4N_9O_3$:785.34, found: $[M+H]^+$786.2

[1438] HPLC: 95.632 % purity at 220 nm.

[1439] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.58 (s, 1H), 10.96 (s, 1H), 8.15 (s, 0.425H), 7.53 (d, J = 8.6 Hz, 1H), 7.27 - 7.17 (m, 2H), 7.08 (s, 2H), 6.93 (d, J = 9.5 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.06 (dd, J = 5.1, 13.3 Hz, 1H), 4.45 - 4.28 (m, 3H), 4.25 - 4.16 (m, 1H), 3.50 (br d, J = 11.7 Hz, 4H), 3.36 (br d, J = 1.4 Hz, 4H), 3.00 - 2.85 (m, 5H), 2.59 (br d, J = 17.5 Hz, 3H), 2.36 (br d, J = 5.6 Hz, 3H), 2.24 (br d, J = 6.4 Hz, 2H), 2.15 - 2.05 (m, 2H), 2.02 - 1.93 (m, 1H), 1.86 (br d, J = 10.4 Hz, 3H), 1.16 (br d, J = 11.6 Hz, 2H)

[1440] SFC: retention time, 2.790 min; Area, 96.569%; Method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

Example 80. Synthesis of (S)-3-(5-(4-((1-(3-fluoro-4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-78



[1441] ***Step 1.*** A mixture of Compound 1 (120 mg, 232 μmol, 1 eq.), Compound 2 (106 mg, 279 μmol, 1.2 eq.) , $PdCl_2(dppf)$ (17.0 mg, 23.2 μmol, 0.1 eq.) and K_2CO_3 (96.3 mg, 697 μmol, 3 eq.) in Dioxane (8 mL) and Water (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 3 hour under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition EA 10 mL at 20 °C, and then diluted with water 30 mL and extracted with EA 30 mL (10 mL * 3). The combined organic layers were washed with EA 30 mL (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude material was purified on silica gel column chromatography (from pure PE to PE/EtOAc = 5/1) to give Compound 3 (100 mg, 161 μmol, 69.4 %) as a yellow solid. LC-MS (ESI^+) m/z: 620.4 $(M+H)^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ: ppm 7.26 - 7.37 (m, 2 H), 6.91 - 6.98 (m, 1 H), 6.58 - 6.84 (m, 2 H), 5.52 - 5.76 (m, 1 H), 4.11 (d, J=6.40 Hz, 1 H), 3.89 - 4.01 (m, 1 H), 3.72 - 3.78 (m, 2 H), 3.36 (d, J=8.00 Hz, 9 H), 3.08 (t, J=7.20 Hz,

2 H), 2.61 - 2.77 (m, 2 H), 2.29 - 2.46 (m, 3 H), 2.04 - 2.21 (m, 3 H), 1.95 (m, 1 H), 1.73 (d, J=3.58 Hz, 4 H), 1.56 - 1.71 (m, 2 H), 1.36 - 1.49 (m, 2 H).

[1442] ***Step 2.*** To a solution of Compound 3 (100 mg, 161 μmol, 1 eq.). in DCM (6 mL) and TFA (2 mL). The mixture was stirred at 20 °C for 1 hour. LCMS showed the reaction was completed. The mixture was concentrated in vacuo to give crude product. No further purification as it is used for the next step directly.

[1443] LC-MS (ESI^+) m/z: 490.2 $(M+H)^+$.

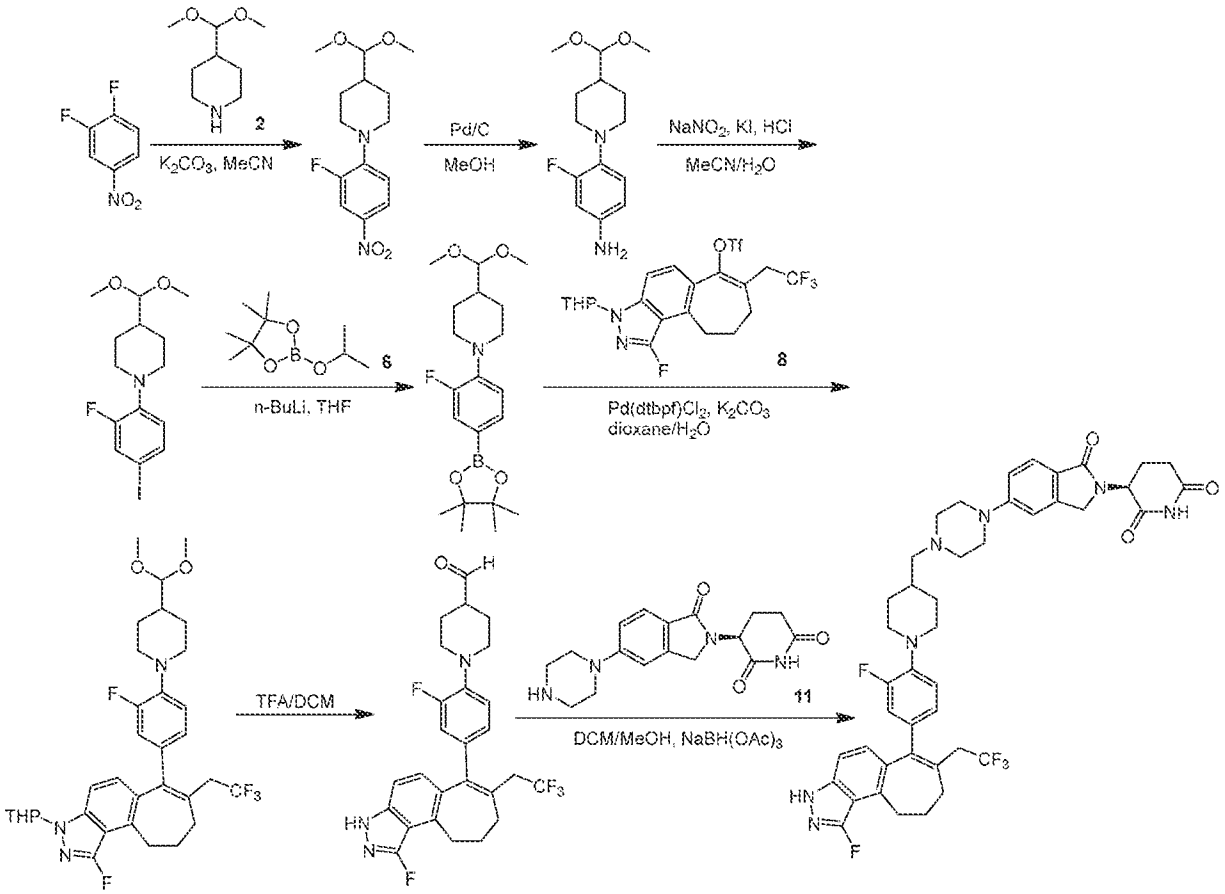
[1444] ***Step 3.*** To a solution of Compound 4 (45 mg, 92 μmol, 1 eq.) and (S)-3-(1-oxo-5-(piperazin-1-yl) isoindolin-2-yl)piperidine-2,6-dione (36 mg, 0.11 mmol, 1.2 eq.) in DCE (3 mL) and MeOH (3 mL) was added sodium triacetoxyborohydride (58 mg, 0.28 mmol, 3 eq.). The mixture was stirred at 20 °C for 12 hour. LCMS showed the reaction was completed. The crude was purified by prep.HPLC together (Phenomenex Gemini NX 150×30mm, 5μm, water (NH_4HCO_3)-ACN as a mobile phase, from 60% to 90%, Gradient Time (min): 11, Flow Rate (ml/min): 25) to give (S)-3-(5-(4-((1-(3-fluoro-4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (23.9 mg, 29.8 μmol, 32 %).

[1445] LCMS: calc. for $C_{43}H_{44}F_5N_7O_3$:801.86, found: $[M+H]^+$ 802.4

[1446] HPLC: 99.01% purity at 220 nm.

[1447] ^1H NMR (400 MHz, METHANOL-d_4) δ: ppm 7.63 - 7.70 (m, 1 H), 7.09 - 7.16 (m, 3 H), 6.99 - 7.04 (m, 1 H), 6.91 (d, J=8.80 Hz, 1 H), 6.81 - 6.85 (m, 1 H), 6.69 - 6.74 (m, 1 H), 5.12 (m, 1 H), 4.36 - 4.49 (m, 2 H), 3.80 (d, J=12.80 Hz, 2 H), 3.38 - 3.42 (m, 4 H), 3.06 - 3.18 (m, 4 H), 2.87 - 2.96 (m, 1 H), 2.75 - 2.83 (m, 3 H), 2.66 (d, J=4.00 Hz, 4 H), 2.40 - 2.53 (m, 3 H), 2.35 (d, J=6.80 Hz, 2 H), 2.14 - 2.20 (m, 3 H), 1.94 (d, J=12.80 Hz, 2 H), 1.82 (s, 1 H), 1.35 - 1.40 (m, 2 H).

Example 81. Synthesis of (S)-3-(5-(4-((1-(2-fluoro-4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-79



[1448] *Step 1.* To a mixture of compound 1 (4 g, 0.03 mol, 1.0 eq.) and K_2CO_3 (7 g, 0.06 mol, 2.0 eq.) in MeCN (40 mL) was added compound 2 (5 g, 0.03 mol, 1.2 eq.) at 25 °C. The mixture was stirred at 80 °C for 2 hrs. LCMS showed the reaction was completed. The mixture was concentrated to give a residue, which was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to give compound 3 (6 g, 80% yield) as a yellow solid.

[1449] LC-MS (ESI^+) m/z: 299.3 $(M+H)^+$.

[1450] *Step 2.* To a mixture of compound 3 (6 g, 0.02 mol, 1.0 eq.) in MeOH (50 mL) and THF (50 mL) was added Pd/C (2 g, 2 mmol, 10% purity, 0.1 eq.) at 20 °C. The mixture was stirred at 20 °C under H_2 (15 psi) for 24 hrs. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give compound 4 (4 g, 70% yield) as red oil.

[1451] LC-MS (ESI^+) m/z: 269.3 $(M+H)^+$.

[1452] *Step 3.* To a mixture of compound 4 (4 g, 15 mmol, 1.0 eq.) in MeCN (60 mL) and H_2O (20 mL) was added $NaNO_2$ (3.1 g, 45 mmol, 3.0 eq.), KI (7.4 g, 45 mmol, 3.0 eq.) and HCl (2.7 g, 75 mmol, 6.2 mL, 5.0 eq.) at 20 °C. The mixture was stirred at 20 °C for 5 hrs. LCMS showed the reaction was completed. A solution of $NaHCO_3$ was added to adjust pH to 9. The mixture was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel eluted with (petroleum ether: EtOAc = 10:1 to 1:1) to give compound 5 (5.0 g, 88% yield) as a yellow solid.

[1453] LC-MS (ESI^+) m/z: 380.0 $(M+H)^+$.

[1454] *Step 4.* To a mixture of compound 5 (2.0 g, 5.3 mmol, 1.0 eq.) in THF (20 mL) was added n-BuLi (440 mg, 6.9 mmol, 2.7 mL, 1.3 eq.) at -78 °C. The mixture was stirred at -78 °C for 0.5 h and then compound 6 (1.3 g, 6.9 mmol, 1.4 mL, 1.3 eq.) was added at -78 °C. The mixture was stirred at -78 °C for 2 hrs. LCMS showed the reaction was completed. H_2O (5 mL) was added at -78 °C and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel eluted with (petroleum ether: EtOAc = 5:1 to 1:1) to give compound 7 (800 mg, 40% yield) as a yellow solid.

[1455] LC-MS (ESI^+) m/z: 379.6 $(M+H)^+$.

[1456] *Step 5.* To a mixture of compound 7 (100 mg, 194 μmol, 1.0 eq.), compound 8 (110 mg, 290 μmol, 1.5 eq.) and $Pd(dtbpf)Cl_2$ (12.6 mg, 19.4 μmol, 0.1 eq.) in dioxane (2 mL) and H_2O (0.4 mL) was added K_2CO_3 (80.3 mg, 581 μmol, 3.0 eq.) at 20 °C. The mixture was stirred at 90 °C for 2 hrs. LCMS showed the reaction was completed. The reaction mixture was concentrated to give a crude, which was purified by column chromatography on silica gel eluted with petroleum ether: EtOAc = 10:1 to 1:1) to give compound 9 (100 mg, 83.3% yield) as a yellow solid.

[1457] LC-MS (ESI^+) m/z: 620.4 $(M+H)^+$.

[1458] *Step 6.* To a mixture of compound 9 (90 mg, 150 μmol, 1.0 eq.) in DCM (3 mL) was added TFA (1 mL) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS showed the

reaction was completed. The reaction mixture was concentrated to give compound 10 (70 mg, crude) as yellow oil.

[1459] LC-MS (ESI^+) m/z: 490.2 $(M+H)^+$.

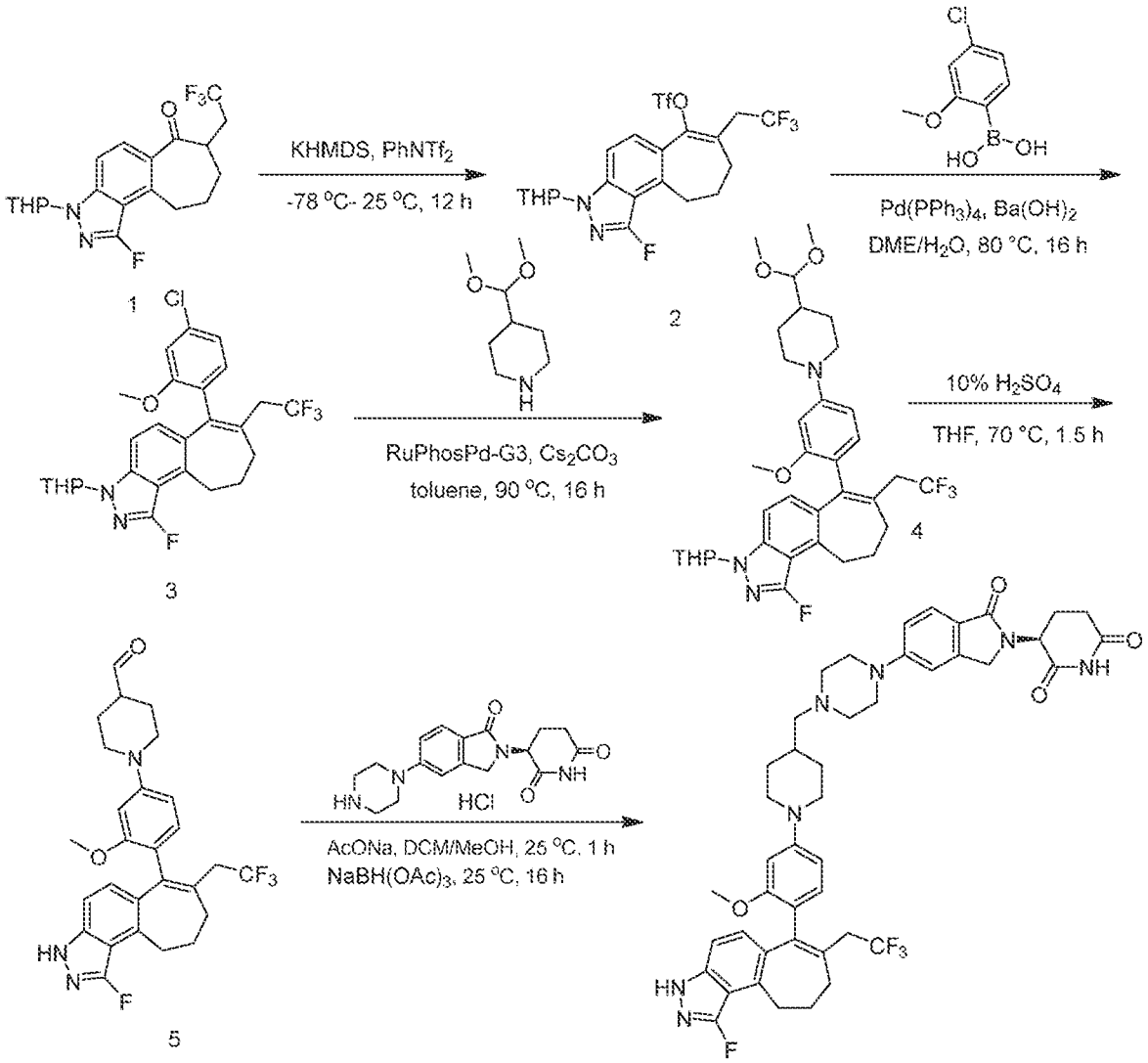
[1460] ***Step 7.*** To a solution of compound 10 (90 mg, 40% Wt, 74 μmol, 1.0 eq.) and compound 11 (24 mg, 74 μmol, 1.0 eq.) in DCM (3 mL) and MeOH (3 mL) was added $NaBH(OAc)_3$ (47 mg, 0.22 mmol, 3.0 eq.) at 25 °C. The mixture was stirred at 25 °C for 3 hrs. The reaction mixture was filtered and concentrated to yield a residue. The residue was purified by preparative HPLC (column: Boston Green ODS 150 x 30 mm x 5 μm; mobile phase: [water (FA)-ACN]; B%: 23%-53%, 12 min) to give (S)-3-(5-(4-((1-(2-fluoro-4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (17.2 mg, 28 % yield) as a white solid. LC-MS (ESI^+) m/z: 802.3 $(M+H)^+$

[1461] LCMS: calc. for $C_{43}H_{44}F_5N_7O_3$: 801.34, found: $[M+H]^+$802.3.

[1462] HPLC: 97.09% purity at 220 nm.

[1463] ^1H NMR (400MHz, DMSO-d6) δ = 12.52 (s, 1H), 10.94 (s, 1H), 8.22 (s, 1H), 7.52 (d, J=8.6 Hz, 1H), 7.21 (dd, J=2.5, 8.7 Hz, 1H), 7.11 - 6.99 (m, 3H), 6.90 - 6.74 (m, 3H), 5.04 (dd, J=5.0, 13.2 Hz, 1H), 4.38 - 4.28 (m, 1H), 4.25 - 4.15 (m, 1H), 3.30 - 3.17 (m, 12H), 2.97 (br t, J=6.6 Hz, 2H), 2.92 - 2.85 (m, 1H), 2.69 (br t, J=10.8 Hz, 2H), 2.58 (br d, J=16.6 Hz, 1H), 2.63 - 2.55 (m, 1H), 2.40 - 2.29 (m, 3H), 2.24 (br d, J=7.3 Hz, 2H), 2.05 (q, J=6.4 Hz, 2H), 2.00 - 1.91 (m, 1H), 1.83 (br d, J=12.2 Hz, 2H), 1.70 (br s, 1H), 1.34 - 1.22 (m, 2H).

Example 82. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-80



[1464] ***Step 1.*** Hexamethyldisilazane potassium solution (710 μL, 1 M, 1.5 Eq, 710 μmol) in THF (8 mL) at r.t. and the mixture was degassed and purged with N_2 for 10 minutes. Then the mixture was stirred until it reached -78 °C. 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-7,8,9,10-tetrahydrocyclohepta[e]indazol-6(3H)-one (200 mg, 1 Eq, 474 μmol) was added to the mixture and stirred at -78 °C for 1 hour, then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (203 mg, 1.2 Eq, 568 μmol) was added to the mixture at -78 °C and stirred at 25 °C for 12 hour. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (20 mL) at ice bath, then treated with H_2O (100 mL), extracted with ethyl acetate (100 mL*2). The combined extracts were dried over anhydrous

Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~30% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuum to give 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (90 mg, 0.12 mmol, 24% yield, 66.202% purity) as a white solid. LC-MS (ESI+) m/z: 517.0 $(M+H)^+$.

[1465] ***Step 2.*** A mixture of 1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl trifluoromethanesulfonate (150 mg, 1 Eq, 290 μmol), (4-chloro-2-methoxyphenyl)boronic acid (65 mg, 1.2 Eq, 349 μmol), $Pd(PPh_3)_4$ (34 mg, 0.1 Eq, 29.0 μmol) and $Ba(OH)_2$(149 mg, 68.2 μL, 3 Eq, 871 μmol) was added in DME (4 mL) and H_2O (2 mL), purged with N_2 for 10 min. Then the reaction was stirred at 80 °C for 16 hour. The mixture was treated with H_2O (100 mL), extracted with ethyl acetate (100 mL*2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~20% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuum to give 6-(4-chloro-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 223 μmol, 76.9% yield, 94.699% purity) as a white solid.

[1466] LC-MS (ESI+) m/z: 509.0 $(M+H)^+$.

[1467] ***Step 3.*** A mixture of 4-(dimethoxymethyl)piperidine (44 mg, 47 μL, 1.5 Eq, 279 μmol), 6-(4-chloro-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (100 mg, 94.699% purity, 1 Eq, 186 μmol), cesium carbonate (182 mg, 45 μL, 3 Eq, 558 μmol), (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methane sulfonate (16 mg, 0.1 Eq, 18.6 μmol) was added in toluene (5 mL), N_2 was bubbled into the mixture for 5 min. Then the reaction was heated to 90 °C for 16 hour. The mixture was quenched with H_2O (100 mL), extracted with ethyl acetate (100 mL*2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was subjected to column chromatography over silica gel (gradient elution: 0~30% ethyl acetate in petroleum ether). The pure fractions were collected and concentrated to dryness in vacuum to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-

pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (85 mg, 0.13 mmol, 72% yield, 100% purity) as a colorless oil.

[1468] LC-MS (ESI+) m/z: 632.1 $(M+H)^+$.

[1469] ***Step 4.*** A mixture of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (75 mg, 1 Eq, 0.12 mmol) was added in THF (1.5 mL) and 10% H_2SO_4 (4.5 mL) and stirred at 70 °C for 1.5 hour. Then the reaction was cooled to room temperature. The solution was added saturated aqueous $NaHCO_3$ to adjust pH=6. The reaction was dissolved in water (50 mL) and extracted by ethyl acetate (50 mL*2). The combined organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (70 mg, 0.11 mmol, 93% yield, 79.067% purity) as a yellow oil.

[1470] LC-MS (ESI+) m/z: 520.1 $(M+H_2O)^+$

[1471] ***Step 5.*** A mixture of 1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (70 mg, 79.067% purity, 1 Eq, 0.11 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (52 mg, 1.3 Eq, 0.14 mmol), sodium acetate (45 mg, 5 Eq, 0.55 mmol) and acetic acid (20 mg, 19 μL, 3 Eq, 0.33 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 1 hour, then sodium triacetoxyborohydride (47 mg, 2 Eq, 0.22 mmol) was added to the mixture and stirred at 25 °C for 16 hour. The reaction was treated with H_2O (50 mL), extracted with ethyl acetate (50 mL*2). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuum to give a residue. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 25%-55%, 7 min). The aqueous phase was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(2,2,2-trifluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (38.4 mg, 47.0 μmol, 43% yield, 99.632% purity) as a white solid.

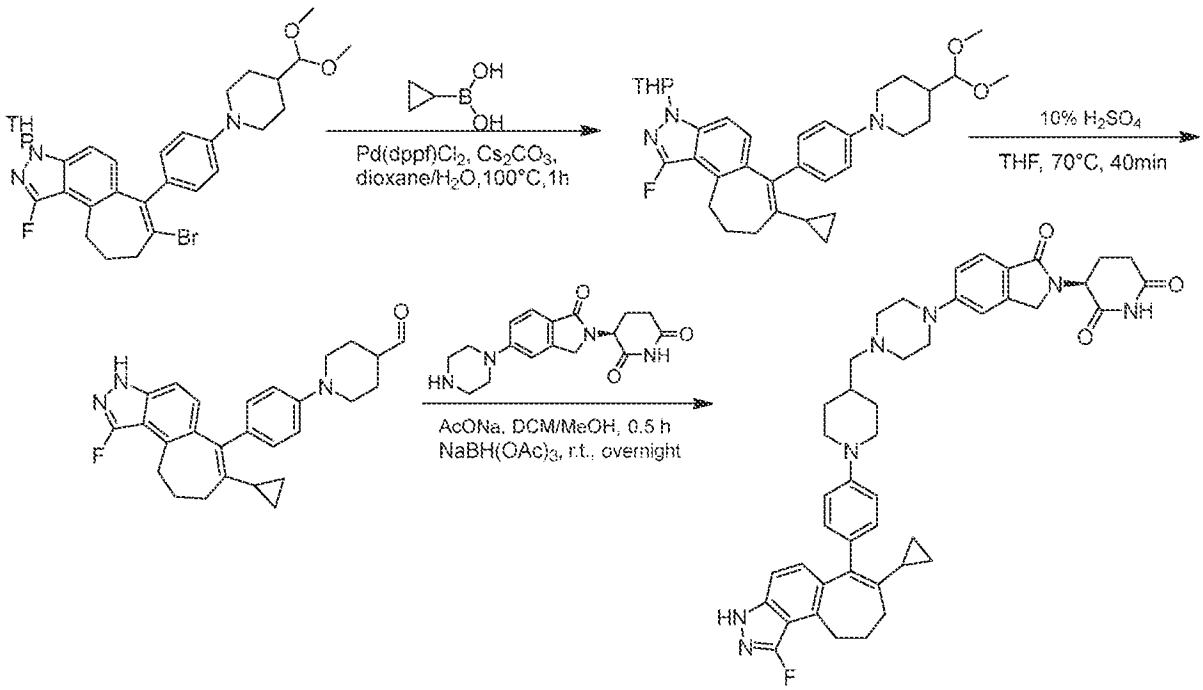
[1472] LC-MS (ESI+) m/z: 814.2 $(M+H)^+$

[1473] HPLC: 99.632%, purity at 220 nm.

[1474] SFC: retention time, 2.434 min; Area, 94.775%; method: IC_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

[1475] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.44 (s, 1H), 10.96 (s, 1H), 8.14 (s, 0.220H), 7.53 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 2.5, 8.8 Hz, 1H), 7.12 - 7.03 (m, 2H), 6.84 (dd, J = 3.8, 8.5 Hz, 2H), 6.59 - 6.47 (m, 2H), 5.06 (dd, J = 5.0, 13.3 Hz, 1H), 4.39 - 4.28 (m, 1H), 4.26 - 4.15 (m, 1H), 3.75 (br d, J = 8.3 Hz, 2H), 3.62 (s, 3H), 3.31 (br d, J = 4.3 Hz, 7H), 3.20 - 2.84 (m, 6H), 2.70 (br t, J = 11.0 Hz, 2H), 2.61 (br s, 1H), 2.39 - 2.21 (m, 5H), 2.07 - 1.92 (m, 3H), 1.84 (br d, J = 11.0 Hz, 2H), 1.78 - 1.67 (m, 1H), 1.30 - 1.17 (m, 2H).

Example 83. Synthesis of (S)-3-(5-(4-((1-(4-(7-cyclopropyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-117



[1476] ***Step 1.*** The mixture of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (200 mg, 1 Eq, 334 μmol), cyclopropylboronic acid (57.4 mg, 2 Eq, 668 μmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (27.3 mg, 0.1 Eq, 33.4 μmol) and cesium carbonate (327 mg, 3 Eq, 1.00 mmol) were added in dioxane (4 mL) and H_2O (1 mL) at r.t. and N_2 was bubbled into the mixture for 5 min. The reaction mixture was heated at 100°C for 1 hour. Then the reaction was cooled to room temperature. TLC (petroleum ether/ethyl acetate=3/1, R_f=0.4). The reaction was diluted with water (50 mL) and

extracted by ethyl acetate (2*50 mL). The combined organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the compound as a brown oil. The brown oil was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, petroleum ether/ethyl acetate from 100/0 to 30/70 @ 30 mL/min)) and the fraction was concentrated in vacuum to give 7-cyclopropyl-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 214 μmol, 64.2% yield, 100% purity) as a colorless oil. LC-MS (ESI+) m/z: 560.1$(M+1)^+$.

[1477] ***Step 2.*** To a solution of 7-cyclopropyl-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (120 mg, 100% purity, 1 Eq, 214 μmol) was added in THF (4 mL), and then added H_2SO_4（12 mL, 10% V/V）at 0°C. The mixture was stirred at 70°C for 40 min. The mixture was adjusted to pH=~8 by adding saturated aq.$NaHCO_3$ (30 mL). Then the reaction mixture was extracted with ethyl acetate (2*50mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. The fraction was concentrated in vacuum to give 1-(4-(7-cyclopropyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (90 mg, 0.18 mmol, 85 % yield, 86.82% purity) as a colorless oil. LC-MS (ESI+) m/z: 448.4$(M+18)^+$.

[1478] ***Step 3.*** A mixture of 1-(4-(7-cyclopropyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (90 mg, 1 Eq, 0.21 mmol), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (76 mg, 1 Eq, 0.21 mmol) and sodium acetate (86 mg, 5 Eq, 1.0 mmol) were added in DCM (2 mL) and MeOH (2 mL) at 25°C for 0.5 hour, then added acetic acid (38 mg, 36 μL, 3 Eq, 0.63 mmol) and sodium triacetoxyhydroborate (89 mg, 2 Eq, 0.42 mmol), then the mixture was stirred at 25°C for 16 hour. The reaction was dilute with water (50 mL) and extracted with ethyl acetate (50 mL*2). The combined organic layers were concentrated to give crude product as a brown oil. The brown oil was purified by preparative high-performance liquid chromatography. Condition: water (FA)-ACN. Column: C18 150×30mm. Begin B: 30%, End B: 60%. Gradient time (min) 6; 100% B hold time (min) 1, Flow rate (ml/min) 30. The aqueous layer was lyophilized to dryness to give (S)-3-(5-(4-((1-(4-(7-cyclopropyl-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (42.7 mg, 57.6 μmol, 27% yield, 100% purity) as a white solid.

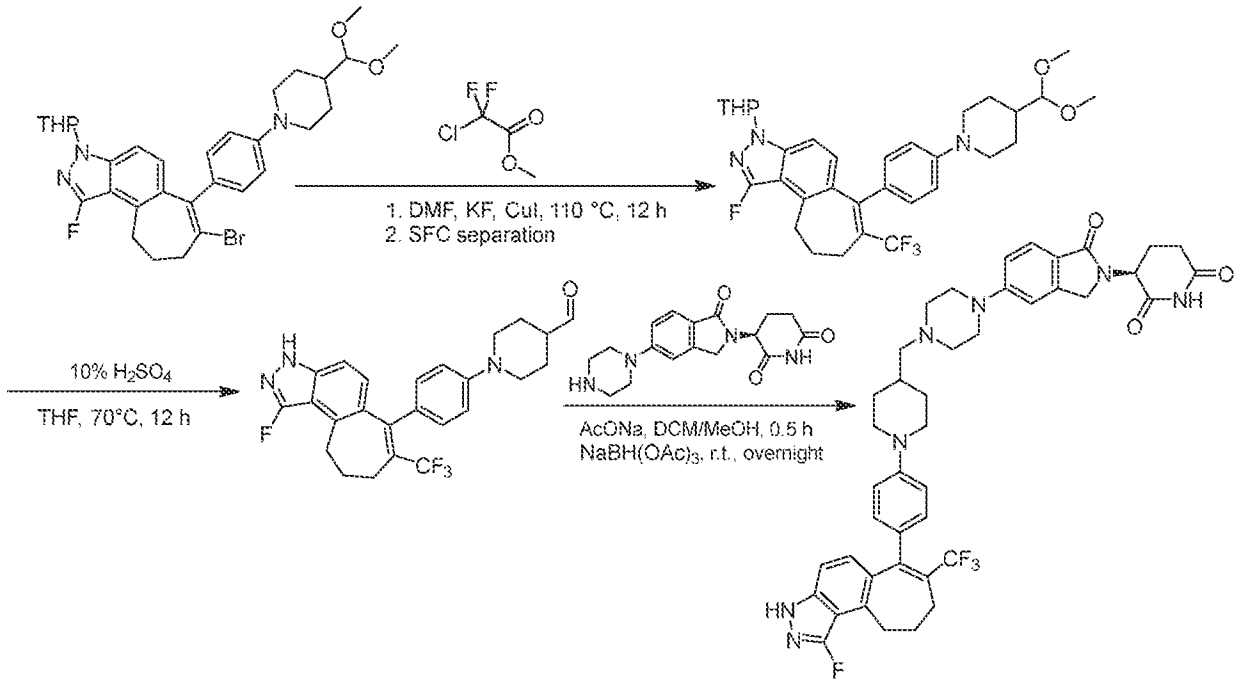
[1479] LCMS: calc. for $C_{44}H_{48}FN_7O_3$: 741.38, found: $[M+H]^+$ 742.2.

[1480] HPLC: 100% purity at 220 nm.

[1481] SFC: retention time, 3.005 min; Area, 88.163 %; Method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

[1482] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.42 (s, 1H), 10.96 (s, 1H), 8.14 (s, 0.4H), 7.52 (d, J = 8.5 Hz, 1H), 7.15 (dd, J = 2.2, 8.8 Hz, 1H), 7.08 - 7.04 (m, 2H), 6.99 (br d, J = 8.5 Hz, 2H), 6.89 (br d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 5.05 (dd, J = 5.1, 13.3 Hz, 1H), 4.37 - 4.28 (m, 1H), 4.24 - 4.17 (m, 1H), 3.69 (br d, J = 11.9 Hz, 2H), 3.29 (br s, 6H), 2.95 - 2.85 (m, 3H), 2.70 - 2.52 (m, 5H), 2.36 (br dd, J = 4.2, 13.2 Hz, 1H), 2.23 (br d, J = 6.8 Hz, 2H), 2.19 - 2.11 (m, 2H), 2.00 - 1.91 (m, 1H), 1.85 - 1.76 (m, 3H), 1.75 - 1.65 (m, 1H), 1.43 (br t, J = 6.6 Hz, 2H), 1.28 - 1.15 (m, 2H), 0.70 (br d, J = 8.2 Hz, 2H), 0.53 (br d, J = 4.4 Hz, 2H)

Example 84. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-77



[1483] ***Step 1.*** To a mixture of chlorodifluoroacetic acid methyl ester (141 µL, 2 Eq, 1.337 mmol), 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (400 mg, 1 Eq, 668.27 µmol) and potassium fluoride (117 mg, 3 Eq, 2.0048 mmol) and cuprous iodide (255 mg, 2 Eq, 1.337 mmol) in DMF (5 mL) was stirred at 110 °C for 12 hour under N_2. TLC (petroleum ether: ethyl acetate=1:1, R_f=0.6, UV) showed one main new spot was observed. The reaction was diluted

with water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layers were washed with brine (50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 80% ethyl acetate). The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (60 mg, 73 μmol, 69.44% purity) as a white solid which confirmed by LC-MS (ESI^+) m/z: 588.2 $(M+H)^+$.

[1484] ***Step 2.*** The mixture was further separated by SFC (condition: column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO_2-i-PrOH(0.1%NH_3H_2O)]; B%:25%-25%) to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (45 mg, 77 μmol, 95.21% purity). LC-MS (ESI^+) m/z: 588.2 $(M+H)^+$.

[1485] ***Step 3.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (45 mg, 1 Eq, 77 μmol) in 10% H_2SO_4 (3 mL) and THF (3 mL) was stirred at 70 °C for 12 hour. LCMS showed 76 % desired MS The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (45 mg, 75 μmol, 76% purity) as a yellow solid. LC-MS (ESI^+) m/z: 477.1 $(M+H_2O+H)^+$.

[1486] ***Step 4.*** To a solution of 1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (40 mg, 1 Eq, 87 μmol) , (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (29 mg, 1 Eq, 87 μmol, HCl salt) and sodium acetate (43 mg, 6 Eq, 0.52 mmol) in DCM (3 mL) and MeOH (3 mL) was stirred at 25 °C for 0.5 h, Then acetic acid (10 μL, 2 Eq, 0.17 mmol) and sodium triacetoxyhydroborate (37 mg, 2 Eq, 0.17 mmol). The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL*2). The organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*3um;mobile phase: [water(FA)-ACN];B%: 25%-55%, 6 min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(trifluoromethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-

yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (11.2 mg, 14.1 μmol, 96.7% purity) was obtained as a white solid.

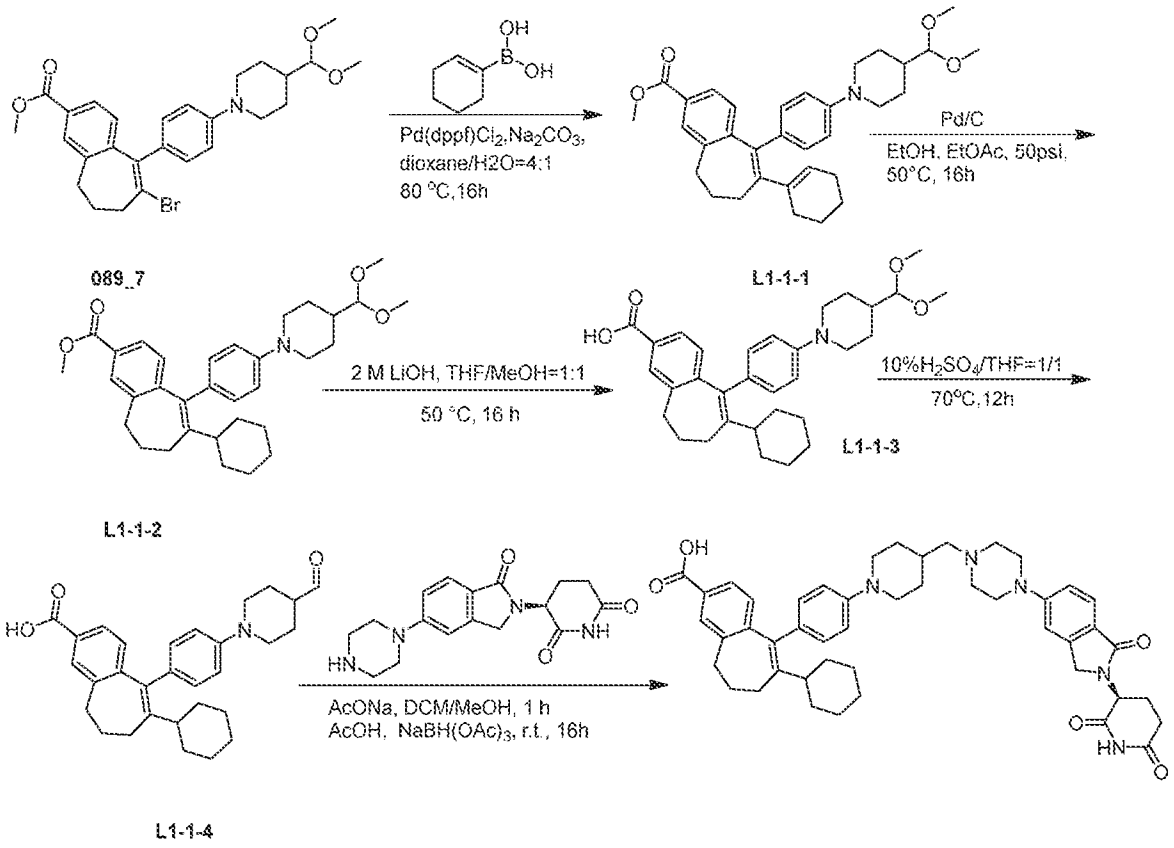
[1487] LCMS: calc. for $C_{42}H_{43}F_4N_7O_3$: 769.34, found: $[M+H]^+$ 770.2.

[1488] HPLC: 96.17% purity at 220 nm.

[1489] ^1H NMR (400 MHz, DMSO-d_6) δ =12.65 (s, 1H), 10.95 (s, 1H), 8.18 (s, 0.389H), 7.52 (d, J = 8.7 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.10 - 7.04 (m, 2H), 6.96 -6.88 (m, 4H), 6.73 (d, J = 8.8 Hz, 1H), 5.08 - 5.01 (m, 1H), 4.37 - 4.29 (m, 1H), 4.24 - 4.17 (m, 1H), 3.75 (br d, J = 12.6 Hz, 2H), 3.30 (br d, J = 4.2 Hz, 6H),3.06 - 2.97 (m, 2H), 2.94 - 2.86 (m, 1H), 2.75 - 2.73 (m, 1H), 2.75 - 2.65 (m, 2H), 2.62 - 2.52 (m, 3H), 2.40 - 2.31 (m, 3H), 2.23 (br d, J = 7.2 Hz, 2H), 2.09 - 2.01 (m, 2H), 2.00 - 1.93 (m, 1H), 1.87 - 1.79 (m, 2H), 1.78 - 1.68 (m, 1H), 1.27 - 1.16 (m, 2H)

[1490] SFC: retention time, 2.099 min; Area, 95.177%; method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM.

Example 85. Synthesis of (S)-8-cyclohexyl-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-15



[1491] ***Step 1.*** A mixture of methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (2 g, 1 Eq, 4 mmol) ,cyclohex-1-en-1-ylboronic acid (0.5 g, 1 Eq, 4 mmol) , Sodium carbonate (1 g, 0.7 mL, 3 Eq, 0.01 mol) ,1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (0.3 g, 0.1 Eq, 0.4 mmol) in 1,4-Dioxane (80 mL) and H_2O (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hour under N_2 atmosphere. TLC (petroleum ether/ethyl acetate=5/1, Rf=0.4) The reaction mixture was quenched by addition H_2O 50 mL , and then diluted with H_2O 100 mL and extracted with ethyl acetate (100 mL * 2). The combined organic layers were washed with brine 50 mL and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 50~50% Ethylacetate/Petroleum ethergradient @ 40 mL/min) and the organic layer was concentrated in vacuo to give methyl 8-(cyclohex-1-en-1-yl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (1.24 g, 2.34 mmol, 60 % yield, 97.1% purity) as a yellow solid. LC-MS (ESI^+) m/z: 516.0 $(M+H)^+$.

[1492] ***Step 2.*** A mixture of methyl 8-(cyclohex-1-en-1-yl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (600 mg, 1 Eq, 1.16 mmol), Pd/C (600 mg, 10% Wt, 0.485 Eq, 564 µmol) in EtOH (10 mL) and EtOAc (10 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 50 °C for 16hr under H_2(50 psi) atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*40mm*5um;mobile phase: [water(FA)-ACN];B% 45%-75%,10min) to give methyl 8-cyclohexyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (150 mg, 290 µmol, 24.9 %, 100% purity) was obtained as a yellow oil. LC-MS (ESI^+) m/z: 518.3 $(M+H)^+$.

[1493] ***Step 3.*** To a solution of methyl 8-cyclohexyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (150 mg, 1 Eq, 290 µmol) in THF (1 mL) and MeOH (1 mL) was added lithium hydroxide (69.4 mg, 1.45 mL, 2 molar, 10 Eq, 2.90 mmol) .The mixture was stirred at 50 °C for 16 hour. The reaction mixture was concentrated under reduced pressure to give 8-cyclohexyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (150 mg, 269 µmol, 92.8 %, 82.14% purity) as a white solid. LC-MS (ESI+) m/z: 504.1 (M+H)+

[1494] ***Step 4.*** A solution 8-cyclohexyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (150 mg, 1 Eq, 298 μmol) in 10% H_2SO_4 (2 mL) and THF (2 mL) was stirred at 70 °C for 12 hour to give a yellow suspension. TLC (petroleum ether/ethyl acetate=5/1, R_f=0.3) showed new spot was detected. The solvent was removed under vaccum. The aqueous solution was added $NaHCO_3$ to adjust pH=6. The residue was dissolved in water (30 mL) and extracted by ethyl acetate (30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give 8-cyclohexyl-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (120 mg, 262 μmol, 88.1 %) as a yellow oil.

[1495] ***Step 5.*** To a solution of 8-cyclohexyl-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (120 mg, 1 Eq, 262 μmol), (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, TsOH salt (131 mg, 1 Eq, 262 μmol) in DCM (3 mL), MeOH (3 mL) was added Sodium acetate (64.5 mg, 3 Eq, 787 μmol) was stirred at 25 °C for 60 mins, Then Sodium triacetoxyborohydride (111 mg, 2 Eq, 524 μmol) and Acetic acid (47.2 mg, 45.3 μL, 3 Eq, 787 μmol) was added .The mixture was stirred at 25 °C for 16 hour. The reaction was treated with H_2O (20 mL), extracted with EtOAc (20 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 32%-62%,7min) to give (S)-8-cyclohexyl-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (26.9 mg, 34.9 μmol, 13.3 %, 100% Purity) was obtained as a white solid.LC-MS (ESI^+) m/z: 770.2 $(M+H)^+$.

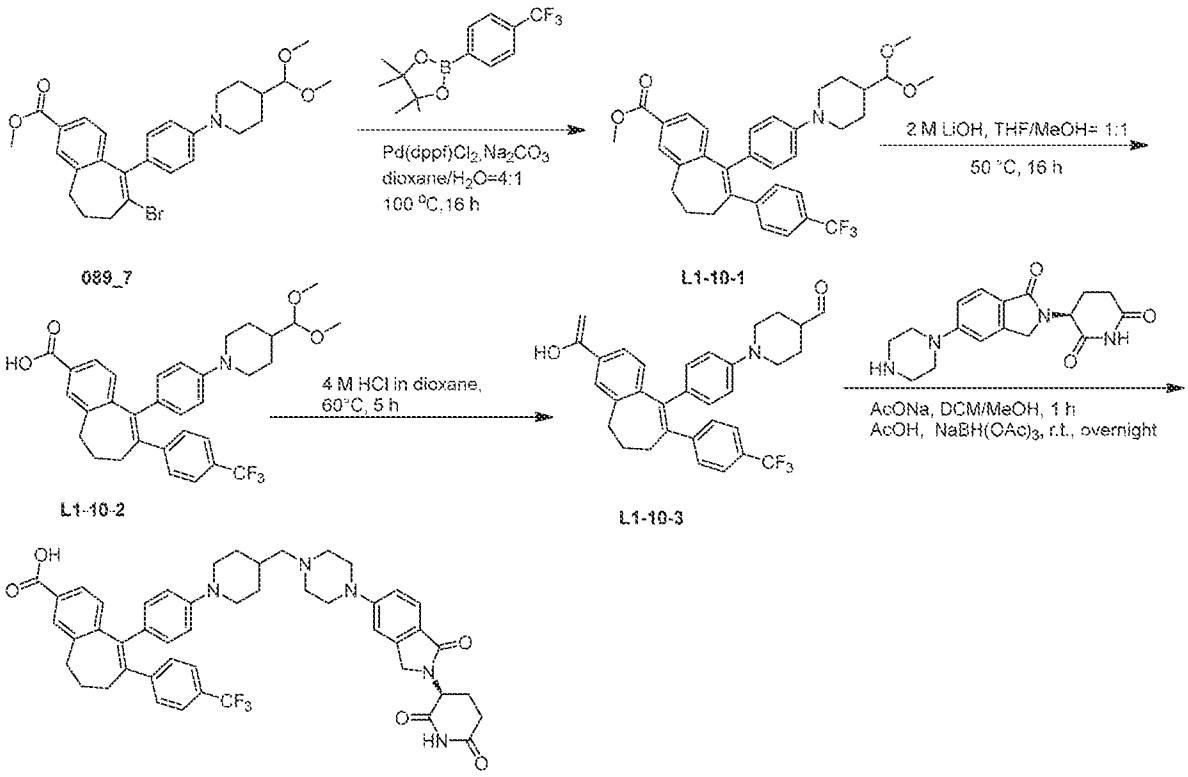
[1496] LCMS: calc. for $C_{47}H_{55}N_5O_5$: 769.42, found: $[M+H]^+$ 770.2.

[1497] HPLC: 96.740% purity at 220 nm.

[1498] ^1H NMR (400 MHz, DMSO-d_6) δ= 11.00 - 10.92 (m, 1H), 8.28 - 8.21 (m, 0.211H), 7.83 - 7.77 (m, 1H), 7.69 - 7.62 (m, 1H), 7.56 - 7.49 (m, 1H), 7.10 - 7.03 (m, 2H), 6.93 - 6.83 (m, 4H), 6.77 - 6.70 (m, 1H), 5.10 - 5.01 (m, 1H), 4.38 - 4.29 (m, 1H), 4.26 - 4.17 (m, 1H), 3.75 - 3.67 (m, 2H), 3.55 - 3.38 (m, 9H), 2.96 - 2.86 (m, 1H), 2.73 - 2.65 (m, 4H), 2.44 - 2.31 (m, 2H), 2.28 - 2.20 (m, 2H), 2.17 - 2.06 (m, 2H), 2.01 - 1.91 (m, 1H), 1.89 - 1.79 (m, 4H), 1.77 - 1.65 (m, 3H), 1.64 - 1.55 (m, 3H), 1.50 - 1.34 (m, 2H), 1.31 - 1.19 (m, 2H), 1.17 - 1.00 (m, 3H)

[1499] SFC: retention time, 9.976 min; Area, 99.105%; method: AD-RH_10-80_B_08ML_20min

Example 86. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-22



[1500] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 777.53 umol, 1 eq) , 4,4,5,5-tetramethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (250 mg, 918.88 umol, 1.18 eq), $Pd(dppf)Cl_2$(30 mg, 36.74 umol, 0.0047 eq) and Na_2CO_3(250 mg, 2.36 mmol, 3.03 eq) in mixture of dioxane (4 mL)and Water (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with 30 mL H_2O and extracted with EtOAc 50 mL (25 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min).

[1501] Compound methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 610.51 umol, 78.52% yield, 88.47% purity) was obtained as a brown solid.

[1502] TLC: petroleum ether: ethyl acetate=3:1, R_f =0.5

[1503] LC-MS (ESI^+) m/z: 580.4 $(M+H)^+$

[1504] ***Step 2.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 690.07 umol, 1 eq) in a mixture of MeOH (4 mL) and THF (4 mL) was added $LiOH·H_2O$ (2 M, 3.5 mL, 10.14 eq) .The mixture was stirred at 50 °C for 16 hr .The reaction mixture was poured into 30 mL of water and the aqueous phase was acidified with 1 M aq. HCl to pH=4. The mixture was extracted with EtOAc(25 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. This reaction was used to next step without purification. Compound 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (400 mg, 677.63 umol, 98.20% yield, 95.82% purity) was obtained as a brown solid.

[1505] LC-MS (ESI^+) m/z: 566.3$(M+H)^+$

[1506] ***Step 3.*** To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (360 mg, 636.47 umol, 1 eq) in HCl/dioxane (5 mL) .The mixture was stirred at 60 °C for 4 hr .The reaction mixture was concentrated to dryness in vacuo, and the mixture was used directly for the next step without purification. Compound 5-[4-(4-formyl-1-piperidyl)phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (300 mg, 577.42 umol, 90.72% yield) was obtained as a brown solid.

[1507] LC-MS (ESI^+) m/z: 520.4 $(M+H)^+$

[1508] ***Step 4.*** To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (100 mg, 192.47 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (150 mg, 299.66 umol, 1.56 eq, p-TSA), AcOH (12.60 mg, 209.82 umol, 12 uL, 1.09 eq) and AcONa (50 mg, 609.50 umol, 3.17 eq) in a mixture of DCM (4 mL) and MeOH (4 mL), the mixture was stirred at 25 °C for 1 hr, and then $NaBH(OAc)_3$ (60 mg, 283.10 umol, 1.47 eq) was added dropwise at 25 °C. The resulting mixture was stirred at 25°C for 16 hr. The reaction mixture was

concentrated to dryness in vacuo. The residue was purified by prep-HPLC (column: Welch Ultimate C18 150*25mm*5um; mobile phase: [water(FA)-ACN];B%: 28%-58%,10min).

[1509] Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-[4-(trifluoromethyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (26 mg, 30.73 umol, 15.97% yield, 98.33% purity) was obtained as a light yellow solid.

[1510] LC-MS (ESI^+) m/z: 832.2$(M+H)^+$

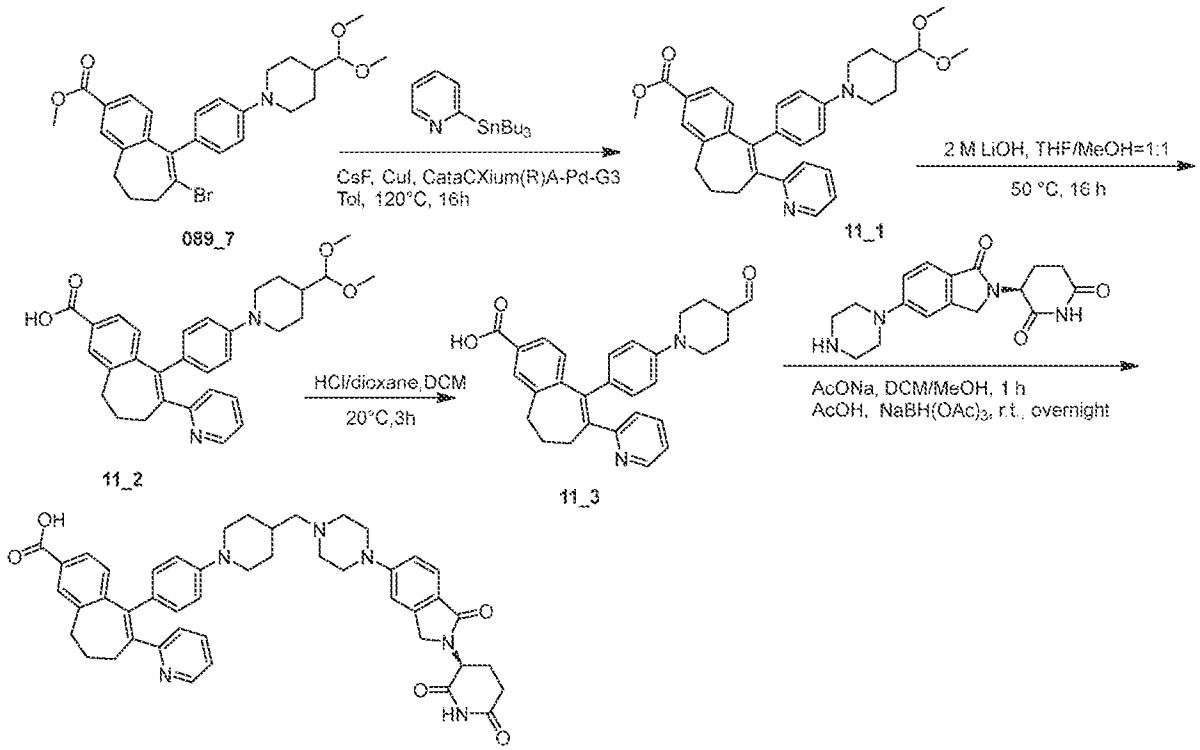
[1511] HPLC: 98.935 % purity at 220 nm

[1512] SFC: Rt: 1.073 min; Area, 100 %; method: OD-3-IPA+ACN(DEA)-60-3ML-35T

[1513] ^1H NMR (400 MHz, DMSO-d_6) δ = 10.98 - 10.85 (m, 1H), 8.22 - 8.19 (m, 1H), 7.96 - 7.84 (m, 1H), 7.80 - 7.67 (m, 1H), 7.60 - 7.48 (m, 3H), 7.44 - 7.34 (m, 2H), 7.10 - 6.99 (m, 2H), 6.93 - 6.82 (m, 1H), 6.74 - 6.62 (m, 4H), 5.10 - 4.99 (m, 1H), 4.39 - 4.28 (m, 1H), 4.26 - 4.15 (m, 1H), 3.68 - 3.57 (m, 3H), 2.95 - 2.79 (m, 4H), 2.69 - 2.65 (m, 1H), 2.63 - 2.54 (m, 5H), 2.45 - 2.30 (m, 3H), 2.30 - 2.24 (m, 2H), 2.20 (br d, J = 6.5 Hz, 2H), 2.16 - 1.84 (m, 4H), 1.81 - 1.74 (m, 2H), 1.71 - 1.61 (m, 1H), 1.21 - 1.10 (m, 2H)

[1514] ^{19}F NMR (377 MHz, DMSO- d_6) δ = -60.74 (br s, 1F)

Example 87. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-23



089_7 11_1 11_2 11_3

[1515] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(500 mg, 971.91 umol, 1 eq) , tributyl(2-pyridyl)stannane(357.80 mg, 971.91 umol, 311.13 uL, 1 eq) , CsF(295.27 mg, 1.94 mmol, 2 eq) , CuI(37.02 mg, 194.38 umol, 0.2 eq) and CataCXium(R)A-Pd-G3(70.78 mg, 97.19 umol, 0.1 eq) in toluene(3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 16 hr under N_2 atmosphere. The reaction mixture was quenched by addition **5** mL **H_2O**, and then diluted with 20 mL H_2O and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with saturated 10 mL brine water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, **Petroleum ether/Ethyl acetate=0/1** to 1/**1**) to give compound methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (310 mg, 604.72 umol, 62.22% yield) as a yellow solid.

[1516] LC-MS (ESI^+) m/z: 53.1 $(M+H)^+$.

[1517] ***Step 2.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(310 mg, 604.72 umol, 1 eq) in THF(1 mL) and MeOH(1 mL) was added LiOH(2 M, 3.02 mL, 10 eq).The mixture was stirred at 50 °C for 16 hr. The reaction was concentrated to dryness in vacuo to give a yellow solid. The crude product 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid(280 mg, 561.56 umol, 92.86% yield) as yellow solid was used into the next step without further purification.

[1518] LC-MS (ESI^+) m/z: 499.1 $(M+H)^+$.

[1519] ***Step 3.*** To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (270 mg, 541.50 umol, 1 eq) in HCl/dioxane (4 mL) and DCM (1 mL). The mixture was stirred at 20 °C for 3 hr. The reaction was concentrated to dryness in vacuo to give a yellow solid. The crude product 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (230 mg, 470.34 umol, 86.86% yield) yellow solid was used into the next step without further purification.

[1520] LC-MS (ESI^+) m/z: 453.3 $(M+H)^+$

[1521] ***Step 4.*** To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid(230 mg, 470.34 umol, 1 eq, HCl) in DCM(1 mL) and MeOH(1 mL) was added acetic acid (56.49 mg, 940.69 umol, 53.80 uL, 2 eq) (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione(185.33 mg, 564.41 umol, 1.2 eq) and sodium acetate (192.92 mg, 2.35 mmol, 5 eq). The mixture was stirred at 20 °C for 1 hr .Then the $NaBH(OAc)_3$(199.37 mg, 940.69 umol, 2 eq) added to the mixture and stirred at 20 °C for 12 hr . The reaction mixture was concentrated under reduced pressure to remove DCM and MeOH. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN];B%: 10%-40%,7min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(2-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (20 mg, 25.87 umol, 5.56% yield, 98.939% purity) was obtained as a yellow solid.

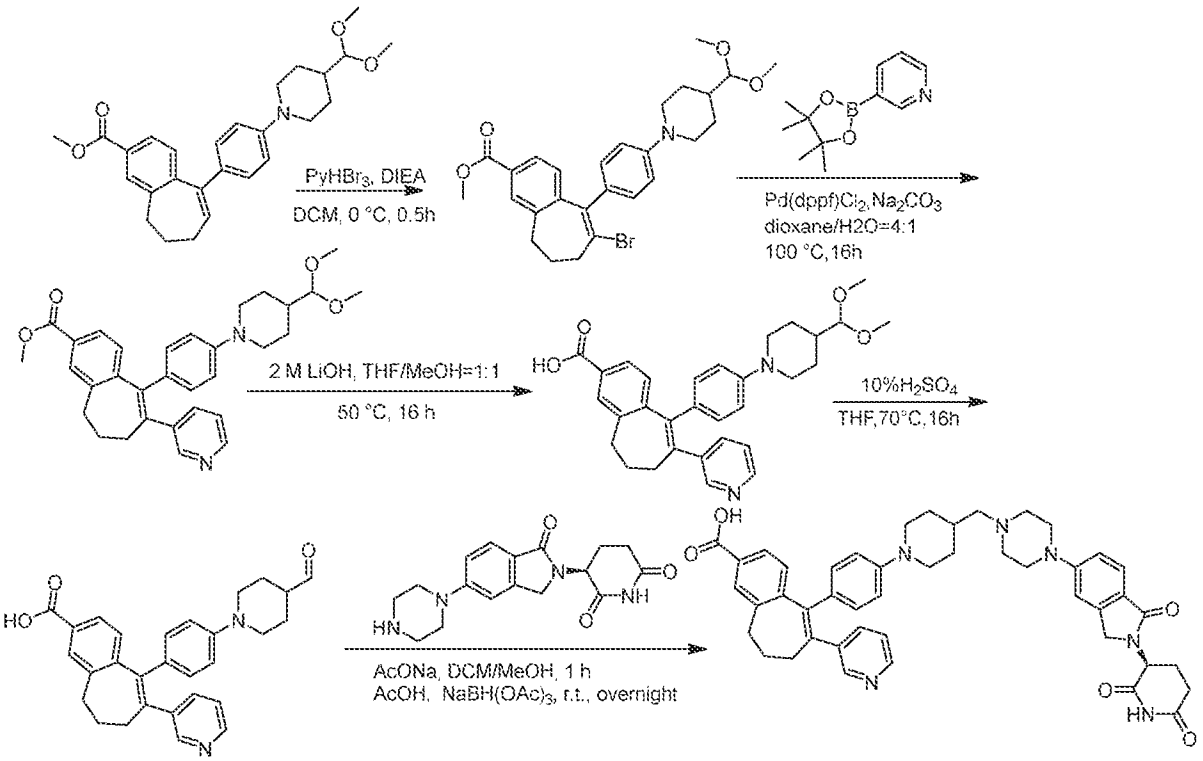
[1522] LC-MS (ESI^+) m/z: 765.5 $(M+H)^+$

[1523] HPLC: 98.939% purity at 220 nm.

[1524] ^{1}H NMR (400 MHz, DMSO-d_6) δ= 10.95 (s, 1H), 8.57 (br d, J = 4.8 Hz, 1H), 8.20 (s, 0.239H), 7.90 (s, 1H), 7.75 (br d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.8 Hz,1H), 7.46 (br t, J = 7.8 Hz, 1H), 7.14 (t, J = 6.0 Hz, 1H), 7.10 - 7.03 (m, 2H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.71 (br d, J = 8.8 Hz, 2H),6.65 (br d, J = 8.8 Hz, 2H), 5.05 (dd, J = 4.9, 13.2 Hz, 1H), 4.33 (br d, J = 17.1 Hz, 1H), 4.21 (br d, J = 17.1 Hz, 1H), 3.74 - 3.52 (m, 6H), 2.95 - 2.74 (m, 4H),2.73 - 2.55 (m, 4H), 2.45 - 2.32 (m, 6H), 2.21 (br d, J = 7.0 Hz, 2H), 2.11 - 2.04 (m, 2H), 2.01 - 1.92 (m, 1H), 1.78 (br d, J = 11.8 Hz, 2H), 1.17 (br d, J = 10.3Hz, 2H)

[1525] SFC: retention time, 8.014 min; Area, 100%; method: AD-RH_10-80_B_08ML_20min

Example 88. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(3-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-11



[1526] ***Step 1.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (1.2 g, 2.76 mmol, 1 eq) in DCM (10 mL) was added Py·HBr_3 (925.20 mg, 2.89 mmol, 1.05 eq) and DIEA(534.12 mg, 4.13 mmol, 719.84 uL, 1.5 eq). The mixture was stirred at 0 °C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by column chromatography (SiO_2,

petroleum ether/ethyl acetate=1/0 to 3/1). Compound methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (1 g, 1.87 mmol, 67.78% yield, 96.067% purity) was obtained as a yellow oil.

[1527] LC-MS (ESI^+) m/z: 516.0 $(M+H)^+$.

[1528] ***Step 2.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (200 mg, 388.76 umol, 1.2 eq) , 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (66.43 mg, 323.97 umol, 1 eq) , $Pd(dppf)Cl_2$(26.46 mg, 32.40 umol, 0.1 eq) , Na_2CO_3 (103.01 mg, 971.90 umol, 3 eq) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The mixture was added LiOH (2 M, 1.62 mL, 10 eq) at 50°C for 16 hr. The reaction mixture was added by addition **5** mL **H_2O**, and then the mixture was adjusted with HCl to pH=5 then diluted with 20 mL ethyl acetate and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with saturated salt water 10 mL, dried over ahydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 14%-44%, 7min). Compound 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(3-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (92 mg, 184.51 umol, 56.95% yield) was obtained as a yellow solid.

[1529] LC-MS (ESI^+) m/z: 499.2 $(M+H)^+$.

[1530] ***Step 3.*** 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(3-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (92 mg, 184.51 umol, 1 eq) was added to THF (2 mL) and H_2SO_4 (2 mL, 10% purity). The mixture was stirred at 70 °C for 16 hr. The reaction mixture was concentrated under reduced pressure to remove **THF and** diluted with **5** mL ethyl acetate. Then the mixture was adjusted with saturated sodium carbonate to pH=5 and extracted with EA (25 mL * 2). The combined organic layers were washed with Saturated salt water 30 mL, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The crude product 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(3-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (70 mg, 154.68 umol, 83.83% yield) as yellow solid was used into the next step without further purification.

[1531] ***Step 4.*** To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(3-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (70 mg, 154.68 umol, 1 eq) in DCM (1 mL) and MeOH (1 mL) was added (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (101.58

mg, 309.36 umol, 2 eq) acetic acid (18.58 mg, 309.36 umol, 17.69 uL, 2 eq) and sodium acetate (63.45 mg, 773.41 umol, 5 eq). The mixture was stirred at 20 °C for 12 hr. Then the $NaBH(OAc)_3$(65.57 mg, 309.36 umol, 2 eq) added to the mixture and stirred at 20 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove DCM and MeOH. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B%: 13%-43%,7min) to give desired compound (**20** mg, yield **15.26**%, purity 67.160%) as a white solid, which was further separated by SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um);mobile phase: [0.1%NH3H2O ETOH];B%: 50%-50%,min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(3-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (13 mg, 15.34 umol, 9.92% yield, 90.271% purity) was obtained as a yellow solid.

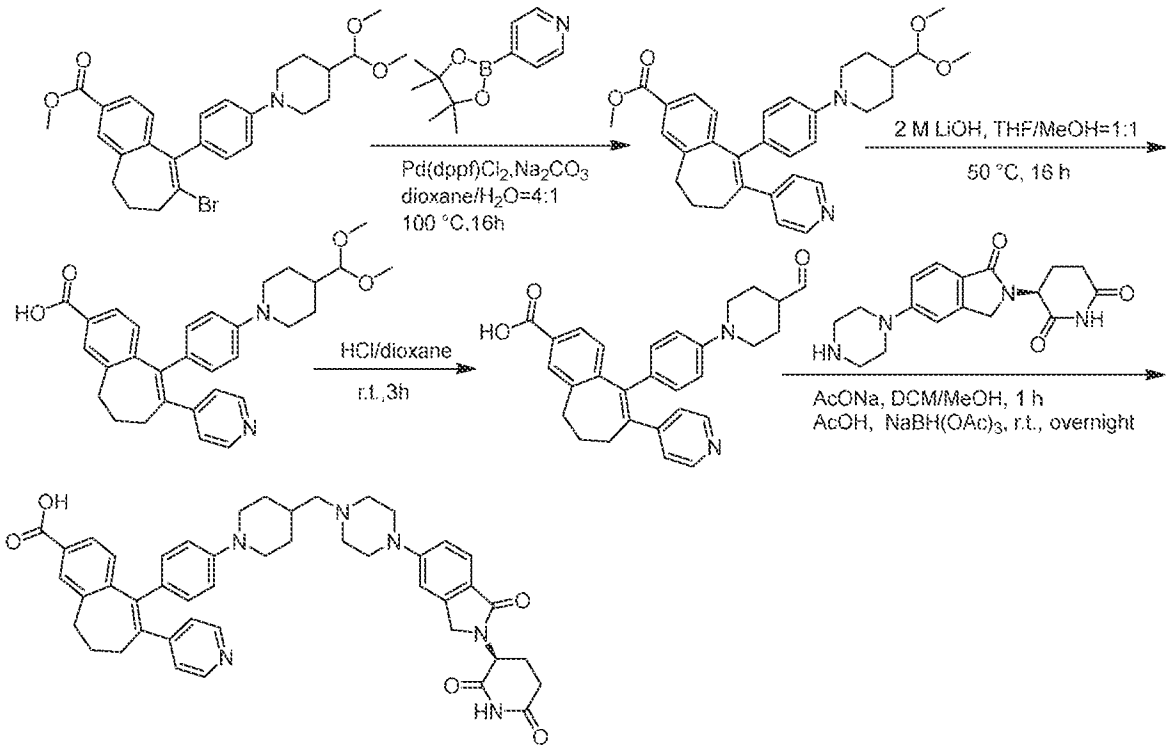
[1532] LC-MS (ESI^+) m/z: 765.6 $(M+H)^+$

[1533] HPLC: 90.271% purity at 220 nm.

[1534] SFC: retention time: 3.840 Area: 98.596%, method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM

[1535] ^1H NMR (400 MHz, DMSO-d_6) δ = 10.95 (br d, J = 5.0 Hz, 1H), 8.29 (s, 1H), 8.29 (d, J = 4.4 Hz, 1H), 7.77 (s, 1H), 7.62 (br d, J = 7.5 Hz, 2H), 7.51 (d, J =8.3 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.08 - 7.03 (m, 2H), 6.73 - 6.64 (m, 5H), 5.04 (br d, J = 18.1 Hz, 1H), 4.31 (s, 1H), 4.22 (s, 1H), 3.61 (br s, 2H), 3.29 - 3.26(m, 4H), 2.99 - 2.83 (m, 3H), 2.78 (br s, 2H), 2.59 (br s, 2H), 2.52 (br s, 2H), 2.47 - 2.45 (m, 3H), 2.29 - 2.15 (m, 5H), 2.09 (br s, 2H), 1.78 (br d, J = 12.3 Hz, 2H), 1.23 (d, J = 5.0 Hz, 2H)

Example 89. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-24



[1536] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 777.53 umol, 1 eq) , 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (239.16 mg, 1.17 mmol, 1.5 eq) , $Pd(dppf)Cl_2$ (63.50 mg, 77.75 umol, 0.1 eq), Na_2CO_3 (247.23 mg, 2.33 mmol, 3 eq) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was quenched by addition **5** mL **H_2O**, and then diluted with 20 mL and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with 10 mL saturated salt water, dried over ahydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1 to 3/1). The crude product methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (254 mg, 495.48 umol, 63.72% yield) as yellow solid was used into the next step without further purification.

[1537] LC-MS (ESI^+) m/z: 513.1 $(M+H)^+$.

[1538] *Step 2.* To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (254 mg, 495.48 umol, 1 eq) in THF (1 mL) and MeOH (1 mL) was added LiOH (2 M, 2.48 mL, 10 eq). The mixture was stirred at 50 °C for 16 hr . The reaction was concentrated to dryness in vacuo to give a yellow solid. The crude product 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (230 mg, 461.28 umol, 93.10% yield) as yellow solid was used into the next step without further purification. LC-MS (ESI^+) m/z: 499.1 $(M+H)^+$.

[1539] *Step 3.* 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (230 mg, 461.28 umol, 1 eq) in HCl/dioxane (4 mL) and DCM (1 mL). The mixture was stirred at 20 °C for 3 hr. The reaction was concentrated to dryness in vacuo to give a white solid. The crude product 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (190 mg, 388.54 umol, 84.23% yield, HCl) as white solid was used into the next step without further purification. LC-MS (ESI^+) m/z: 453.0 $(M+H)^+$

[1540] *Step 4.* To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (190 mg, 388.54 umol, 1 eq, HCl) in DCM (1 mL) and MEOH (1 mL) was added acetic acid (46.67 mg, 777.09 umol, 44.44 uL, 2 eq) (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (153.10 mg, 466.25 umol, 1.2 eq) and sodium acetate (159.37 mg, 1.94 mmol, 5 eq). The mixture was stirred at 20 °C for 12 hr .Then the $NaBH(OAc)_3$(164.70 mg, 777.09 umol, 2 eq) added to the mixture and stirred at 20 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove DCM and MeOH. The residue was purified by prep-HPLC (column: Phenomenex C18 80*30mm*3um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 0%-30%, 7min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(4-pyridyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (36 mg, 44.85 umol, 11.54% yield, 95.298% purity) was obtained as a yellow solid.

[1541] LC-MS (ESI^+) m/z: 765.4 $(M+H)^+$

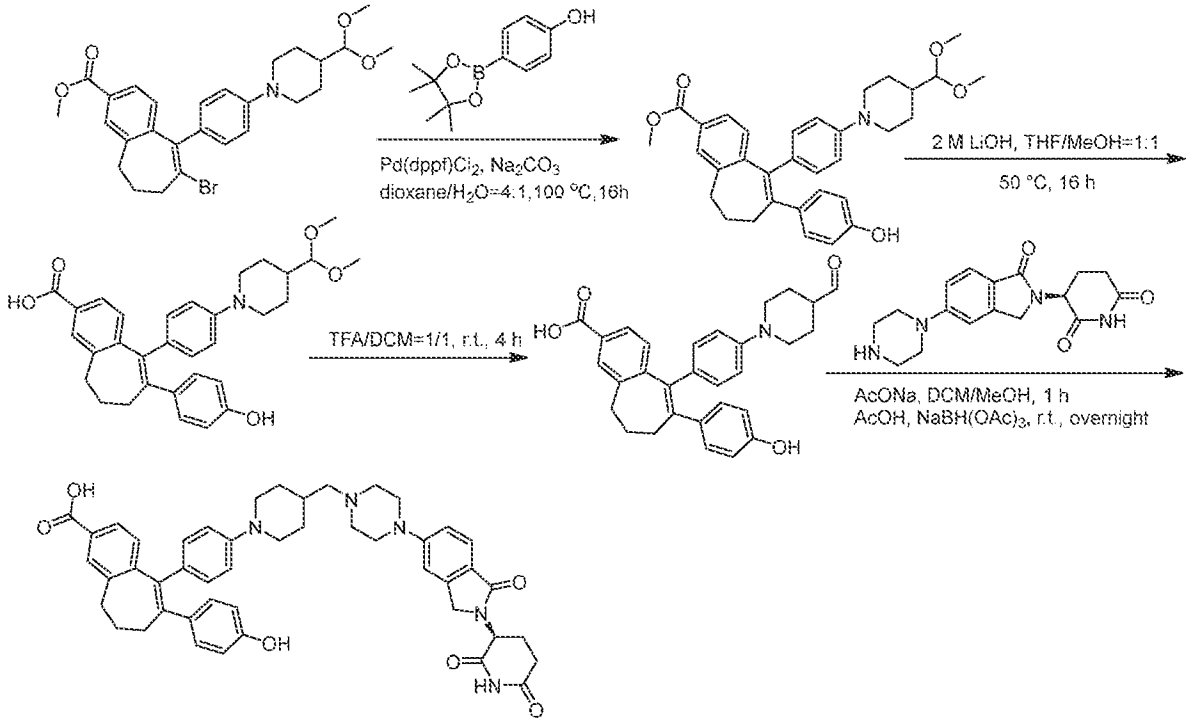
[1542] HPLC: 95.298 % purity at 220 nm.

[1543] ^1H NMR (400 MHz, DMSO-d_6) δ= 10.95 (s, 1H), 8.39 (d, J = 5.5 Hz, 2H), 7.90 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.53 (br d, J = 9.0 Hz, 1H), 7.16 (d, J = 5.8Hz, 2H), 7.08 (br s, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.69 (q, J = 8.9 Hz, 4H), 5.05 (dd, J = 5.0, 13.1 Hz, 1H), 4.33 (br d, J = 17.1 Hz, 1H), 4.21 (br d, J = 17.1 Hz, 1H), 3.66 (br d, J = 12.5 Hz, 2H), 3.29 (br s, 4H), 2.96 - 2.78

(m, 3H), 2.68 - 2.55 (m, 4H), 2.44 - 2.30 (m, 3H), 2.24 (br d, J = 6.8 Hz, 3H), 2.12 (br d, J =6.0 Hz, 3H), 2.07 - 1.88 (m, 2H), 1.84 - 1.66 (m, 3H), 1.19 (br s, 2H)

[1544] SFC: retention time, 7.694 min; Area, 100%; method: OJ-RH_10-80_B_08ML_20min.

Example 90. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-25



[1545] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(500 mg, 971.91 umol, 1 eq) , 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol(320.84 mg, 1.46 mmol, 1.5 eq) , $Pd(dppf)Cl_2$(79.37 mg, 97.19 umol, 0.1 eq), Na_2CO_3(309.0 mg, 2.92 mmol, 3 eq) in dioxane (3 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was quenched by addition 5 mL H_2O, and then diluted with 20 mL H_2O and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with saturated salt water 10 mL, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=0/1 to 3/1). The crude product methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-hydroxyphenyl)-8,9-

dihydro-7H-benzo[7]annulene-2-carboxylate (500 mg, 947.60 umol, 97.50% yield, 100% purity) as yellow solid. LC-MS (ESI^+) m/z: 528.2 $(M+H)^+$.

[1546] ***Step 2.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(500 mg, 947.60 umol, 1 eq) in THF (1 mL) and MeOH (1 mL) was added LiOH (2 M, 4.74 mL, 10 eq).The mixture was stirred at 50 °C for 16 hr . The reaction was concentrated to dryness in vacuo to give a yellow oil. The crude product 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (480 mg, 934.54 umol, 98.62% yield) as yellow oil was used into the next step without further purification.

[1547] ***Step 3.*** To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid(240 mg, 467.27 umol, 1 eq) in DCM(2 mL) and TFA(2 mL) .The mixture was stirred at 20 °C for 4 hr . The reaction was concentrated to dryness in vacuo to give a yellow solid. The crude product 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid(200 mg, 396.81 umol, 84.92% yield) as yellow solid was used into the next step without further purification.

[1548] LC-MS (ESI^+) m/z: 468.0 $(M+H)^+$

[1549] ***Step 4.*** To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (200 mg, 396.81 umol, 1 eq, TFA)in DCM (1 mL) and MeOH (1 mL) was added acetic acid(47.66 mg, 793.63 umol, 45.39 uL, 2 eq) (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione(156.36 mg, 476.18 umol, 1.2 eq) and sodium acetate(162.76 mg, 1.98 mmol, 5 eq).The mixture was stirred at 20 °C for 1 hr. Then the $NaBH(OAc)_3$(168.20 mg, 793.63 umol, 2 eq) added to the mixture and stirred at 20 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove DCM and MeOH. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN];B%: 20%-50%,7min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(4-hydroxyphenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (37 mg, 47.33 umol, 11.93% yield, 99.776% purity) was obtained as a yellow solid.

[1550] LC-MS (ESI^+) m/z: 514.1 $(M+H)^+$.

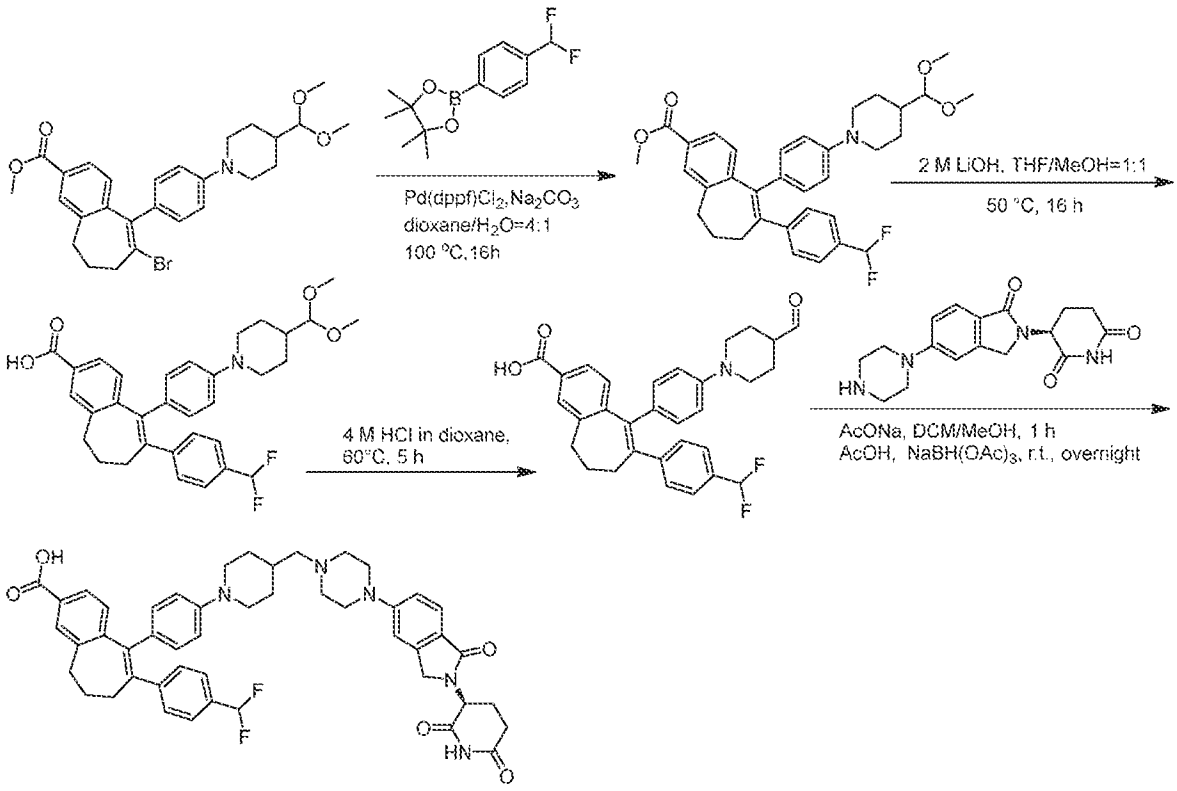
[1551] LC-MS (ESI^+) m/z: 780.3 $(M+H)^+$

[1552] HPLC: 99.776% purity at 220 nm.

[1553] ^{1}H NMR (400 MHz, DMSO-d_6) δ= 10.95 (s, 1H), 9.33 (s, 1H), 8.13 (s, 0.288H), 7.85 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.09 - 7.03(m, 2H), 6.98 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.0 Hz, 1H), 6.71 - 6.63 (m, 4H), 6.58 (br d, J = 8.0 Hz, 2H), 5.10 - 4.97 (m, 1H), 4.38 - 4.28 (m, 1H), 4.26 -4.14 (m, 1H), 3.72 - 3.53 (m, 2H), 3.32 - 3.21 (m, 8H), 2.88 (br d, J = 12.5 Hz, 1H), 2.78 (br d, J = 6.0 Hz, 2H), 2.57 (br d, J = 12.3 Hz, 4H), 2.42 - 2.36 (m,2H), 2.24 - 2.13 (m, 3H), 2.12 - 2.05 (m, 2H), 2.00 - 1.92 (m, 1H), 1.69 (br s, 3H), 1.24 - 1.10 (m, 2H)

[1554] SFC: retention time, 8.892 min; Area, 100%; method: OJ-RH_10-80_B_08ML_20min

Example 91. Synthesis of 6-[4-(difluoromethyl)phenyl]-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-26



[1555] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro- 7H-benzo[7]annulene-2-carboxylate(400 mg, 777.53 umol, 1 eq), 2-[4-(difluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(240 mg, 944.58 umol,1.21 eq), $Pd(dppf)Cl_2$(320 mg,391.85 umol,0.05 eq) and Na_2CO_3 (250 mg,2.36 mmol, 3.03 eq) in mixture of dioxane (4 mL) and water (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 16hr under N_2 atmosphere. The reaction mixture was diluted

with 30 mL H_2O and extracted with EtOAc 50 mL (25 mL*2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography(ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleumethergradient@ 60mL/min).Compound methyl6-[4-(difluoromethyl)phenyl]-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 612.69 umol, 78.80% yield, 86.03% purity) was obtained as a yellow solid.

[1556] TLC: petroleum ether: ethyl acetate=3:1, R_f =0.4

[1557] LC-MS (ESI^+) m/z: 562.2 $(M+H)^+$

[1558] ***Step 2.*** To a solution of methyl 6-[4-(difluoromethyl)phenyl]-5-[4-[4-(dimethoxymethyl)-1-piperidyl] phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400.00 mg,712.18 umol,1 eq) in a mixture of MeOH (4 mL) and THF (4 mL) was added LiOH H2O (2 M, 3.6 mL, 10.11 eq) .The mixture was stirred at 50 °C for 16hr .The reaction mixture was poured into 30 mL of water and the aqueous phase was acidified with 1 M aq. HCl to pH=4. The mixture was extracted with EtOAc (25 mL * 2). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. This reaction was used to next step without purification. Compound 6-[4-(difluoromethyl)phenyl]- 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (400 mg, 682.87umol, 95.88% yield, 93.49% purity) was obtained as a yellow solid.

[1559] LC-MS (ESI+) m/z: 548.3$(M+H)^+$

[1560] ***Step 3.*** To a solution of 6-[4-(difluoromethyl)phenyl]-5-[4-[4-(dimethoxymethyl)-1-piperidyl] phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylicacid(400mg,730.42umol,1eq) in HCl/dioxane (5 mL) .The mixture was stirred at 60°C for 4hr . The reaction mixture was concentrated to dryness in vacuo, and the mixture was used directly for the next step without purification.Compound 6-[4-(difluoromethyl)phenyl]-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylicacid (350 mg, 697.82 umol, 95.54% yield) was obtained as a yellow solid.

[1561] LC-MS (ESI^+) m/z: 502.2 $(M+H)^+$

[1562] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.63 - 9.62 (m, 1H), 9.68 - 9.54 (m, 1H), 7.93 - 7.90 (m, 1H), 7.78 - 7.73 (m, 1H), 7.44 - 7.38 (m, 2H), 7.35 - 7.29 (m,2H), 6.97 (s, 1H), 6.92 - 6.74

(m, 4H), 3.57 (s, 4H), 2.90 - 2.77 (m, 3H), 2.32 - 2.25 (m, 2H), 2.17 - 2.08 (m, 2H), 2.01 -1.90 (m, 2H), 1.74 - 1.52 (m, 3H),0.89 - 0.70 (m, 4H)

[1563] ^{19}F NMR (376 MHz, DMSO- d_6) δ = -107.47 - -111.63 (m, 1F)

[1564] ***Step 4.*** To a solution of 6-[4-(difluoromethyl)phenyl]-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro -7H-benzo[7]annulene-2-carboxylic acid(100 mg, 199.38 umol,1 eq), (3S)-3-(1-oxo-5-piperazin -1-yl-isoindolin-2-yl)piperidine-2,6-dione (150 mg, 299.66 umol, 1.5eq, p-TSA salt), AcONa (50 mg, 609.53 umol, 3.0 eq) ,and AcOH (12.60 mg, 209.82 umol, 12 uL, 1.05 eq) in a mixture of DCM(4 mL) and MeOH (4mL),the mixture was stirred at 25°C for 1hr, and then $NaBH(OAc)_3$ (60 mg, 283.10 umol, 1.42 eq)was added dropwise at 25°C. The resulting mixture was stirred at 25°C for 16hr.The residue was purified by prep-HPLC (column: Welch Ultimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];B%: 24%-54%,10min). Compound 6-[4-(difluoromethyl)phenyl]-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (9 mg, 10.79 umol, 5.41% yield, 97.54% purity) was obtained as a light yellow solid.

[1565] LC-MS (ESI^+) m/z: 814.2 $(M+H)^+$

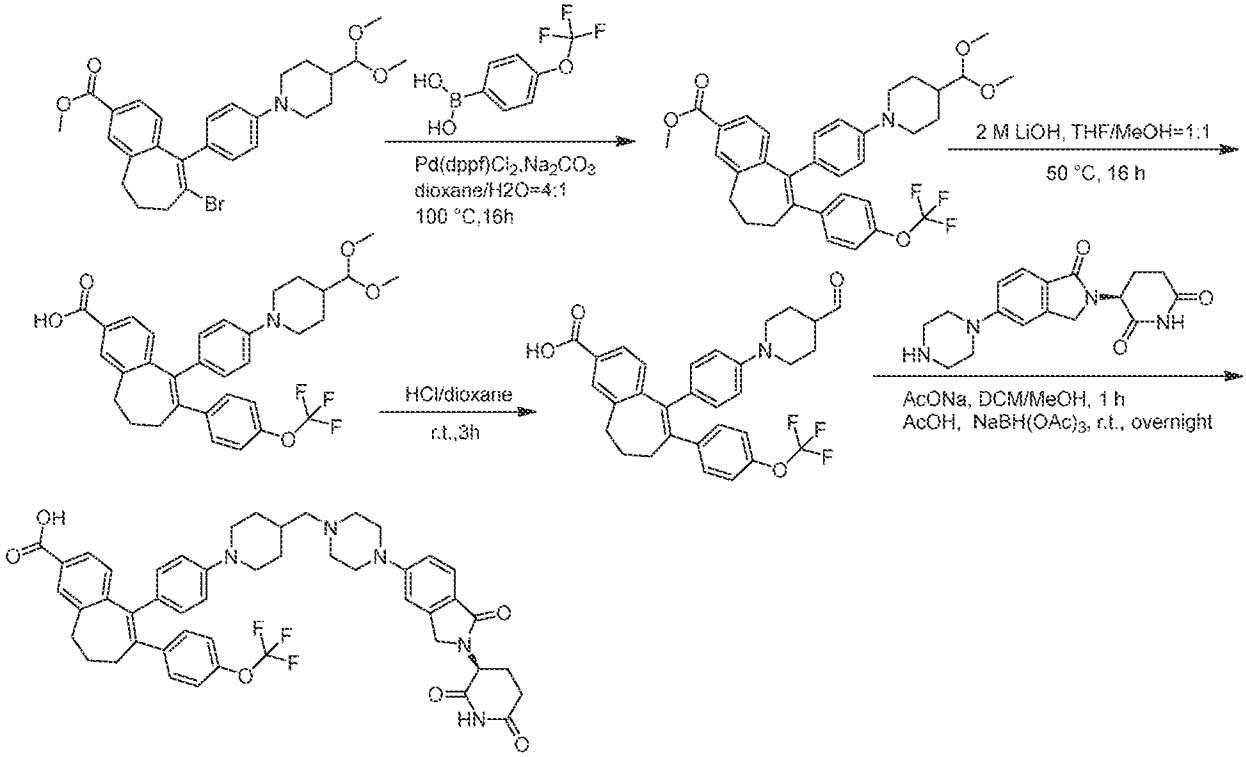
[1566] HPLC: 99.015 % purity at 220 nm

[1567] SFC: Rt: 1.148 min; Area, 100 %; method: OD-3-IPA+ACN(DEA)-60-3ML-35T

[1568] ^{1}H NMR (400 MHz, DMSO- d_6) δ = 10.91 (s, 1H), 8.19 (s, 1H), 7.91 (s, 1H), 7.78 - 7.70 (m, 1H), 7.54 - 7.47 (m, 1H), 7.43 - 7.36 (m, 2H), 7.32 (br d, J = 7.1 Hz, 2H), 7.08 - 7.01 (m, 2H), 6.91 - 6.84 (m, 1H), 6.67 (br s, 4H), 5.08 - 5.00 (m, 1H), 4.36 - 4.28 (m, 2H), 4.23 - 4.16 (m, 2H), 2.86 - 2.79 (m, 5H), 2.67 (br d, J = 1.6 Hz, 2H), 2.62 - 2.53 (m, 8H), 2.25 (br d, J = 5.5 Hz, 2H), 2.20 (br d, J = 5.3 Hz, 2H), 2.14 - 2.07 (m, 3H), 1.99 - 1.91 (m, 2H), 1.77 (br d, J = 11.6 Hz, 2H), 1.19 - 1.12 (m, 2H)

[1569] ^{19}F NMR (377 MHz, DMSO- d_6) δ = -109.03 - -109.28 (m, 1F)

Example 92. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-27



[1570] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 777.53 umol, 1 eq) , [4-(trifluoromethoxy)phenyl]boronic acid (240.17 mg, 1.17 mmol, 1.5 eq), $Pd(dppf)Cl_2$(63.50 mg, 77.75 umol, 0.1 eq), Na_2CO_3 (247.23 mg, 2.33 mmol, 3 eq) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was quenched by addition 5 mL H_2O, and then diluted with 20 mL ethyl acetate and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with 10 mL saturated salt water, dried over ahydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1 to 3/1). The crude product methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (342 mg, 574.17 umol, 73.84% yield) as yellow solid was used into the next step without further purification.

[1571] LC-MS (ESI^+) m/z: 596.2 $(M+H)^+$.

[1572] *Step 2.* To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (342 mg, 574.17 umol, 1 eq) in THF (2 mL) and MeOH(2mL)was added lithium hydroxide (2 M, 2.87 mL, 10 eq). The mixture was stirred at 50 °C for 16 hr. The reaction was concentrated to dryness in vacuo to give a yellow solid. The crude product 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (300 mg, 515.80 umol, 89.83% yield) as a yellow solid was used into the next step without further purification. LC-MS (ESI^+) m/z: 582.1 $(M+H)^+$.

[1573] *Step 3.* To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (300 mg, 515.80 umol, 1 eq) in HCl/dioxane (4 mL) and DCM (1 mL) .The mixture was stirred at 20 °C for 3 hr . The reaction was concentrated to dryness in vacuo to give a white solid. The crude product 5-[4-(4-formyl-1-piperidyl)phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (240 mg, 419.57 umol, 81.34% yield, HCl salt) as white solid was used into the next step without further purification.

[1574] *Step 4.* To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (240 mg, 419.57 umol, 1 eq, HCl)in DCM (1 mL) and MEOH (1 mL) was added sodium acetate(177.85 mg, 839.14 umol, 2 eq) (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (275.54 mg, 839.14 umol, 2 eq) and acetic acid (50.39 mg, 839.14 umol, 47.99 uL, 2 eq). The mixture was stirred at 20 °C for 12 hr .Then the $NaBH(OAc)_3$ (172.09 mg, 2.10 mmol, 5 eq) added to the mixture and stirred at 20 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove DCM and MeOH. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN];B%: 30%-60%,7 min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-[4-(trifluoromethoxy)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (78.5 mg, 91.08 umol, 21.71% yield, 98.385% purity) as yellow solid was obtained as a yellow solid.

[1575] LC-MS (ESI^+) m/z: 848.1 $(M+H)^+$

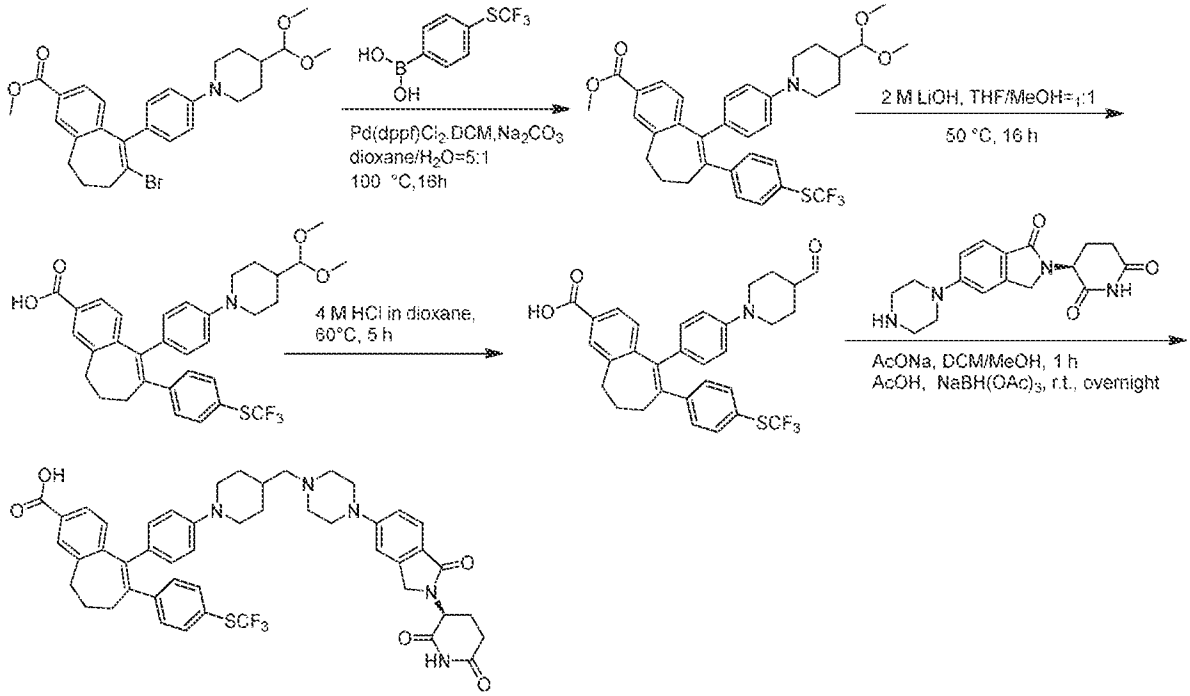
[1576] HPLC: 98.197% purity at 220 nm.

[1577] ^1H NMR (400 MHz, DMSO-d_6) δ= 10.95 (s, 1H), 8.14 (s, 0.163H), 7.89 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H),7.20 (br d, J = 8.3 Hz, 2H),

7.11 - 7.02 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.71 - 6.62 (m, 4H), 5.05 (dd, J = 5.0, 13.3 Hz, 1H), 4.33 (br d, J = 16.8 Hz, 1H), 4.20 (br d, J = 16.8 Hz, 1H), 3.63 (br d, J = 11.5 Hz, 2H), 3.30 - 3.25 (m, 4H), 2.96 - 2.80 (m, 3H), 2.67 - 2.54 (m, 5H), 2.46 - 2.21 (m, 6H), 2.12 (br d, J = 6.3Hz, 2H), 2.03 - 1.91 (m, 1H), 1.78 (br d, J = 11.5 Hz, 2H), 1.34 - 1.04 (m, 4H)

[1578] SFC: retention time, 2.330 min; Area, 95.986%; method: ID_MeOH_DEA_100_1ML_10MIN_10CM.

Example 93. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid I-14



[1579] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (300 mg, 583.15 umol, 1 eq) , [4-(trifluoromethylsulfanyl)phenyl]boronic acid (155 mg, 698.22 umol, 1.2 eq) , $Pd(dppf)Cl_2$·DCM(50 mg, 61.23 umol, 1.05e-1 eq) and Na_2CO_3 (190 mg, 1.79 mmol, 3.07 eq) in mixture of dioxane (5 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with water 30 mL and extracted with ethyl acetate 50 mL (25 mL*2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue as black solid. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl

acetate/Petroleum ether @ 60 mL/min). Compound methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (330 mg, 469.58 umol, 80.53% yield, 87.045% purity) was obtained as a yellow solid. LC-MS (ESI^+) m/z: 612.2 $(M+H)^+$

[1580] ***Step 2.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (300 mg, 490.43 umol, 1 eq) in mixture of MeOH (2 mL) and THF (2 mL) was added LiOH (2 M, 2.5 mL, 10.2 eq). The mixture was stirred at 50 °C for 16 hr. The reaction mixture was poured into 20 mL of ice-water carefully and acidified with 1M HCl to pH=4. The resulting solution was extracted with ethyl acetate 60 mL (30 mL × 2).dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue as a yellow solid. Compound 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (295 mg, 456.7 umol, 93.1% yield, 92.542% purity) was obtained as a yellow solid. This reaction was used to next step without purification. LC-MS (ESI^+) m/z: 516.1 $(M+H)^+$

[1581] ***Step 3.*** To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7Hbenzo[7]annulene-2-carboxylic acid (150 mg, 250.97 umol, 1 eq) in HCl/dioxane (2 mL) .The mixture was stirred at 60 °C for 5 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Compound 5-[4-(4-formyl-1-piperidyl)phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (140 mg, crude) was obtained as a brown solid. This reaction was not purified for the next reaction.

[1582] TLC(petroleum ether/ethyl acetate=3/1,R_f=0.45) confirmed

[1583] ***Step 5.*** To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (70 mg, 126.90 umol, 1 eq) in DCM (2 mL) was added (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (96 mg, 191.78 umol, 1.51 eq, p-TSA salt), AcOH (7.62 mg, 126.90 umol, 7.26 uL, 1 eq)and AcONa (31.23 mg, 380.70 umol, 3 eq) at 25°C. After addition, the mixture was stirred at this temperature for 1 hr, and then $NaBH(OAc)_3$ (40.34 mg, 190.35 umol, 1.5 eq) in MeOH (2 mL) was added dropwise at 25°C. The resulting mixture was stirred at 25 °C for 15 hr. The reaction mixture concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile

phase: [water(FA)-ACN];B%: 28%-58%,10min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-[4-(trifluoromethylsulfanyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (6.1 mg, 6.86 umol, 5.4% yield, 97.1% purity) was obtained as a yellow solid.

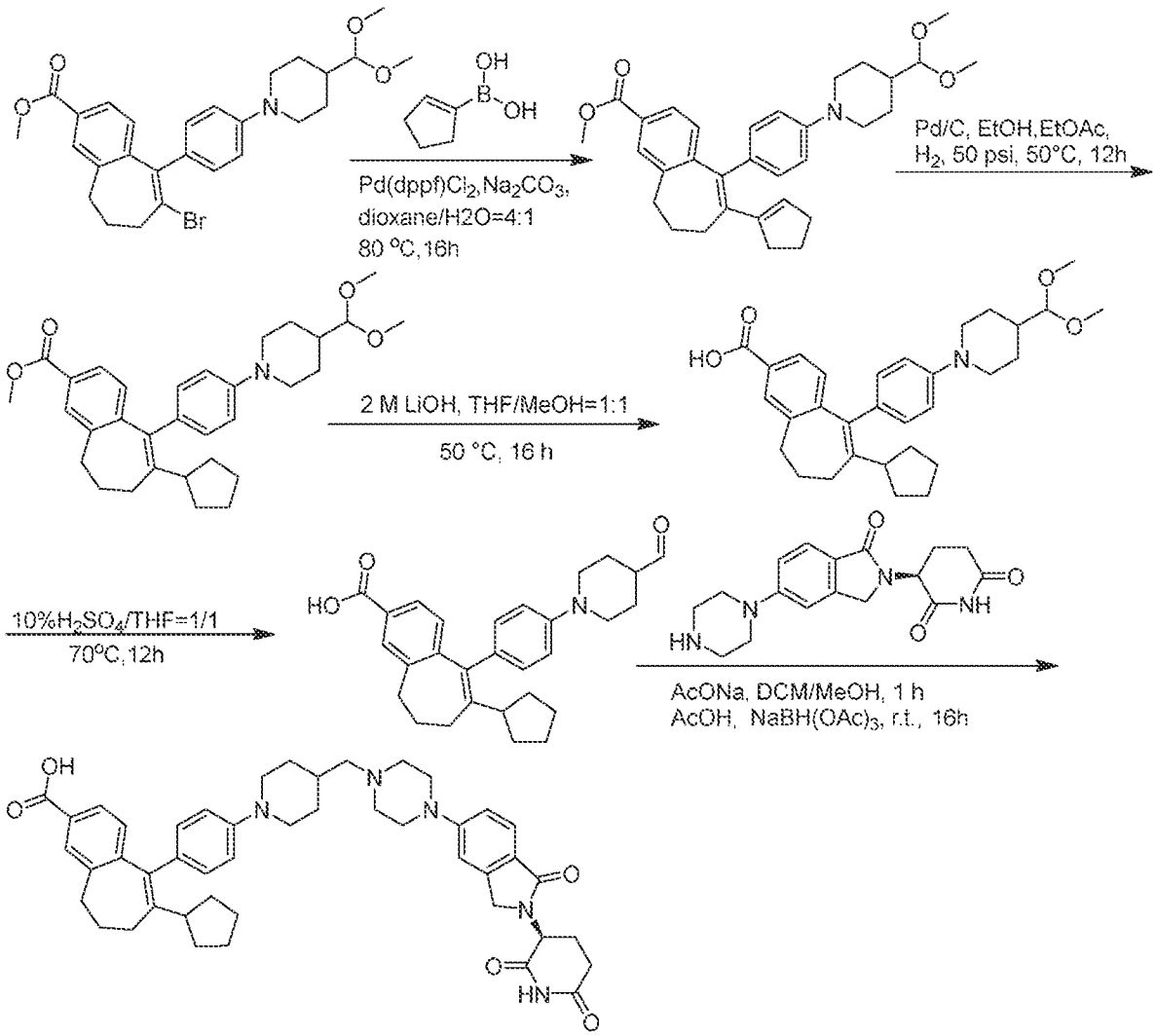
[1584] LC-MS (ESI+) m/z: 864.1 $(M+H)^+$

[1585] HPLC: 97.101 % purity at 220 nm

[1586] SFC: R_t: 1.002 min; Area, 88.243 %; method: AS-3-MeOH+ACN(DEA)-50-3ML-35T

[1587] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.37 (s, 1 H) 7.94 (d, J=1.13 Hz, 1 H) 7.79 (dd, J=8.07, 1.44 Hz, 1 H) 7.65 (d, J=8.51 Hz, 1 H) 7.48 (d, J=8.13Hz, 2 H) 7.30 (d, J=8.25 Hz, 2 H) 7.08 - 7.13 (m, 2 H) 6.90 - 6.95 (m, 1 H) 6.74 (s, 4 H) 5.01 - 5.20 (m, 2 H) 4.33 - 4.47 (m,2 H) 3.59 - 3.70 (m, 2 H) 3.37 -3.50 (m, 5 H) 2.84 - 2.92 (m, 3 H) 2.74 - 2.83 (m, 5 H)2.62-2.70 (m, 2 H) 2.44 - 2.52 (m, 3 H) 2.39 (br t, J=6.75 Hz, 2 H) 2.13 - 2.25 (m, 3 H) 1.80 - 1.91(m, 3 H) 1.31 - 1.39 (m, 2 H)

Example 94. Synthesis of (S)-8-cyclopentyl-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-16



[1588] ***Step 1.*** A mixture of methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (1 g, 1 Eq, 2 mmol), (cyclopent-1-en-1-yl)boronic acid (0.2 g, 1 Eq, 2 mmol) , Sodium carbonate (0.6 g, 0.4 mL, 3 Eq, 6 mmol) ,1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (0.1 g, 0.1 Eq, 0.2 mmol) in 1,4-Dioxane (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hour under N_2 atmosphere. LCMS showed 67.675% of desired compound was detected. TLC(petroleum ether/ethyl acetate=5/1, R_f=0.4) The reaction mixture was quenched by addition H_2O 20 mL, and then diluted with H_2O 50 mL and extracted with Ethyl acetate (50 mL * 2). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The

residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 50~50% Ethyl acetate /Petroleum ether gradient @ 40 mL/min) and the organic layer was concentrated in vacuo to give methyl 8-(cyclopent-1-en-1-yl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (690 mg, 953 µmol, 50 %yield, 69.3% purity)as a yellow solid.

[1589] TLC: petroleum ether: ethyl acetate=5:1, R_f = 0.5.

[1590] LC-MS (ESI^+) m/z: 502.1 $(M+H)^+$.

[1591] ***Step 2.*** A mixture of methyl 8-(cyclopent-1-en-1-yl)-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (690 mg, 1 Eq, 1.38 mmol), Pd/C(500 mg, 10% Wt, 0.342 Eq, 470 µmol) in EtOH (10 mL) and EtOAc (10 mL) was degassed and purged with H_2(50 psi) for 3 times, and then the mixture was stirred at 50 °C for 12hr under H_2 atmosphere. The reaction was filtered and concentrated to dryness in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*40mm*5um;mobile phase: [water(FA)-ACN];B% 50%-80%,10min) to give methyl 8-cyclopentyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (240 mg, 476 µmol, 34.6 %, 100% Purity) was obtained as a yellow oil.

[1592] TLC: petroleum ether: ethyl acetate=5:1, R_f = 0.5.

[1593] LC-MS (ESI^+) m/z: 504.3 $(M+H)^+$

[1594] ***Step 3.*** To a solution of methyl 8-cyclopentyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (240 mg, 1 Eq, 476 µmol) in THF (2 mL) and MeOH (2 mL) was added lithium hydroxide (114 mg, 2.38 mL, 10 Eq, 4.76 mmol). The mixture was stirred at 50 °C for 16 hour .LCMS showed 95.975% of desired MS. The reaction mixture was concentrated under reduced pressure to give 8-cyclopentyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (200 mg, 392 µmol, 82.3 %, 95.975% Purity) as a white solid.

[1595] LC-MS (ESI^+) m/z: 490.1 $(M+H)^+$

[1596] ***Step 4.*** A solution of 8-cyclopentyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (200 mg, 1 Eq, 408 µmol) in 10% H_2SO_4 (7 mL) and THF (7 mL) was stirred at 70 °C for 12 hour to give a yellow suspension. LCMS showed 93.795% of desired MS. The solvent was removed under vaccum. The aqueous solution

was added $NaHCO_3$ to adjust pH=6. The residue was dissolved in water (20 mL) and extracted by ethyl acetate (50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give 8-cyclopentyl-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (170 mg, 359 μmol, 88.0 %, 93.795% purity) as a yellow oil.

[1597] LC-MS (ESI+) m/z: 490.1 (M+H) +

[1598] ***Step 5.*** To a solution of 8-cyclopentyl-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (150 mg, 1 Eq, 338 μmol), (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione TsOH salt(169 mg, 1 Eq, 338 μmol) in DCM (3 mL), MeOH (3 mL) was added Sodium acetate (83.2 mg, 3 Eq, 1.01 mmol) was stirred at 25 °C for 30 mins, Then Sodium triacetoxyborohydride (143 mg, 2 Eq, 676 μmol) and acetic acid (60.9 mg, 58.4 μL, 3 Eq, 1.01 mmol) was added .The mixture was stirred at 25 °C for 16 hour. The reaction was treated with H_2O (20 mL), extracted with EtOAc (50 mL). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B% 29%-59%,7min) to give (S)-8-cyclopentyl-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (68.2 mg, 88.7 μmol, 26.2 %, 98.361% purity) was obtained as a white solid.

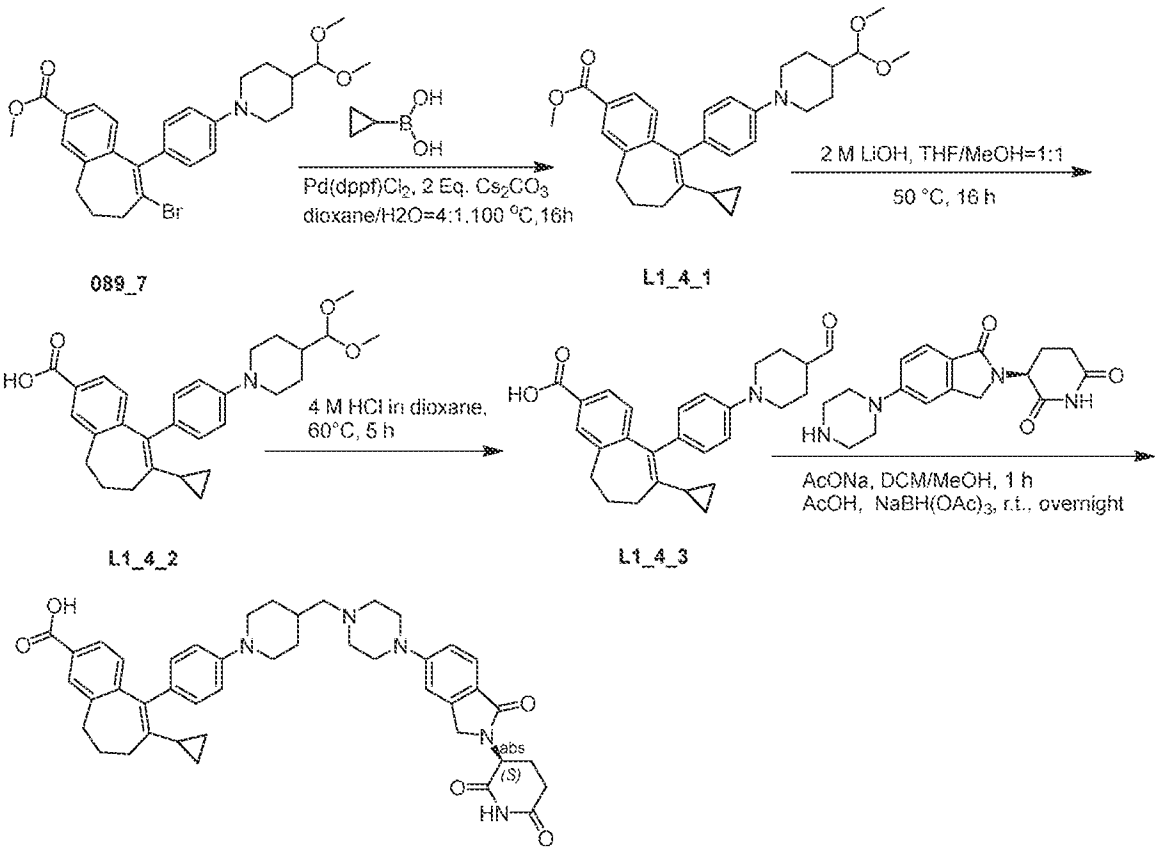
[1599] LCMS: calc. for $C_{46}H_{53}N_5O_5$: 755.40, found: $[M+H]^+$ 746.2.

[1600] HPLC: 98.361 % purity at 220 nm

[1601] ^1H NMR (400 MHz, DMSO-d_6) δ= 10.99 - 10.91 (m, 1H), 8.30 - 8.26 (m, 0.124H), 7.86 - 7.77 (m, 1H), 7.69 - 7.61 (m, 1H), 7.57 - 7.48 (m, 1H), 7.12 - 7.01 (m, 2H), 6.95 - 6.83 (m, 4H), 6.76 - 6.67 (m, 1H), 5.11 - 4.99 (m, 1H), 4.39 - 4.29 (m, 1H), 4.27 - 4.16 (m, 1H), 3.76 - 3.64 (m, 2H), 3.45 - 3.31 (m, 7H), 2.98 - 2.80 (m, 2H), 2.76 - 2.59 (m, 5H), 2.44 - 2.29 (m, 2H), 2.28 - 2.20 (m, 2H), 2.18 - 2.07 (m, 2H), 2.04 - 1.92 (m, 1H), 1.89 - 1.77 (m, 4H), 1.75 - 1.60 (m, 5H), 1.56 - 1.42 (m, 4H), 1.28 - 1.15 (m, 2H)

[1602] SFC: retention time, 9.542min; Area, 97.554%; method: OJ-RH_10-80_B_08ML_20min.

Example 95. Synthesis of (S)-8-cyclopropyl-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid, I-18



[1603] ***Step 1.*** The mixture of methyl 8-bromo-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (1 g, 1 Eq, 2 mmol), cyclopropylboronic acid (0.3 g, 2 Eq, 4 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)Complex With Dichloromethane (0.2 g, 0.1 Eq, 0.2 mmol) and cesium carbonate (2 g, 3 Eq, 6 mmol) in Dioxane (5 mL) and H_2O (1 mL) at r.t. N_2 was bubbled into the mixture for 5 min. The reaction mixture was heated at 100 °C for 16 hour. Then the reaction was cooled to room temperature. The solvent was removed under vaccum. The residue was dissolved in water (30 mL) and washed by ethyl acetate (2*30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give the compound as a yellow oil. The reaction was purified by flash column (petroleum ether/ethyl acetate from 100/0 to 40/60) and the organic layer was concentrated in vacuo to give methyl 8-cyclopropyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (700 mg, 1.2 mmol, 60%, 83% Purity) as a yellow solid.

[1604] LC-MS (ESI+) m/z: 476.3 $(M+H)^+$.

[1605] ***Step 2.*** To a solution of methyl 8-cyclopropyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (350 mg, 1 Eq, 611 µmol) in THF (1 mL) and MeOH (1 mL) was added LiOH (146 mg, 3.05 mL, 2 molar, 10 Eq, 6.11 mmol).The mixture was stirred at 50 °C for 16 hour. The reaction mixture was concentrated under reduced pressure to give 8-cyclopropyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (300 mg, 650 µmol, 106%) as a white solid.

[1606] ***Step 3.*** A solution 8-cyclopropyl-9-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (150 mg, 1 Eq, 325 µmol) in 4M HCl/dioxane (2 mL) and DCM (2 mL) was stirred at 60 °C for 5 hour to give a yellow suspension. The mixture was dissolved in water (10 mL) and washed by ethyl acetate (2*10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vaccum to give 8-cyclopropyl-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (70 mg, 0.17 mmol, 52%) as a yellow oil. LC-MS (ESI+) m/z: 476.3 (M+H)+.

[1607] ***Step 4.*** A mixture of 8-cyclopropyl-9-(4-(4-formylpiperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (70 mg, 1 Eq, 0.17 mmol), (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, Tosylic acid (0.11 g, 1.3 Eq, 0.22 mmol), Sodium acetate (69 mg, 5 Eq, 0.84 mmol) and Acetic acid (30 mg, 29 µL, 3 Eq, 0.51 mmol) in DCM (2 mL) and MeOH (2 mL) at 25 °C for 1 hour, then Sodium triacetoxyborohydride (71 mg, 2 Eq, 0.34 mmol) was added to the mixture and was stirred at 25 °C for 16 hour. The mixture was treated with H_2O (10 mL), extracted with EtOAc (10 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep.HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 24%-54%, 7min). The aqueous phase was lyophilized to dryness to give (S)-8-cyclopropyl-9-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylic acid (39 mg, 52 µmol, 31% yield, 96.589% purity) as a white solid.

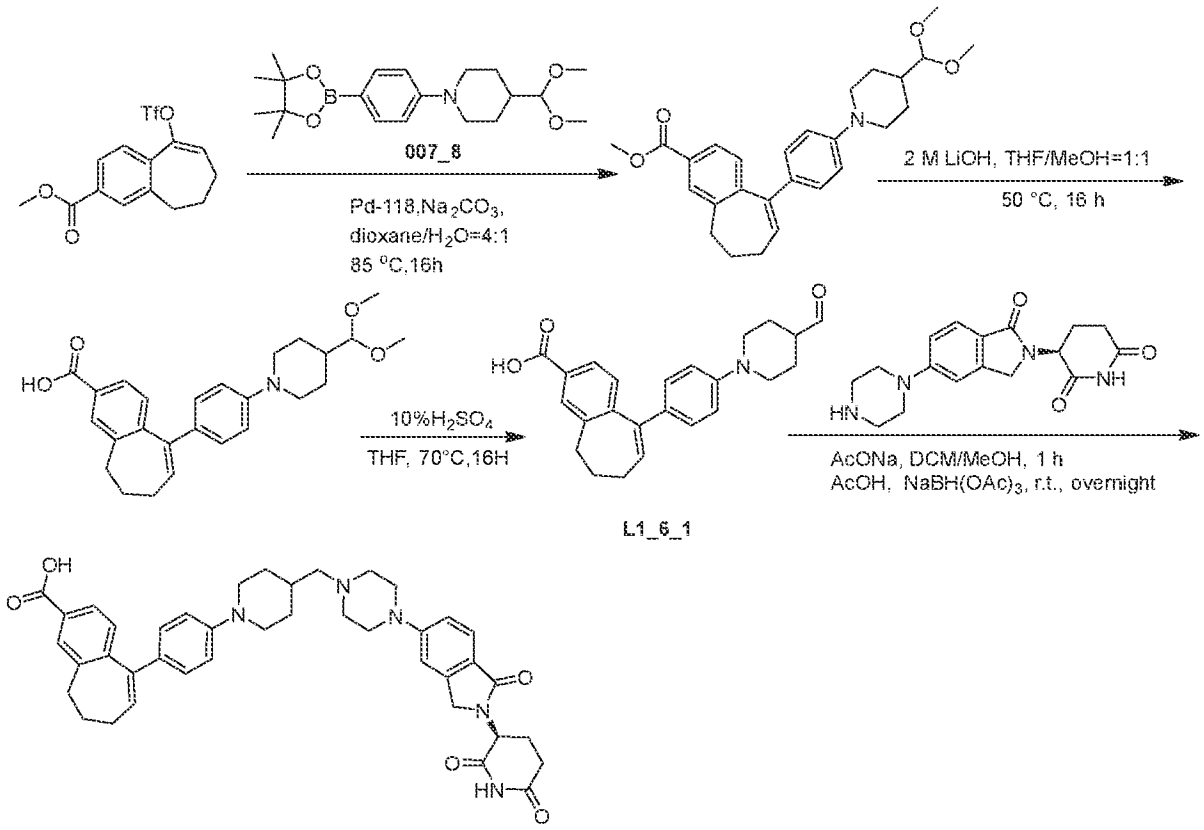
[1608] LC-MS (ESI+) m/z: 728.4 $(M+H)^+$.

[1609] HPLC: 96.589%, purity at 220 nm.

[1610] SFC: Retention time: 9.158 min; Area, 96.301%, method: AD_RH_10_80_B_08ML_20MIN_1CM

[1611] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.98 - 10.94 (m, 1H), 8.18 - 8.15 (m, 0.832H), 7.82 - 7.79 (m, 1H), 7.69 - 7.65 (m, 1H), 7.55 - 7.50 (m, 1H), 7.09 - 7.04 (m, 2H), 7.01 - 6.96 (m, 2H), 6.93 - 6.88 (m, 2H), 6.79 - 6.75 (m, 1H), 5.10 - 5.00 (m, 1H), 4.39 - 4.29 (m, 1H), 4.26 - 4.16 (m, 1H), 3.77 - 3.63 (m, 3H), 2.96 - 2.86 (m, 1H), 2.73 - 2.59 (m, 7H), 2.38 - 2.30 (m, 2H), 2.28 - 2.19 (m, 3H), 2.10 - 1.92 (m, 4H), 1.87 - 1.68 (m, 5H), 1.45 - 1.37 (m, 2H), 1.31 - 1.13 (m, 3H), 0.75 - 0.68 (m, 2H), 0.60 - 0.53 (m, 2H).

Example 96. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-9



[1612] ***Step 1.*** A mixture of methyl 5-(trifluoromethylsulfonyloxy)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (5.75 g, 16.41 mmol, 1.1 eq) , 4-(dimethoxymethyl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (5.39 g, 14.92 mmol, 1 eq), Pd-118(972.35 mg, 1.49 mmol, 0.1 eq) , Na_2CO_3 (4.74 g, 44.76 mmol, 3 eq) in 20 mL dioxane and 5 mL H_2O was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 85 °C for 16 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove **dioxane**. The residue was diluted with **50** mL H_2O and extracted with ethyl acetate (100 mL * **3**). The combined organic layers were washed with saturated salt solution (25

mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, **petroleum ether/Ethyl acetate=1/0** to 5/**1**). Compound methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (4 g, 8.35 mmol, 55.97% yield, 90.931% purity) was obtained as a yellow oil.

[1613] LC-MS (ESI^+) m/z: 436.1 $(M+H)^+$.

[1614] ***Step 2.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (300 mg, 688.78 umol, 1 eq) in THF (2 mL) and MeOH (2 mL) was added LiOH (2 M, 3.44 mL, 10 eq). The mixture was stirred at 50 °C for 16 hr. The reaction was concentrated to dryness in vacuo to give a yellow oil. Ethyl acetate (7 mL) was added, the mixture was adjust to pH=5 with 1M HCl. 50 mL water was added and the mixture was extracted with ethyl acetate (25 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness in vacuo to give a yellow solid. The crude product 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (280 mg, 664.25 umol, 96.44% yield, 100% purity) as a yellow solid was used into the next step without further purification.

[1615] LC-MS (ESI^+) m/z: 422.0 $(M+H)^+$.

[1616] ***Step 3.*** 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (280 mg, 664.25 umol, 1 eq) was added to THF (2 mL) and H_2SO_4 (2 mL, 10% purity).The mixture was stirred at 70 °C for 16 hr. The reaction mixture was concentrated under reduced pressure to remove THF and diluted with 5 mL ethyl acetate. Then the mixture was adjusted with saturated sodium carbonate to pH=7 and extracted with ethyl acetate (25 mL * 2). The combined organic layers were washed with saturated salt water 30 mL, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The crude product 5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (194 mg, 516.70 umol, 77.79% yield) as yellow solid was used into the next step without further purification.

[1617] ***Step 4.*** To a solution of 5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (194 mg, 516.70 umol, 1 eq) in DCM (1 mL) and MeOH (1 mL) was added (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (339.33 mg, 1.03 mmol, 2 eq) acetic acid (62.06 mg, 1.03 mmol, 59.10 uL, 2 eq) and sodium acetate (211.93 mg, 2.58 mmol, 5 eq). The mixture was stirred at 20 °C for 12 hr .Then the $NaBH(OAc)_3$(219.02

mg, 1.03 mmol, 2 eq) added to the mixture and stirred at 20 °C for 12 hr . The reaction mixture was concentrated under reduced pressure to remove DCM and MeOH. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 23%-53%,7min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (80 mg, 116.31 umol, 22.51% yield, 100% purity) was obtained as a white solid.

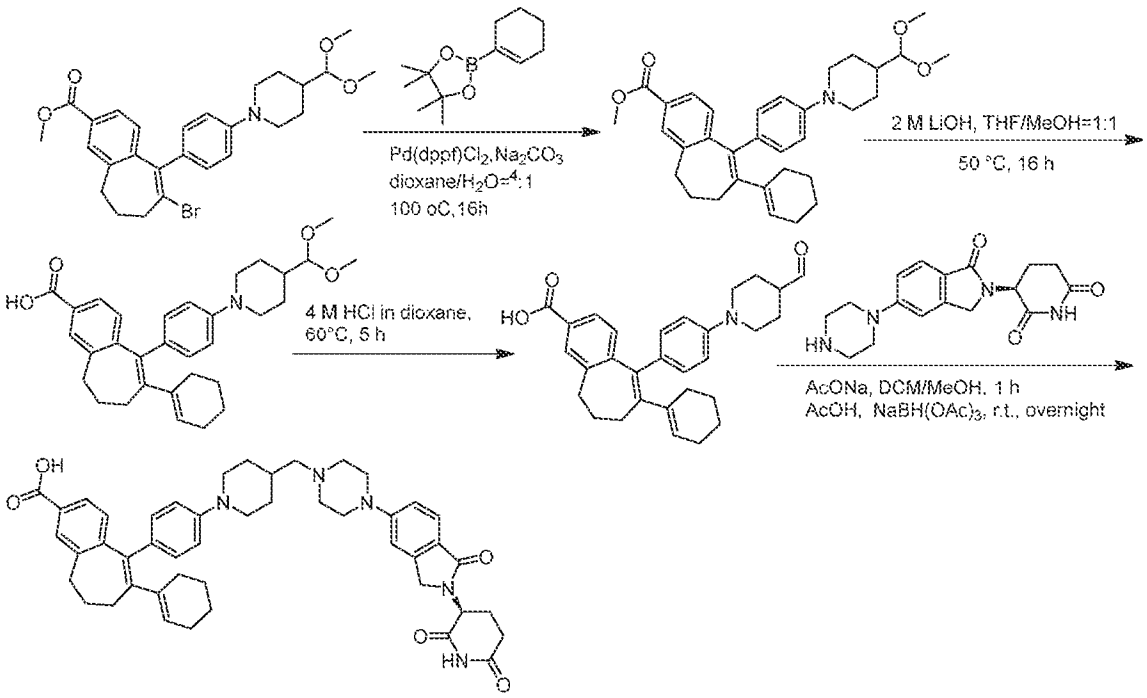
[1618] MS: LC-MS (ESI^+) m/z: 688.3 $(M+H)^+$

[1619] HPLC: 100% purity at 220 nm.

[1620] SFC: retention time: 2.704 Area: 94.640% method: IE_MeOH_DEA_MeCN_50_1ML_10MIN_5CM

[1621] ^1H NMR (400 MHz, DMSO-d_6) δ = 10.96 (s, 1H), 8.13 (s, 0.056H), 7.90 (s, 1H), 7.79 (br d, J = 8.0 Hz, 1H), 7.58 (br d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz,1H), 7.14 (br s, 1H), 7.11 (br d, J = 8.0 Hz, 1H), 7.06 (br d, J = 8.8 Hz, 2H), 7.02 (s, 1H), 6.90 (br d, J = 8.5 Hz, 2H), 6.43 (t, J = 7.3 Hz, 1H), 5.06 (br dd, J =5.1, 13.2 Hz, 1H), 4.35 (br d, J = 16.8 Hz, 1H), 4.23 (br d, J = 17.3 Hz, 1H), 3.73 (br d, J = 11.8 Hz, 2H), 3.33 (br s, 3H), 3.28 - 3.18 (m, 2H), 2.99 - 2.82 (m,2H), 2.77 - 2.59 (m, 5H), 2.53 - 2.51 (m, 3H), 2.42 - 2.31 (m, 1H), 2.28 (s, 2H), 2.18 - 2.07 (m, 2H), 2.00 - 1.94 (m, 1H), 1.91 - 1.78 (m, 4H), 1.29 (br d, J = 9.5 Hz, 2H)

Example 97. Synthesis of 6-(cyclohexen-1-yl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-20



[1622] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(400 mg, 777.53 umol, 1 eq) , 2-(cyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (210.35 mg, 1.01 mmol, 217.30 uL,1.3 eq) , $Pd(dppf)Cl_2$ (63.50 mg, 77.75 umol, 0.1 eq), Na_2CO_3(247.23 mg, 2.33 mmol, 3 eq) and in mixture of dioxane (5 mL) and Water (1 mL)was degassed and purged with N2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with 30 mL H_2O and extracted with EtOAc 100 mL (50 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min).Compound methyl 6-(cyclohexen-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (250 mg, 343.01 umol, 44.12% yield, 70.753% purity) was obtained as a yellow solid.

[1623] TLC: petroleum ether: ethyl acetate=5:1, R_f =0.51

[1624] LC-MS (ESI^+) m/z: 516.5 $(M+H)^+$

[1625] ***Step 2.*** To a solution of methyl 6-(cyclohexen-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (246 mg, 477.04 umol, 1 eq) in mixture of MeOH (2 mL) and THF (2 mL) was added LiOH (2 M, 2.4 mL, 10.06 eq) .The mixture was stirred at 50 °C for 16 hr .

[1626] The reaction mixture was poured into 20 mL of ice-water carefully and acidified with 1M

[1627] HCl to pH=4. The resulting solution was extracted with ethyl acetate 60 mL (30 mL ×2).dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue as a yellow solid. This reaction was used to next step without purification. Compound 6-(cyclohexen-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (300 mg, 406.83 umol, 85.28% yield, 68.030% purity) was obtained as a yellow solid.

[1628] LC-MS (ESI^+) m/z: 502.4 $(M+H)^+$

[1629] ***Step 3.*** To a solution of 6-(cyclohexen-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (250 mg, 498.35 umol, 1 eq) in HCl/dioxane (5 mL) .The mixture was stirred at 60 °C for 4 hr .The reaction mixture was concentrated to dryness in vacuo, and the mixture was used directly for the next step without purification. Compound 6-(cyclohexen-1-yl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (400 mg, 426.84 umol, 85.65% yield, 48.616% purity) was obtained as a orange solid.

[1630] LC-MS (ESI^+) m/z: 455.9 $(M+H)^+$

[1631] ***Step 4.*** To a solution of 6-(cyclohexen-1-yl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (200 mg, 438.99 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (329.62 mg, 658.49 umol, 1.5 eq, p-TSA), AcOH (26.36 mg, 438.99 umol, 25.11 uL, 1 eq) and AcONa (108.03 mg, 1.32 mmol, 3 eq) in a mixture of DCM (4 mL) and MeOH (4 mL), the mixture was stirred at 25 °C for 1 hr, and then NaBH(OAc)3 (139.56 mg, 658.49 umol, 1.5 eq) was added dropwise at 25 °C. The resulting mixture was stirred at 25°C for 16hr. The reaction mixture was concentrated to dryness in vacuo. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 28%-58%,8min).Compound 6-(cyclohexen-1-yl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-

piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (22 mg, 28.13 umol, 6.41% yield, 98.20% purity) was obtained as a orange solid.

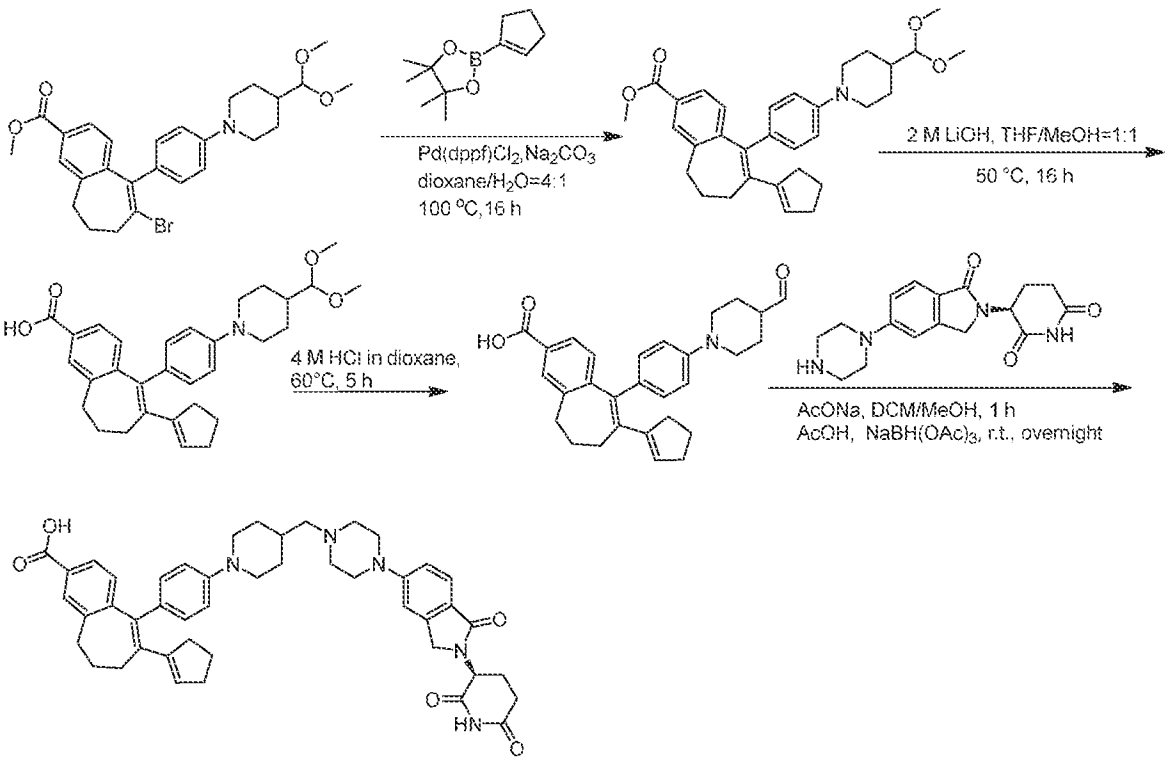
[1632] LC-MS (ESI^+) m/z: 768.3 $(M+H)^+$

[1633] HPLC: 99.330% purity at 220 nm

[1634] SFC: Rt: 1.214min; Area, 100 %; method: OD-3-IPA+ACN(DEA)-60-3ML-35T

[1635] ^1H NMR (400 MHz, DMSO-d_6) δ= 10.96 (s, 1H), 8.14 (br d, J = 11.4 Hz, 1H), 7.84 - 7.79 (m, 1H), 7.69 (dd, J = 1.9, 8.0 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.08 - 7.04 (m, 2H), 6.90 - 6.86 (m, 2H), 6.85 - 6.80 (m, 3H), 5.56 - 5.51 (m, 1H), 5.08 (s, 1H), 4.37 - 4.29 (m, 1H), 4.25 - 4.16 (m, 1H), 3.77 - 3.63 (m, 3H), 2.96 - 2.83 (m, 2H), 2.70 - 2.60 (m, 8H), 2.40 - 2.31 (m, 3H), 2.23 (br d, J = 6.5 Hz, 2H), 2.14 - 2.03 (m, 3H), 2.00 - 1.91 (m, 8H), 1.81 (br d, J = 11.5 Hz, 2H), 1.51- 1.43 (m, 4H), 1.25 - 1.18 (m, 2H)

Example 98. Synthesis of 6-(cyclopenten-1-yl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-21, I-127



[1636] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(400 mg, 777.53 umol, 1 eq), 2-(cyclopenten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (190 mg, 978.99 umol, 1.26 eq) , $Pd(dppf)Cl_2$(64

mg, 78.37 umol, 0.1 eq) and Na_2CO_3(250mg, 2.36 mmol, 3.03 eq) in mixture of dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with 30 mL H_2O and extracted with EtOAc 100 mL (50 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound methyl 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (120 mg, 153.85 umol, 19.79% yield, 64.316% purity) was obtained as a yellow oil.

[1637] TLC: petroleum ether: ethyl acetate=5:1, R_f =0.5

[1638] LC-MS (ESI^+) m/z: 502.4 $(M+H)^+$

[1639] ***Step 2.*** To a solution of methyl 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (120 mg, 239.21 umol, 1 eq) in mixture of MeOH (2 mL)and THF (2 mL) was added LiOH (2 M, 1.20 mL, 10eq).The mixture was stirred at 50 °C for 16 hr . The reaction mixture was poured into 20 mL of ice-water carefully and acidified with 1M HCl to pH=4. The resulting solution was extracted with ethyl acetate 60 mL (30 mL ×2).dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue as a yellow solid. This reaction was used to next step without purification. Compound 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (128 mg, 174.60 umol, 72.99% yield, 66.514% purity) was obtained as a yellow solid.

[1640] LC-MS (ESI^+) m/z: 488.3 $(M+H)^+$

[1641] ***Step 3.*** To a solution of 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (100 mg, 205.07 umol, 1 eq) in HCl/dioxane (3 mL) .The mixture was stirred at 60 °C for 5 hr .This reaction mixture was concentrated under reduced pressure to give a residue as a brown solid. This reaction was used to next step without purification. Compound 6-(cyclopenten-1-yl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (100 mg, crude) was obtained as a brown solid.

[1642] LC-MS (ESI^+) m/z: 542.1 $(M+H)^+$

[1643] *Step 3.* To a solution of 6-(cyclopenten-1-yl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (140 mg, 317 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (240 mg, 479.46 umol, 1.51 eq, p-TSA salt), AcONa (80 mg, 975.25 umol, 3.08 eq) and AcOH (20 mg, 333.04 umol, 19.05 uL, 1.05 eq) in DCM (3 mL) and MeOH (3 mL) at 25°C over 1hr, and then $NaBH(OAc)_3$ (100 mg, 471.83 umol, 1.49 eq) was added dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 16 hr. The reaction mixture was concentrated to dryness in vacuo. The residue was purified twice by prep-HPLC. First: The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN];B%: 28%-58%,15min). Second: The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um;mobile phase: [water(NH4HCO3)-ACN];B%: 32%-62%,9min).Compound 6-(cyclopenten-1-yl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (7 mg, 9.17 umol, 2.89% yield, 98.80% purity) was obtained as a yellow solid.

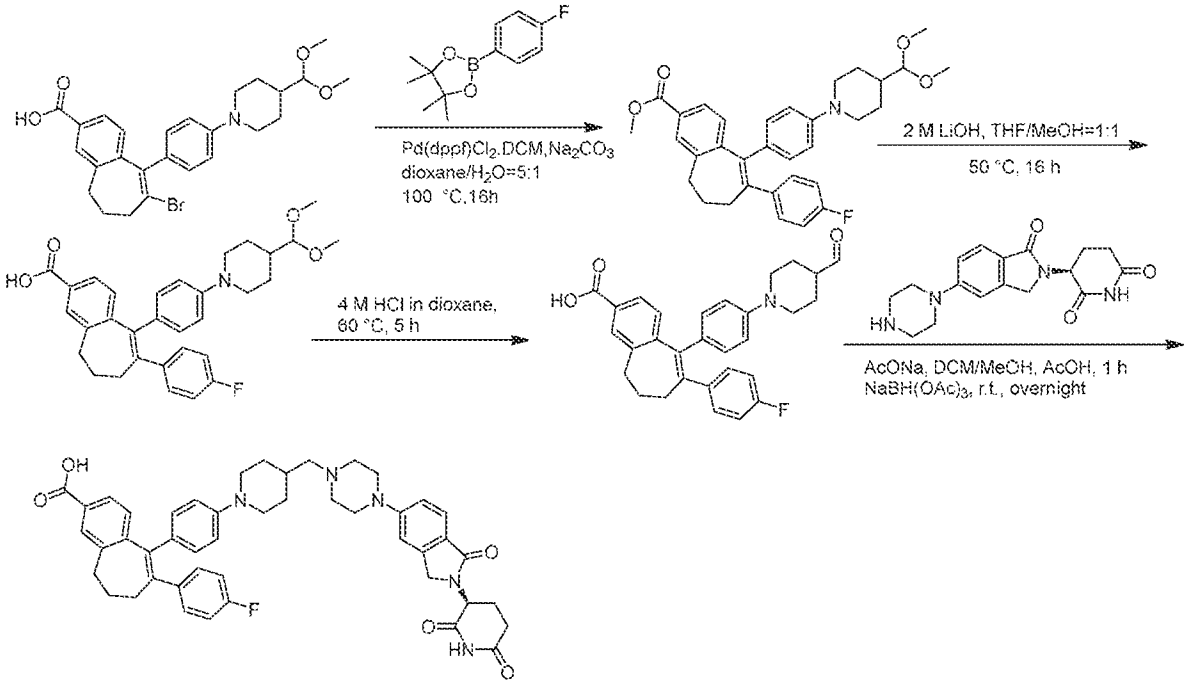
[1644] LC-MS (ESI^+) m/z: 754.3$(M+H)^+$

[1645] HPLC: 99.874% purity at 220 nm

[1646] SFC: Rt: 1.378 min; Area, 74.754%; Rt: 0.763 min; Area, 25.246 %; method: AS-3-EtOH+ACN(DEA)-50-3mL-35T

[1647] ^1H NMR (400 MHz, DMSO-d_6) δ = 10.97 (s, 1H), 7.82 - 7.78 (m, 1H), 7.63 (br d, J = 1.9 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.09 - 7.04 (m, 2H), 6.85 - 6.83 (m,3H), 5.86 - 5.81 (m, 1H), 5.08 - 4.98 (m, 1H), 4.39 - 4.29 (m, 1H), 4.24 - 4.15 (m, 1H), 3.70 (br d, J = 12.8 Hz, 2H), 2.69 - 2.65 (m, 6H), 2.37 - 2.31 (m, 3H),2.30 - 2.19 (m, 6H), 2.17 - 2.03 (m, 6H), 2.00 - 1.91 (m, 4H), 1.89 - 1.78 (m, 3H), 1.75 - 1.62 (m, 4H), 1.28 - 1.17 (m, 3H)

Example 99. Synthesis of 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(4-fluorophenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-13



[1648] ***Step 1.*** A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (400 mg, 777.53 umol, 1 eq) , 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (210 mg, 945.68 umol, 1.22 eq) , $Pd(dppf)Cl_2$·DCM(64 mg, 78.37 umol, 0.1 eq) and Na_2CO_3 (250 mg, 2.36 mmol, 3.03 eq) in mixture of dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with water 30 mL and extracted with ethyl acetate 50 mL (25 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether @ 60 mL/min). Compound methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-fluorophenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (350 mg, 579.8 umol, 74.6% yield, 87.7% purity) was obtained as a yellow solid.

[1649] LC-MS (ESI^+) m/z: 530.5 $(M+H)^+$

[1650] ***Step 2.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-fluorophenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (310 mg, 585.30 umol, 1 eq) in

mixture of MeOH (4 mL) and THF (4 mL)was added LiOH (2 M, 2.93 mL, 10 eq) .The mixture was stirred at 50 °C for 16 hr . The reaction mixture was poured into 20 mL of ice-water carefully and acidified with 1M HCl to pH=4. The resulting solution was extracted with ethyl acetate 60 mL (30 mL * 2) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-fluorophenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (280 mg, 513.25 umol, 87.7% yield, 94.5% purity) was obtained as a yellow oil. This reaction was used to next step without purification.

[1651] LC-MS (ESI^+) m/z: 516.1 $(M+H)^+$

[1652] ***Step 3.*** To a solution of 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-(4-fluorophenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (280 mg, 543.04 umol, 1 eq) in HCl/dioxane (4 mL) .The mixture was stirred at 60 °C for 5 hr . This reaction mixture was concentrated under reduced pressure to give a residue as a brown solid. Compound 6-(4-fluorophenyl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (290 mg, crude) was obtained as a brown solid. This reaction was used to next step without purification

[1653] LC-MS (ESI+) m/z: 470.0 $(M+H)^+$

[1654] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.64 (s, 1 H) 7.91 (d, J=1.50 Hz, 1 H) 7.73 - 7.77 (m, 1 H) 7.27 - 7.49 (m, 2 H) 7.20 (dd, J=8.57, 5.57 Hz, 3 H) 7.03 (t, J=8.82 Hz, 3 H) 6.89 - 6.97 (m, 2 H) 6.81 - 6.86 (m, 1 H) 3.83 - 3.90 (m, 1 H) 3.46 - 3.53 (m, 2 H) 3.27 - 3.35 (m, 1 H) 2.86 (br t, J=6.44 Hz, 3 H) 2.60 - 2.72 (m, 1 H) 2.25 - 2.31 (m, 2 H) 2.05 - 2.19 (m, 5 H) 1.82 - 2.03 (m, 3 H)

[1655] ***Step 4.*** To a solution of 6-(4-fluorophenyl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (50 mg, 106.49 umol, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (53 mg, 161.41 umol, 1.52 eq, p-TSA salt) in DCM (1 mL)and MeOH (1 mL) was added AcONa (26 mg, 316.94 umol, 2.98 eq) , AcOH (7.35 mg, 122.39 umol, 7 uL,1.15 eq) at 25 °C . After addition, the mixture was stirred at this temperature for 1hr, and then $NaBH(OAc)_3$ (34 mg, 160.42 umol, 1.51 eq) was added at 25 °C. The resulting mixture was stirred at 25 °C for 15 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Ultimate XB-CN 250*50*10 um; mobile phase: [Hexane-EtOH];B%: 5%-40%,30min). Compound 5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-

yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-(4-fluorophenyl)-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (11.2 mg, 14.24 umol, 9.28% yield, 99.409% purity) was obtained as a yellow solid.

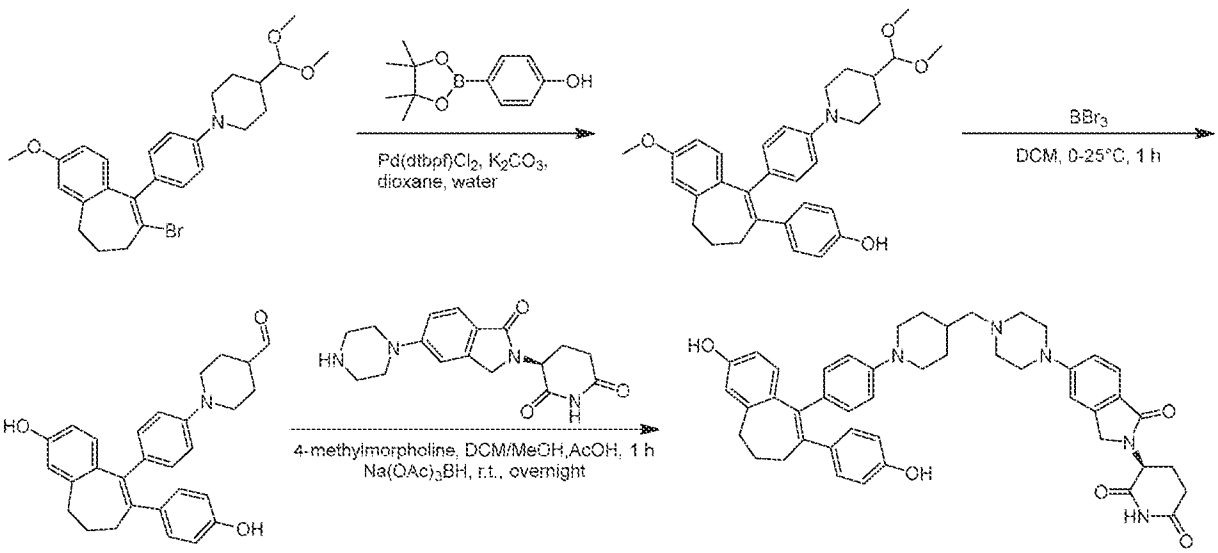
[1656] LC-MS (ESI+) m/z: 782.2 $(M+H)^+$

[1657] HPLC: 99.409 % purity at 220 nm

[1658] SFC: R_t: 0.679 min; Area, 93.965 %; method: AS-3-MeOH+ACN(DEA)-60-3ML-35T

[1659] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.93 - 10.96 (m, 1 H) 8.21 - 8.22 (m, 0.239 H) 7.87 (d, J=1.50 Hz, 1 H) 7.71 - 7.75 (m, 1 H) 7.49 - 7.53 (m, 1 H) 7.18 - 7.23 (m, 2 H) 7.00 - 7.08 (m, 4 H) 6.85 - 6.88 (m, 1 H) 6.63 - 6.70 (m, 4 H) 5.04 (dd, J=13.26, 5.13 Hz, 1 H) 4.17 - 4.35 (m, 2 H) 3.54 - 3.70 (m, 4 H) 2.85 - 2.97 (m, 2 H) 2.82 (br t, J=5.94 Hz, 2 H) 2.53 - 2.69 (m, 6 H) 2.36 - 2.42 (m, 1 H) 2.31 - 2.36 (m, 1 H) 2.19 - 2.25 (m, 4 H) 2.07 - 2.14 (m, 2 H) 1.91 - 1.99 (m, 1 H) 1.74 - 1.82 (m, 2 H) 1.62 - 1.71 (m, 1 H) 1.11 - 1.21 (m, 2 H)

Example 100. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(4-hydroxyphenyl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-36



[1660] ***Step 1.*** To a solution of compound 1 (300 mg, 616.73 µmol, 1 eq) and compound 2 (162.87 mg, 740.08 µmol, 1.2 eq) in dioxane (6 mL) and Water (2 mL) was added ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (401.95 mg, 616.73 µmol, 1 eq) and K2CO3 (170.48 mg, 1.23 mmol, 2 eq). The reaction mixture was stirred at 70°C for 2h in the presence of N_2. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated

under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give compound 3 (220 mg, 396.29 µmol, 64.26% yield, 90% purity) was obtained as a Black Brown solid.

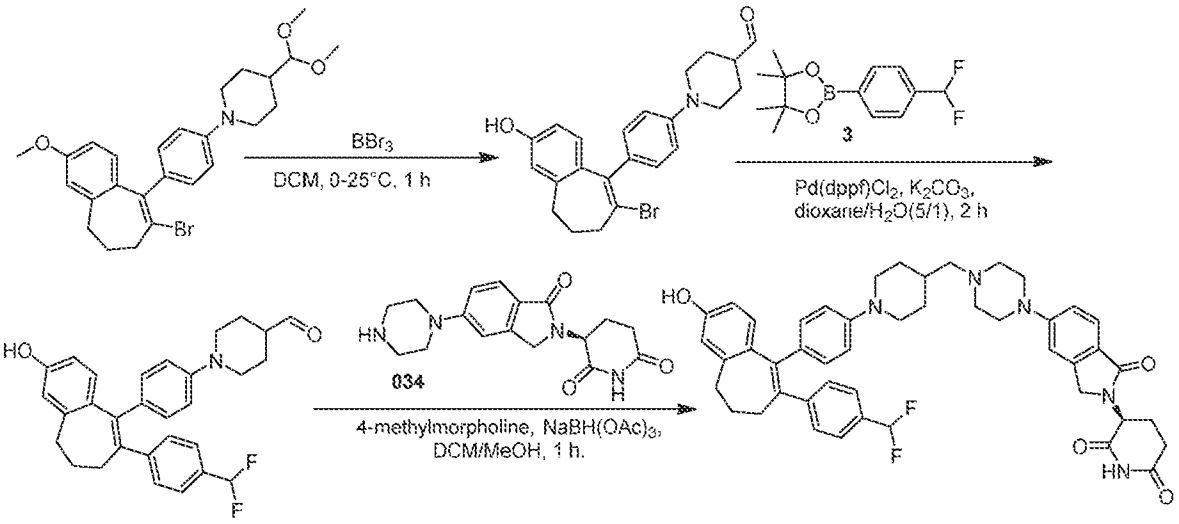
[1661] LC-MS (ESI^+) m/z: 500.2 $(M+H)^+$. 1H NMR (400 MHz, DMSO-d6) δ = 6.94 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.76 - 6.43 (m, 3H), 4.03 (d, J = 7.0 Hz, 1H), 3.93 (s, 1H), 3.76 (s, 1H), 3.29 - 3.24 (m, 3H), 2.21 (s, 1H), 2.04 (s, 1H), 1.66 (s, 1H)

[1662] ***Step 2.*** To a mixture of compound 3 (220 mg, 440.32 µmol, 1 eq) in DCM (10 mL) ,and then BBr_3 (551.54 mg, 2.20 mmol, 212.13 µL, 5 eq) was added dropwise at 0°C. The resulting mixture was stirred at 25°C for 1 h. The reaction mixture was quenched by addition $NaHCO_3$ 50 mL at 25 °C, and then diluted with H_2O 200mL and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude compound was used into the next step without further purification. compound 4 (190 mg, 378.19 µmol, 85.89% yield, 87.49% purity) was obtained as a black brown solid. LC-MS (ESI^+) m/z: 554.2 $(M+H)^+$.

[1663] ***Step 3.*** A solution of compound 4 (56.1 mg, 136.26 µmol) and compound 5 (50 mg, 109.55 µmol, TFA salt) and AcONa (17.1 mg, 272.51 µmol) in DCM (0.5 mL) and methanol (0.5 mL) was stirred at 20°C for 30 mins, Then acetic acid (16.4 mg, 272.51 µmol, 15.59 µL) and $NaBH_3CN$ (33.5 mg, 408.77 µmol) was added .The mixture was stirred at 20°C for 16 h. The reaction was concentrated and purified by prep-HPLC (FA condition : column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 18%-38%,58min) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(4-hydroxyphenyl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (31.1 mg, 42.15µmol, 31% yield) was obtained as a white solid. LC-MS (ESI^+) m/z: 752.2 $[M+H]^+$

[1664] 1H NMR (400 MHz, METHANOL-d4) δ = 8.31 (s, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.15-7.07 (m, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.80-6.71 (m, 4H), 6.68 (d, J = 2.5 Hz, 1H), 6.66-6.60 (m, 1H), 6.60-6.50 (m, 3H), 5.10 (dd, J = 5.1, 13.2 Hz, 1H), 4.58 (br s, 4H), 4.41 (d, J = 6.0 Hz, 2H), 3.62 (br d, J = 12.4 Hz, 2H), 3.44 (br s, 4H), 2.89-2.81 (m, 4H), 2.71 (s, 4H), 2.60-2.50 (m, 2H), 2.49-2.40 (m, 1H), 2.32 (br t, J = 6.9 Hz, 2H), 2.19-2.08 (m, 3H), 1.89 (br d, J = 13.4 Hz, 2H), 1.86-1.73 (m, 1H), 1.47-1.33 (m, 2H)

Example 101. Synthesis of 3-(5-(4-((1-(4-(8-(4-(difluoromethyl)phenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-37, I-125



[1665] ***Step 1.*** To a solution of compound 1 (150 mg, 308.36 μmol, 1 eq) in DCM (4 mL) was added BBr_3 (77.25 mg, 308.36 μmol, 29.71 μL, 1 eq) at 0 °C . The reaction mixture stirring at 20 °C for 1h. Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40mL x 3). The combined organic layers were washed with brine (100mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give compound 2 (154 mg, 258.26 μmol, 83.75% yield) as a red solid.

[1666] LC-MS (ESI^+) m/z: 428.1 $(M+H)^+$.

[1667] ***Step 2.*** To a solution of compound 2 (150 mg, 351.83 μmol, 1 eq) and compound 3 (89.39 mg, 351.83 μmol, 1 eq) in Dioxane/H_2O (4 mL) was added $Pd(dppf)Cl_2$ (25.74 mg, 35.18 μmol, 0.1 eq) and K_2CO_3 (97.25 mg, 703.66 μmol, 2 eq) under N_2. The mixture was stirred at 90 °C for 2 h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40mL x 3). The combined organic layers were washed with brine (100mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 4 (92 mg, 101.02 μmol, 28.71% yield) as a yellow solid.

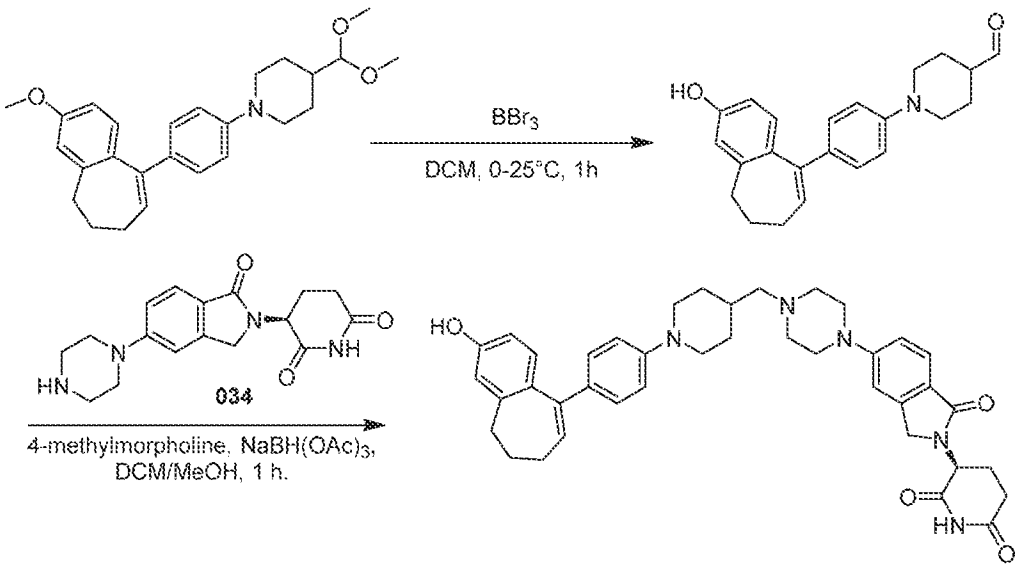
[1668] LC-MS (ESI^+) m/z: 474.3 $(M+H)^+$.

[1669] *Step 3.* To a solution of compound 4 (92 mg, 194.28 μmol, 1 eq) in DCM/MeOH (2 mL) was added 4-methylmorpholine (39.30 mg, 388.55 μmol, 42.72 μL, 2 eq) and Compound 034 (63.79 mg, 194.28 umol, 1 eq) in DCM/MeOH (2 mL). After stirring at 20 °C for 20 min, the mixture is adding $NaBH_3CN$ (24.42 mg, 388.55 μmol, 2 eq) and stirring at 20 °C for 1h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40mL x 3). The combined organic layers were washed with brine (100mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters xbridge 150*25mm 10um; mobile phase: [water (NH4HCO3)-ACN];B%: 50%-80%,9min) to give the 3-(5-(4-((1-(4-(8-(4-(difluoromethyl)phenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (18.7 mg, 23.16 μmol, 11.92% yield) as a pink solid.

[1670] LC-MS (ESI+) m/z: 786.3. $(M+H)^+$.

[1671] ^1H NMR: (400 MHz, METHANOL-d4) δ 7.63 (d, J = 8.4 Hz, 1H), 7.28 (q, J = 8.4 Hz, 4H), 7.15 - 6.99 (m, 2H), 6.82 - 6.63 (m, 7H), 6.60 - 6.54 (m, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 1H), 4.48 - 4.32 (m, 2H), 3.61 (br d, J = 12.4 Hz, 2H), 3.38 - 3.35 (m, 4H), 2.95 - 2.84 (m, 1H), 2.82 - 2.71 (m, 3H), 2.69 - 2.57 (m, 6H), 2.46 (br dd, J = 5.0, 13.3 Hz, 1H), 2.39 (br t, J = 6.8 Hz, 2H), 2.30 (br d, J = 7.2 Hz, 2H), 2.19 - 2.07 (m, 3H), 1.88 (br d, J = 11.6 Hz, 2H), 1.79 - 1.66 (m, 1H), 1.35 - 1.29 (m, 2H)

Example 102. Synthesis of 3-(5-(4-((1-(4-(3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-12



[1672] ***Step 1.*** To a solution of compound 1 (100 mg, 245.37 μmol, 1 eq) in DCM (10 mL) was added BBr_3 (61.47 mg, 245.37 μmol, 23.64 μL, 1 eq) at 0 °C. The mixture was stirred at 20°C for 1h. Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give compound 2 (60 mg, 136.42 μmol, 55.60% yield) as a yellow oil.

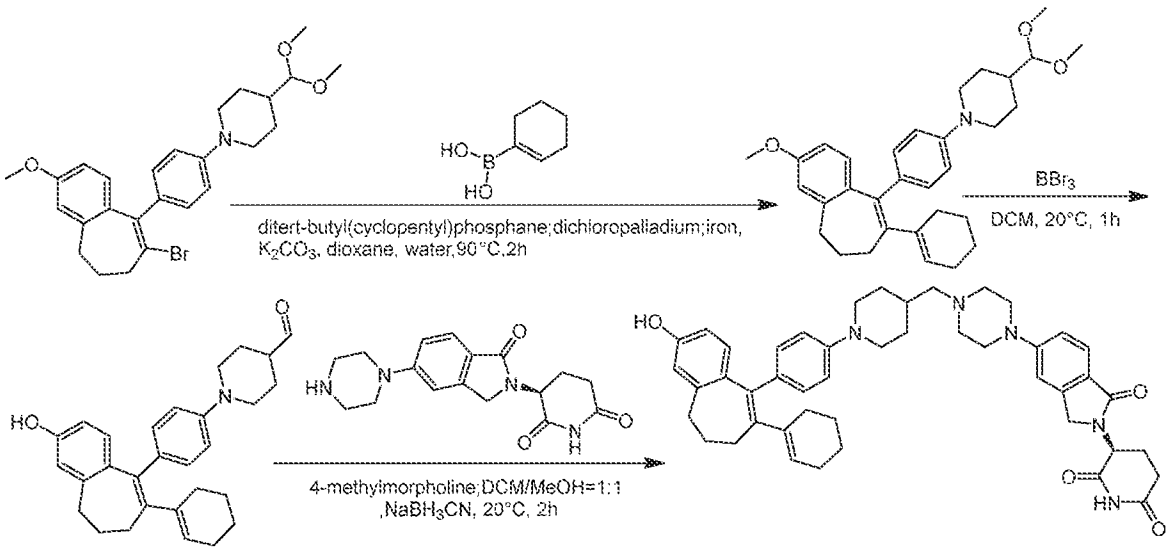
[1673] LC-MS (ESI+) m/z: 348.2$(M+H)^+$.

[1674] ***Step 2.*** To a solution of compound 2 (60 mg, 172.69 μmol, 1 eq) in DCM/MeOH (2 mL) was added 4-methylmorpholine (52.40 mg, 518.06 μmol, 56.96 μL, 3 eq) and Compound 034 (56.70 mg, 172.69 μmol, 1 eq) in DCM/MeOH (2 mL) at 20 °C. After stirring at 20 °C for 20 min, the mixture was added $NaBH_3CN$ (21.70 mg, 345.37 μmol, 2 eq) and stirred at 20 °C for 1h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 150*25mm*10um; mobile phase: [water (NH4HCO3)-ACN];B%: 42%-72%,8min) to give 3-(5-(4-((1-(4-(3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (8 mg, 11.52 μmol, 6.67% yield) as a yellow solid.

[1675] LC-MS (ESI+) m/z: 660.2 $(M+H)^+$.

[1676] 1H NMR: (400 MHz, CHLOROFORM-d) δ 7.95 - 7.84 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.03 - 6.97 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.90 - 6.85 (m, 3H), 6.76 (d, J = 2.4 Hz, 1H), 6.67 - 6.64 (m, 1H), 6.29 - 6.27(m, 1H), 5.25 - 5.16 (m, 1H), 4.47 - 4.36 (m, 1H), 4.31 - 4.19 (m, 1H), 3.73 - 3.70 (m, 2H), 3.34 (s, 4H), 2.95 - 2.79 (m, 2H), 2.76 - 2.68 (m, 2H), 2.61 (s, 6H), 2.33 - 2.27 (m, 2H), 2.17 - 2.11 (m, 2H), 1.98 - 1.87 (m, 4H), 1.76 - 1.62 (m, 2H), 1.42 - 1.35 (m, 2H), 1.30 - 1.24 (m, 1H)

Example 103. Synthesis of (S)-3-(5-(4-((1-(4-(8-(cyclohex-1-en-1-yl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-31



[1677] ***Step 1.*** To a stirred solution of compound 1 (100 mg, 205.58 μmol, 1 eq) in dioxane (1 mL) and Water (0.2 mL) was added K2CO3 (85.24 mg, 616.73 μmol, 3 eq), compound 3 (38.84 mg, 308.36 μmol, 1.5 eq) and ditert-butyl (cyclopentyl) phosphane;dichloropalladium;iron (26.80 mg, 41.12 μmol, 0.2 eq) at 20 °C. Then the reaction was stirred at 90 °C for 2 h under N2. The reaction was concentrated and purified by flash silica gel chromatography (from PE/EtOAc = 0/1 to 5/1, R f =0.54) to give compound 2 (67 mg, 129.14 μmol, 62.82% yield) as a yellow solid.

[1678] LC-MS (ESI^+) m/z: 488.4 $(M+H)^+$.

[1679] ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.03 - 6.97 (m, 2H), 6.83 - 6.73 (m, 4H), 6.69 - 6.65 (m, 1H), 5.50 - 5.45 (m, 1H), 4.16 – 4.10 (m, 2H), 3.81 (s, 3H), 3.71 (d, J = 11.8 Hz, 3H), 3.39 (s, 6H), 2.67 - 2.63 (m, 4H), 2.14 - 2.11 (m, 2H), 1.98 - 1.95 (m, 4H), 1.87 (d, J = 5.6 Hz, 3H), 1.77 (d, J = 5.6 Hz, 1H), 1.52 (d, J = 5.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 2H).

[1680] *Step 2.* To a stirred solution of compound 2 (180 mg, 369.10 μmol, 1 eq) in DCM (10 mL) was added BBr_3 (462.34 mg, 1.85 mmol, 5 eq) by drop at 0 °C. Then was stirred at 20°C for 1hr. The reaction was concentrated on a rotary evaporator to give compound 4 (187 mg, 349.88 μmol, 94.79% yield) as yellow solid.

[1681] LC-MS (ESI^+) m/z: 446 $(M+H)^+$.

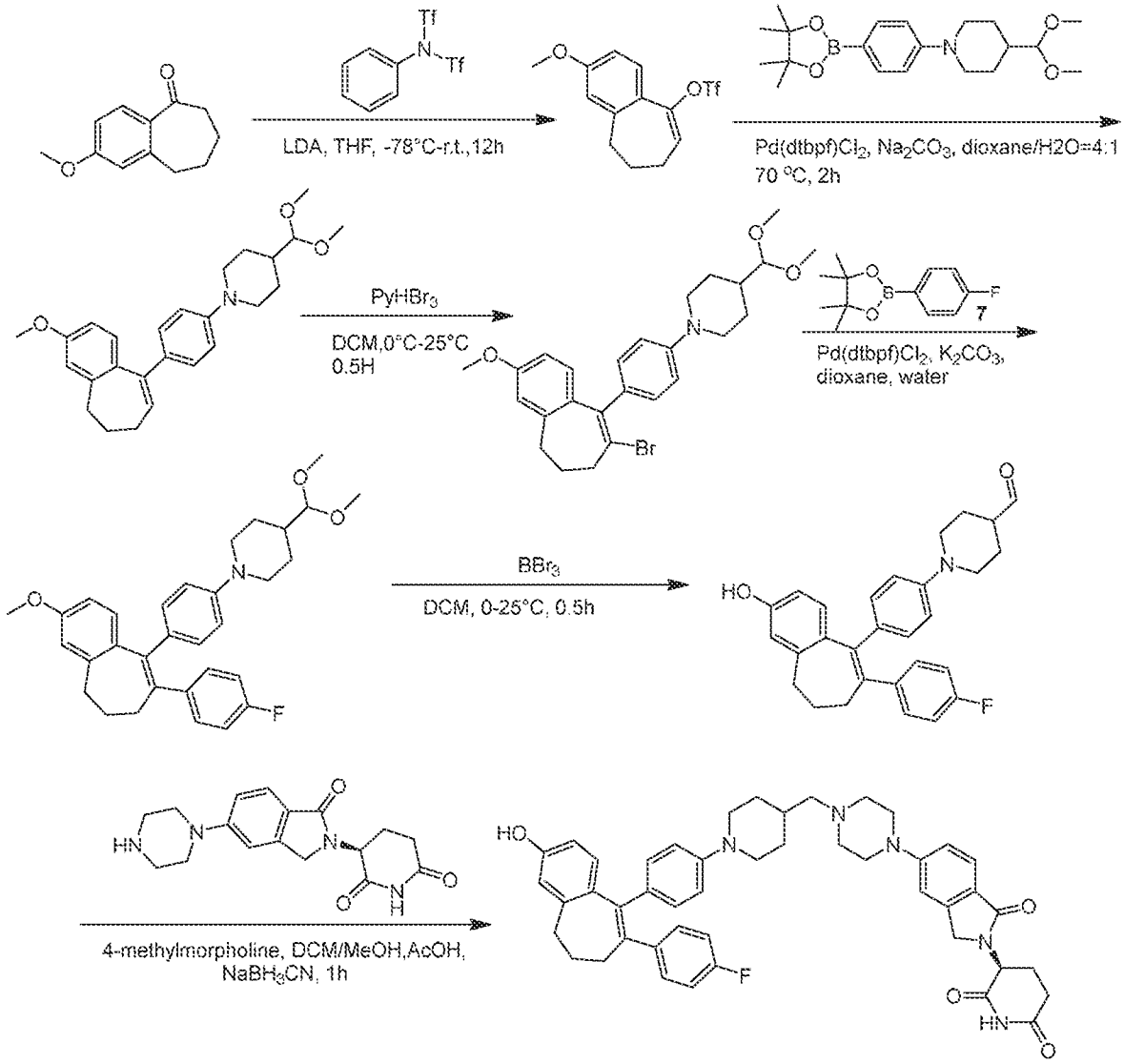
[1682] *Step 3.* To a solution of compound 4 (187 mg, 437.35 μmol， 1 eq) in DCM:MeOH=1:1 (6 mL) was added compound 5 (143.61 mg, 437.35 μmol, 1 eq) and 4-methylmorpholine (132.71 mg, 1.31 mmol, 3 eq).Then stirred at 20°C for 10 min. Then was added sodium;cyanoboranuide (54.97 mg, 874.70 μmol, 2 eq) .The reaction was stirred at 20 °C for 2hr. The mixture was filtered celite plate, and the filtrate was concentrated and purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (HCl)-ACN]; B%: 17%-47%, 8min) to give (S)-3-(5-(4-((1-(4-(8-(cyclohex-1-en-1-yl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione as yellow solid.

[1683] LCMS: LC-MS (ESI+) m/z: 740.3 (M+H) +.

[1684] ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.13 (s, 1H), 7.74 - 7.70 (m, 1H), 7.56 (s, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.22 (s, 2H), 7.20 (s, 1H), 6.80 - 6.78 (m, 2H), 5.15-5.10 (m, 1H), 4.45 (d, J = 6.4 Hz, 2H), 4.13 - 4.05 (m, 2H), 3.81 - 3.77 (m, 7H), 2.95 - 2.87 (m, 1H), 2.80 - 2.76 (m, 1H), 2.50 - 2.46 (m, 5H), 2.35 - 2.18 (m, 8H), 2.19 - 2.15 (m, 1H), 2.07 - 1.88 (m, 12H), 1.62 - 1.52 (m, 1H), 1.31 (d, J = 11.3 Hz, 2H).

Example 104. Synthesis of 3-(5-(4-((1-(4-(8-(4-fluorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-

yl)piperidine-2,6-dione, I-10



[1685] ***Step 1.*** To a solution of compound 1 (14 g, 73.59 mmol, 1.0 eq) in THF (100 mL) was added dropwise LDA (2 M, 55.19 mL, 1.5 eq) at -78°C under N_2. The mixture was stirred at -78°C for 2 hours. Compound 2 (28.92 g, 80.95 mmol, 1.1 eq) dissolved in THF (50 mL) was then added dropwise. The mixture was stirred at -78°C-20°C for 12 hours. The reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (200mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give compound 3 (9.5 g, 28.00 mmol, 38.05% yield) was obtained as a yellow oil.

[1686] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.39-7.36 (m, 1H), 6.94-6.91 (m, 2H), 6.24-6.20 (m, 1H), 3.79 (s, 3H), 2.71-2.67 (m, 2H), 2.24-2.18 (m, 2H), 1.99-1.91 (m, 2H).

[1687] ***Step 2.*** To a solution of compound 3 (1 g, 3.10 mmol, 1.0 eq) and compound 4 (1.12 g, 3.10 mmol, 1.12 eq) in dioxane (12 mL) and H_2O (3 mL) was added Na_2CO_3 (986.57 mg, 9.31 mmol, 3.0 eq) and Pd(dtbpf)Cl_2 (202.22 mg, 310.27 μmol, 0.1 eq) at 25°C. The mixture was stirred at 70°C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give compound 5 (700 mg, 1.58 mmol, 51.04% yield) was as a yellow oil. LC-MS (ESI^+) m/z: 408.3 $(M+H)^+$.

[1688] ***Step 3.*** To a solution of compound 5 (360 mg, 883.34 μmol, 1.0 eq) in DCM (5 mL) was added $PyHBr_3$ (282.51 mg, 883.34 μmol, 1.0 eq) at 25°C. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 6 (400 mg, 703.07 μmol, 79.59% yield) was as a yellow oil. LC-MS (ESI^+) m/z: 487.9 $(M+H)^+$.

[1689] ***Step 4.*** To a solution of compound 6 (530 mg, 1.09 mmol, 1.0 eq) and compound 7 (241.95 mg, 1.09 mmol, 1.0 eq) in dioxane (4 mL) and H_2O (1 mL) was added Pd(dtppf)Cl_2 (71.01 mg, 108.95 μmol, 0.1 eq) and Na_2CO_3 (271.30 mg, 3.27 mmol, 3.0 eq) at 25°C. The mixture was stirred at 70°C for 2 hours under N_2. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give compound 8 (310 mg, 499.33 μmol, 45.83% yield) was as a yellow solid.

[1690] LC-MS (ESI^+) m/z: 502.2 $(M+H)^+$.

[1691] ***Step 5.*** To a solution of compound 8 (100 mg, 199.35 μmol, 1.0 eq) in DCM (10 mL) was added BBr_3 (249.71 mg, 996.75 μmol, 96.04 μL, 5.0 eq) and at 0°C under N_2. After 10 mins, the reaction was stirred at 25°C for 0.5 hour. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give

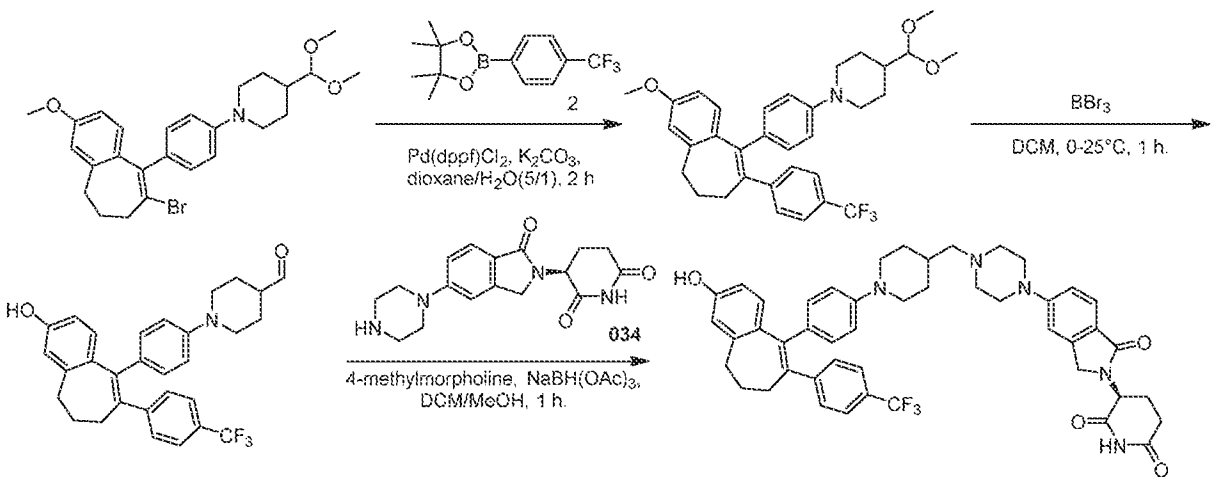
compound 9 (80 mg, 123.93 μmol, 62.17% yield) was as a yellow solid. LC-MS (ESI^+) m/z: 442.3 $(M+H)^+$.

[1692] ***Step 6.*** To a solution of compound 9 (80 mg, 181.19 μmol, 1.0 eq) in DCM (2 mL) and MeOH (2 mL) was added compound 10 (54.98 mg, 543.56 μmol, 59.76 μL, 1.0 eq), 4-methylmorpholine (59.50 mg, 181.19 μmol, 3.0 eq) and $NaBH_3CN$ (22.77 mg, 362.37 μmol, 2.0 eq) at 25°C. The reaction was stirred at 25°C for 1 hour. The reaction was concentrated and purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN];B%: 22%-52%,10min) to give 3-(5-(4-((1-(4-(8-(4-fluorophenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (14.9 mg, 18.99 μmol, 10.48% yield) was as a white solid.

[1693] LC-MS (ESI^+) m/z: 754.2 $(M+H)^+$

[1694] ^1H NMR (400 MHz, MeOD-d_6) δ ppm = 8.31 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.22 - 6.98 (m, 5H), 6.89 - 6.33 (m, 8H), 6.01 (t, J = 7.0 Hz, 1H), 5.10 (dd, J = 5.1, 13.2 Hz, 1H), 4.47 - 4.36 (m, 2H), 3.75 (br d, J = 12.5 Hz, 1H), 3.63 (br d, J = 12.3 Hz, 1H), 3.45 (br s, 4H), 2.97 - 2.84 (m, 5H), 2.81 - 2.71 (m, 3H), 2.66 (br t, J = 11.4 Hz, 1H), 2.56 (br t, J = 6.4 Hz, 2H), 2.51 - 2.41 (m, 1H), 2.35 (br t, J = 6.9 Hz, 1H), 2.27 (br t, J = 6.6 Hz, 1H), 2.17 - 2.10 (m, 2H), 2.09 - 2.01 (m, 1H), 1.97 - 1.80 (m, 4H), 1.45 - 1.32 (m, 2H)

Example 105. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-32



[1695] ***Step 1.*** To a solution of compound 1 (150 mg, 308.36 μmol, 1 eq) and compound 2 (92.29 mg, 339.20 μmol, 1.1 eq) in Dioxane/H_2O (3 mL) was added K_2CO_3 (127.86 mg, 925.09 μmol, 3 eq) and $Pd(dppf)Cl_2$ (20.10 mg, 30.84 μmol, 0.1 eq) under N_2. The mixture was stirred at 90 °C for 2h. LCMS showed that the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 20/1 to 10/1, TLC: PE/EtOAc = 5/1, Rf= 0.5) to yield the compound 3 (150 mg, 233.85 μmol, 75.84% yield) as a yellow solid.

[1696] LC-MS (ESI+) m/z: 552.1 $(M+H)^+$.

[1697] ***Step 2.*** To a solution of compound 3 (150 mg, 271.92 μmol, 1 eq) in DCM (5 mL) was added BBr_3 (68.12 mg, 271.92 μmol, 26.20 uL, 1 eq) at 0°C. The mixture was stirred at 20°C for 1 h, Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give the compound 4 (120 mg, 151.36 μmol) as a yellow solid.

[1698] LC-MS (ESI+) m/z: 492.3 $(M+H)^+$.

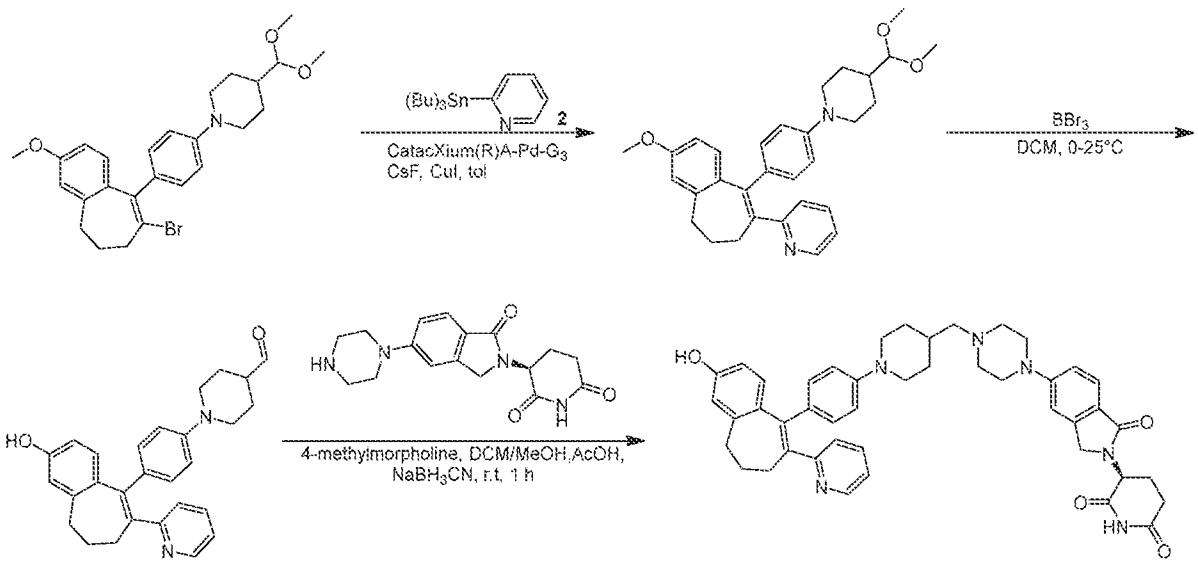
[1699] ***Step 3.*** To a solution of compound 4 (120 mg, 244.13 μmol, 1 eq) in DCM/MeOH (2 mL) was added 4-methylmorpholine (74.08 mg, 732.39 μmol, 80.52 uL, 3 eq) and Compound 034 (80.16 mg, 244.13 μmol, 1 eq) at 0 °C. After stirring at 0 °C for 20 min, the mixture was added $NaBH_3CN$ (30.68 mg, 488.26 μmol, 2 eq) at 0 °C and stirred at 20 °C for 1h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 27%-57%, 10min) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (12 mg, 13.77 μmol, 5.64% yield) as a yellow solid.

[1700] LC-MS (ESI^+) m/z: 804.8. $(M+H)^+$.

[1701] ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.99 - 7.87 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.29 (br s, 2H), 7.06 - 6.98 (m, 1H), 6.93 - 6.87 (m, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.79 - 6.74 (m, 3H), 6.67 (br d, J = 8.8 Hz, 2H), 6.63 (dd, J = 2.8, 8.4 Hz, 1H), 5.22 (dd, J = 5.1, 13.4 Hz, 1H), 4.47 - 4.38 (m, 1H), 4.32 - 4.22 (m, 1H), 3.66 (br d, J = 11.8 Hz, 2H), 3.37 (br s, 4H), 2.96 - 2.83 (m, 2H), 2.76 (br t, J = 6.8 Hz, 2H), 2.69 - 2.60 (m, 6H), 2.38 (br d, J = 7.6

Hz, 2H), 2.33 (br d, J = 5.4 Hz, 2H), 2.27 - 2.18 (m, 2H), 2.18 - 2.13 (m, 2H), 1.91 (br s, 2H), 1.40 (br s, 3H)

Example 106. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-2-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-33



[1702] ***Step 1.*** To a solution of compound 1 (300 mg, 616.73 µmol, 1.0 *eq*) and compound 2 (340.57 mg, 925.09 µmol, 1.5 *eq*) in toluene (5 mL) and was added CatacXium(R)A-Pd-G3 (44.91 mg, 61.67 µmol, 0.1 *eq*), CuI (23.49 mg, 123.35 µmol, 0.2 *eq*) and CsF (281.05 mg, 1.85 mmol, 68.22 µL, 3.0 *eq*) at 25°C under N_2. The mixture was stirred at 120°C for 12 hours under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give compound 3 (180 mg, 345.05 µmol, 55.95% yield) was as a yellow solid. LC-MS (ESI^+) m/z: 485.5 $(M+H)^+$.

[1703] ***Step 2.*** To a solution of compound 3 (200 mg, 412.69 µmol, 1.0 *eq*) in DCM (10 mL) was added BBr_3 (516.93 mg, 2.06 mmol, 198.82 µL, 5.0 *eq*) and at 0 °C. After 10 mins, the reaction was stirred at 25°C for 0.5 hour. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 4 (130 mg, 289.07 µmol, 70.05% yield) was as a yellow solid.

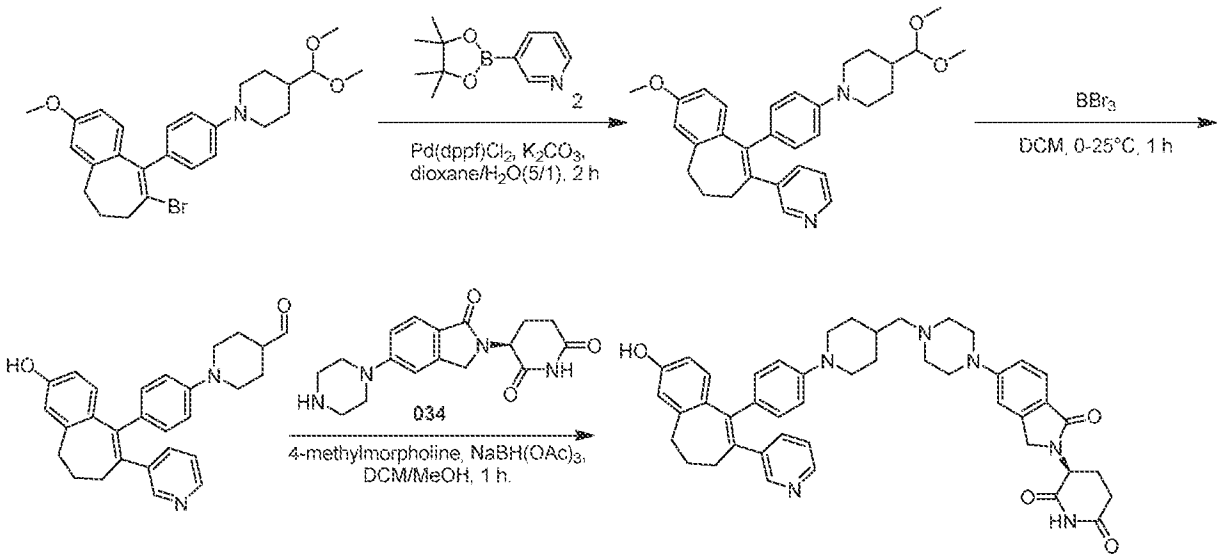
[1704] LC-MS (ESI^+) m/z: 425.3 $(M+H)^+$.

[1705] ***Step 3.*** To a solution of compound 4 (130 mg, 306.22 µmol, 1.0 *eq*) in DCM (2 mL) and MeOH (2 mL) was added compound 5 (92.92 mg, 918.66 µmol, 101.00 µL, 1.0 *eq*), 4-methylmorpholine (100.55 mg, 306.22 µmol, 3.0 *eq*) and $NaBH_3CN$ (38.49 mg, 612.44 µmol, 2.0 *eq*) at 25 °C. The reaction was stirred at 25°C for 1 hour. The reaction was concentrated and purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water(FA)-ACN];B%: 2%-27%,10min) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-2-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (30 mg, 40.51 µmol, 13.23% yield) was as a yellow solid.

[1706] LC-MS (ESI^+) *m/z*: 737.3 $(M+H)^+$.

[1707] ^1H NMR (400 MHz, MeOD-d_6) δ ppm = 8.61 (d, *J* = 5.6 Hz, 1H), 8.38 (dt, *J* = 1.5, 7.9 Hz, 1H), 7.88 - 7.81 (m, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.21 - 7.16 (m, 4H), 6.84 (d, *J* = 1.9 Hz, 1H), 6.66 - 6.60 (m, 2H), 5.11 (dd, *J* = 5.1, 13.3 Hz, 1H), 4.49 - 4.39 (m, 2H), 4.06 (br d, *J* = 13.3 Hz, 2H), 3.84 - 3.65 (m, 6H), 3.49 - 3.31 (m, 6H), 2.96 - 2.76 (m, 4H), 2.60 - 2.44 (m, 4H), 2.33 - 2.22 (m, 4H), 2.16 (tdd, *J* = 2.7, 5.2, 12.7 Hz, 1H), 2.03 - 1.91 (m, 2H)

Example 107. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-3-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-34



[1708] ***Step 1.*** To a solution of compound 1 (154.45 mg, 317.52 µmol, 1 *eq*) and compound 2 (71.62 mg, 349.27 µmol, 1.1 *eq*) in Dioxane/H_2O (3 mL) was added K_2CO_3 (131.65 mg, 952.56

μmol, 3 *eq*) and $Pd(dppf)Cl_2$ (41.39 mg, 63.50 μmol, 0.2 *eq*) under N_2. The reaction mixture was stirred at 90 °C for 2h. LCMS showed that the material was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 3/1 to 1/1, TLC: PE/EtOAc = 1/1, Rf= 0.35) to give compound 3 (116 mg, 196.27 μmol, 61.82% yield) as a yellow solid.

[1709] LC-MS (ESI+) m/z: 485.0$(M+H)^+$.

[1710] ***Step 2.*** To a solution of compound 3 (110 mg, 226.98 μmol, 1 *eq*) in DCM (3 mL) was added BBr_3 (56.86 mg, 226.98 μmol, 21.87 μL, 1 *eq*) at 0 °C. The reaction mixture was stirred at 20°C for 1h. Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give compound 4 (71 mg, 145.50 μmol, 64.10% yield) as a yellow solid.

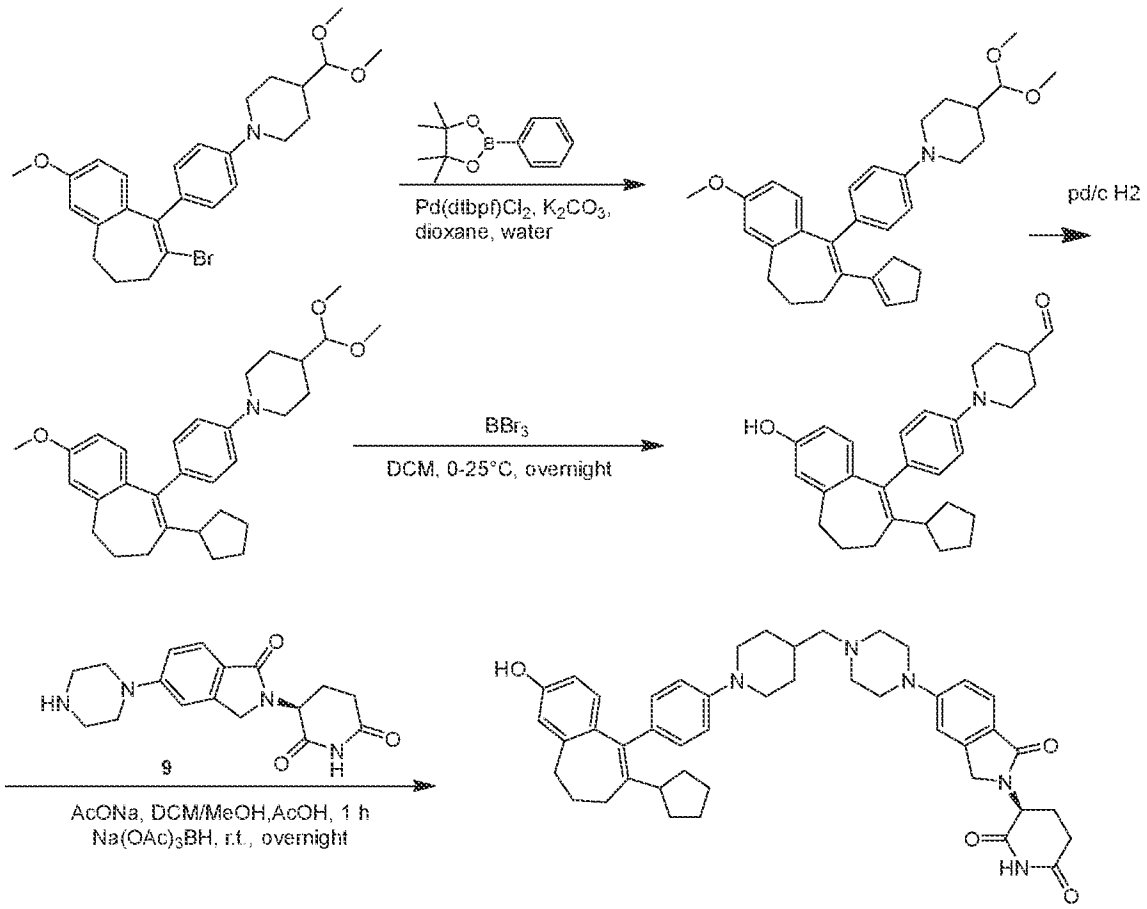
[1711] LC-MS (ESI+) m/z: 425.1 $(M+H)^+$.

[1712] ***Step 3.*** To a solution of compound 4 (61.32 mg, 144.44 μmol, 1 *eq*) in DCM/MeOH (2 mL) was added 4-methylmorpholine (43.83 mg, 433.33 μmol, 47.64 μL, 3 *eq*) and Compound 034 (47.43 mg, 144.44 μmol, 1 *eq*) in DCM/MeOH (2 mL). After stirring at 0 °C for 20 min, the mixture was added $NaBH_3CN$ (18.15 mg, 288.89 μmol, 2 *eq*) at 0 °C and stirred at 20 °C for 1h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (**column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];B%: 5%-35%,10min**) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-3-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (20.2 mg, 25.90 μmol, 17.93% yield) as a yellow solid.

[1713] LC-MS (ESI+) m/z: 737.3 $(M+H)^+$.

[1714] ^1H NMR: (400 MHz, METHANOL-d4) δ 8.58 - 8.50 (m, 2H), 8.41 (br d, *J* = 8.0 Hz, 1H), 7.86 (dd, *J* = 6.0, 8.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.23 - 7.11 (m, 4H), 7.00 (br d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.67 - 6.58 (m, 2H), 5.12 (dd, *J* = 5.2, 13.1 Hz, 1H), 4.50 - 4.37 (m, 2H), 4.15 - 3.94 (m, 2H), 3.81 - 3.68 (m, 4H), 3.24 (br d, *J* = 6.8 Hz, 6H), 2.93 - 2.74 (m, 4H), 2.53 - 2.43 (m, 3H), 2.36 - 2.01 (m, 7H), 1.79 - 1.61 (m, 2H), 1.43 - 1.17 (m, 1H)

Example 108. Synthesis of (S)-3-(5-(4-((1-(4-(8-cyclopentyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-29



[1715] ***Step 1.*** A mixture of 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl) -4-(dimethoxymethyl)piperidine (300 mg, 1 Eq, 617 µmol), REACTANT , Reactant III (196 mg, 3 Eq, 1.85 mmol) , Reactant IV (40.2 mg, 0.1 Eq, 61.7 µmol) in Dioxane (5 mL)and whate (2ml) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 90°C for 8 hours under N2 atmosphere. LC-MS showed 0% of Reactant 1 was remained. Only one new peaks were shown on LC-MS and 94% of desired compound was detected. The reaction mixture was partitioned between brine 100 mL and Ethyl acetate 100 mL. The organic phase was separated, washed with whate 50 mL (50 mL *2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue.The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1)Compound 1-(4-(8-(cyclopent-1-en-1-yl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (280 mg, 0.56 mmol, 91 %, 95% Purity) was obtained as a white solid. LC-MS (ESI^+) *m/z*: 474.3$(M+H)^+$.

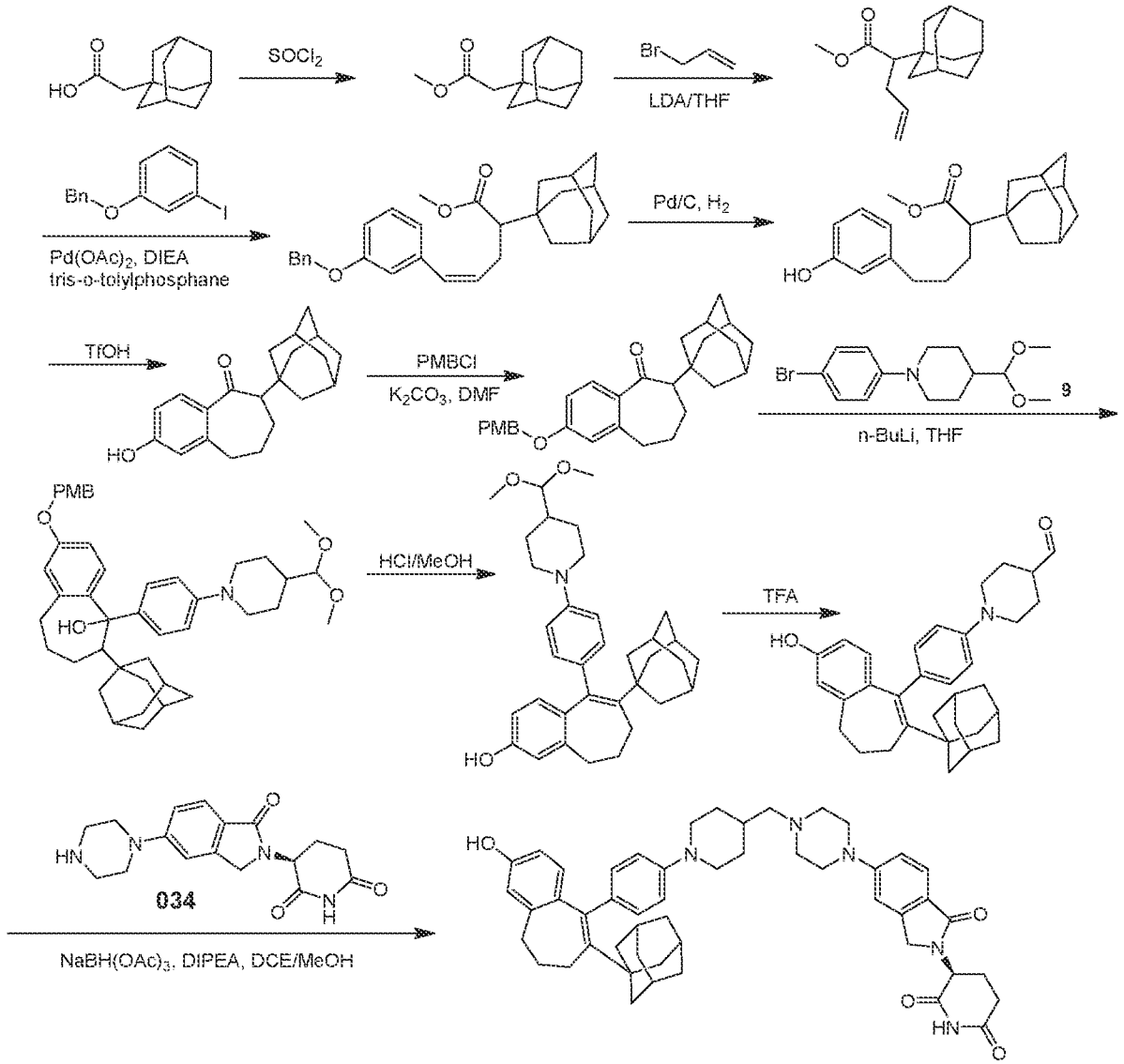
[1716] *Step 2.* To a solution of 1-(4-(8-(cyclopent-1-en-1-yl)-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (280 mg, 1 Eq, 591 µmol) in Ethyl acetate (20 mL) was added Pd-C (10%, 0.06 g) under N2. The suspension was degassed under vacuum and purged with H2 several times. The mixture was stirred under H2 (15psi) at 25°C for 12hours. TLC (Petroleum ether/Ethyl acetate = 5:1) or HPLC showed the starting material was consumed completely. The reaction mixture was filtered and the filter was concentrated. The crude product was purified by silica gel chromatography eluted with Petroleum ether/Ethylacetate=5:1togive1-(4-(8-cyclopentyl-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (270 mg, 0.55 mmol, 93 %, 97% Purity)as white solid. LC-MS (ESI^+) *m/z*: 476.3$(M+H)^+$.

[1717] *Step 3.* To a mixture 1-(4-(8-cyclopentyl-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl) phenyl)-4-(dimethoxymethyl)piperidine (250 mg, 1 Eq, 526 µmol) in DCM (10 mL)at 25°C and stirred for ten minters. To a stirred solution of compound was added a solution of BBr3 (658 mg, 248 µL, 5 Eq, 2.63 mmol) in CH2Cl2 via syringe over 5 min.TLC (ethyl acetate: petroleum ether = 1:3, iodide fuming) showed that the new spot was observed. The misture was added H2O (2 mL) and stirred for 30 minters.1H NMR showed the desired product was correct .The mixture was quenched with NH4Cl (20 mL, aqueous, sat.) under 25°C.The mixture was extracted with ethyl acetate (100 mL x 2), the combine organic layer was washed with water (200 mL), then washed with brine (200 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluted with petroleum / ethyl acetate=3:1 to give 1-(4-(8-cyclopentyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine-4-carbaldehyde (217 mg, 0.48 mmol, 91 %, 92% Purity) as yellow oil

[1718] *Step 4.* To a mixture of 1-(4-(8-cyclopentyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl) phenyl)piperidine-4-carbaldehyde(230mg,1Eq,553µmol)and(S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (363 mg, 2 Eq, 1.11 mmol) in DCE (5 mL). The mixture was stirred at 25 °C for 10 min,The pH was adjusted to around 6 by progressively adding 4-methylmorfolin (56.0 mg, 61 µL, 1 Eq, 553 µmol). Then added sodium triacetoxyhydroborate (235 mg, 2 Eq, 1.11 mmol) in the solution. The mixture was stirred for 2 hours. TLC showed the reaction was completed. LCMS show the product is correct. The aqueous phase was extracted with ethyl acetate (50mL*2). The combined organic phase was washed with brine (50 mL*2), dried with anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified

by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 meshsilicagel,Petroleumether/Ethylacetate=3/1,N/1)to afford (S)-3-(5-(4-((1-(4-(8-cyclopentyl-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (89 mg, 0.12 mmol, 22 %, 98.9% Purity) as white solid. LC-MS (ESI+) m/z: 728.3(M+H)+

Example 109. Synthesis of (3*S*)-3-[5-[4-[[1-[4-[6-(1-adamantyl)-2-hydroxy-8,9-dihydro-7*H*-benzo[7]annulen-5-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-30



[1719] ***Step 1.*** To a solution of 2-(1-adamantyl)acetic acid (10 g, 51.47 mmol, 1 eq) in MeOH (50 mL) was added $SOCl_2$ (12.25 g, 102.95 mmol, 7.47 mL, 2 eq) under 0 °C. The mixture was stirred at 80 °C for 3 h. The reaction mixture was quenched by addition of water (100 mL), extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (10

mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield methyl 2-(1-adamantyl)acetate (11 g, 47.53 mmol, 92.33% yield, 90% purity) as yellow oil which was used in the next step without further purification.

[1720] ***Step 2.*** To a solution of methyl 2-(1-adamantyl)acetate (11 g, 47.53 mmol, 1 eq) in THF (110 mL) was added LDA (2 M, 35.65 mL, 1.5 eq) under -68 °C over 10 min, after stirred 1 h was added 3-bromoprop-1-ene (5.75 g, 47.53 mmol, 1 eq). The mixture was stirred at -68 °C for 12 h. The reaction mixture was quenched by addition to saturation solution of NH_4Cl (150 mL) under 0 °C, extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 10/1, TLC: PE/EtOAc = 10/1, R_f = 0.59) to yield methyl 2-(1-adamantyl)pent-4-enoate (10.36 g, 40.88 mmol, 86.01% yield, 98% purity) as colourless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.77 - 5.63 (m, 1H), 5.10 - 4.92 (m, 2H), 3.64 (s, 3H), 2.40 - 2.22 (m, 2H), 2.15 - 2.07 (m, 1H), 1.98 (br s, 3H), 1.76 - 1.61 (m, 9H), 1.45 (br d, J=12.0 Hz, 3H)

[1721] ***Step 3.*** To a solution of methyl 2-(1-adamantyl)pent-4-enoate (8.36 g, 32.99 mmol, 1 eq) and 1-benzyloxy-3-iodo-benzene (10.23 g, 32.99 mmol, 1 eq) in DMF (120 mL) was added $Pd(OAc)_2$ (370.30 mg, 1.65 mmol, 0.05 eq), tris-o-tolylphosphane (1.00 g, 3.30 mmol, 0.1 eq) and DIEA (10.23 g, 79.17 mmol, 13.79 mL, 2.4 eq). The mixture was stirredunder N_2 at 100 °C for 12 h. The reaction mixture was quenched by addition of water (100 mL), extracted with EtOAc (130 mL x 3). The combined organic layers were washed with brine (100 mL x 5), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 10/1, TLC: PE/EtOAc = 10/1, R_f = 0.0.74) to yield compound 5 (9.2 g, 20.08 mmol, 60.89% yield, 94% purity) as colorless oil. LC-MS (ESI^+) *m/z* 431.4 $[M+H]^+$. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.47 - 7.44 (m, 2H), 7.44 - 7.40 (m, 2H), 7.36 (d, *J*=7.0 Hz, 1H), 7.22 (t, *J*=7.9 Hz, 1H), 6.97 - 6.92 (m, 2H), 6.84 (dd, *J*=2.0, 8.0 Hz, 1H), 6.39 (d, *J*=15.7 Hz, 1H), 6.12 - 6.04 (m, 1H), 5.08 (s, 2H), 3.64 (s, 3H), 2.56 - 2.40 (m, 2H), 2.20 (dd, *J*=3.2, 11.7 Hz, 1H), 2.02 (br s, 3H), 1.79 - 1.67 (m, 9H), 1.50 (br d, *J*=12.3 Hz, 3H)

[1722] ***Step 4.*** To a solution of methyl (compound 5 (9.2 g, 20.08 mmol, 1 eq) in THF (50 mL) and MeOH (50 mL) was added Pd/C (9 g, 10% purity, 1.00 eq). The mixture was stirred under H_2 (15 Psi) at 25 °C for 24 h. The reaction mixture was filtered and concentrated to yield compound 6 (7.1 g, 18.24 mmol, 90.83% yield, 88% purity) as brown oil which was used in the

next step without further purification. LC-MS (ESI+) m/z 343.3 [M+H]+. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.06 (t, *J*=7.7 Hz, 1H), 6.66 (d, *J*=7.4 Hz, 1H), 6.61 - 6.56 (m, 2H), 3.58 (s, 3H), 2.54 - 2.44 (m, 2H), 1.93 - 1.83 (m, 4H), 1.66 - 1.58 (m, 8H), 1.54 - 1.40 (m, 4H), 1.34 (br d, *J*=12.6 Hz, 4H)

[1723] ***Step 5.*** A mixture of methyl 2-(1-adamantyl)-5-(3-hydroxyphenyl)pentanoate (3 g, 7.71 mmol, 1 eq) in TfOH (15 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched by addition to saturation solution of $NaHCO_3$(100 mL), extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.56) to yield 6-(1-adamantyl)-2-hydroxy-6,7,8,9-tetrahydrobenzo[7]annulen-5-one (2.2 g, 6.02 mmol, 78.14% yield, 85% purity) as colourless oil. LC-MS (ESI+) m/z 311.2 [M+H]+. ^{1}H NMR (500MHz, CD_3OD) δ = 7.38 - 7.35 (m, 1H), 6.66 - 6.63 (m, 2H), 3.01 - 2.86 (m, 2H), 2.61 (dd, *J*=6.6, 12.2 Hz, 1H), 2.14 (ttd, *J*=2.2, 7.0, 14.2 Hz, 1H), 1.95 - 1.92 (m, 5H), 1.74 - 1.67 (m, 12H), 1.47 - 1.43 (m, 1H)

[1724] ***Step 6.*** To a solution of compound 7 (1 g, 2.74 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (1.14 g, 8.21 mmol, 3 eq) and PMB-Cl (471.70 mg, 3.01 mmol, 408.75 µL, 1.1 eq). The mixture was stirred at 25 °C for 3 h. The reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was added PE/EA (10/1, 10 mL), and stirred at 15°C for 2h. The slurry was filtered, and the cake was rinsed with PE (2 x 30 mL). The solid was collected and dried in vacuo to yield compound 8 (800 mg, 1.77 mmol, 64.46% yield, 95% purity) as a white solid. LC-MS (ESI+) m/z 431.3 [M+H]+. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.53 (d, *J*=8.5 Hz, 1H), 7.38 - 7.33 (m, 2H), 6.95 - 6.91 (m, 2H), 6.86 - 6.81 (m, 1H), 6.79 (d, *J*=2.1 Hz, 1H), 5.01 (s, 2H), 3.83 (s, 3H), 3.04 - 2.91 (m, 2H), 2.59 (dd, *J*=6.6, 12.2 Hz, 1H), 2.18 - 2.07 (m, 1H), 2.01 - 1.91 (m, 4H), 1.87 (br d, *J*=11.7 Hz, 4H), 1.72 - 1.61 (m, 10H)

[1725] ***Step 7.*** To a solution of 1-(4-bromophenyl)-4-(dimethoxymethyl)piperidine (665.00 mg, 2.12 mmol, 1.37 eq) in THF (10 mL) was slowly added n-BuLi (2.5 M, 926.66 µL, 1.5 eq) under -68 °C , after stirred 30 min was added compound 8 (700 mg, 1.54 mmol, 1 eq) in THF (10 mL). The mixture was stirred at -68 °C for 5 h. The reaction mixture was quenched by add to

saturation solution of NH_4Cl (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.48) to yield compound 10 (1.2 g, 1.35 mmol, 87.51% yield, 75% purity) as blue oil. LC-MS (ESI+) m/z 666.6 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$) δ = 7.58 - 7.53 (m, 1H), 7.42 (br s, 1H), 7.32 (d, *J*=8.6 Hz, 2H), 7.20 (t, *J*=8.0 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 6.76 - 6.72 (m, 3H), 6.59 (d, *J*=2.6 Hz, 1H), 4.90 (s, 2H), 3.81 (s, 3H), 3.66 (br d, *J*=11.8 Hz, 2H), 3.37 (s, 6H), 2.62 - 2.58 (m, 2H), 2.38 (br d, *J*=7.6 Hz, 1H), 1.97 (br d, *J*=3.9 Hz, 4H), 1.89 - 1.81 (m, 8H), 1.75 - 1.67 (m, 8H), 1.60 (br s, 8H)

[1726] ***Step 8.*** A mixture of compound 10 (200 mg, 225.26 μmol, 1 eq) in HCl/MeOH (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 30 min under N_2 atmosphere. The reaction mixture was quenched by addition to saturation solution of $NaHCO_3$ (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (PE/EtOAc = 1/1, TLC: PE/EtOAc = 3/1, R_f = 0.37) to yield compound 11 (80 mg, 125.82 μmol, 55.86% yield, 83% purity) as a pink solid. LC-MS (ESI+) m/z 528.4 $[M+H]^+$.

[1727] ^1H NMR (400MHz, $CDCl_3$) δ = 7.24 - 7.11 (m, 1H), 6.98 - 6.79 (m, 2H), 6.79 - 6.71 (m, 1H), 6.64 (d, *J*=2.6 Hz, 1H), 6.53 (br d, *J*=8.3 Hz, 1H), 6.39 (br d, *J*=8.2 Hz, 1H), 4.12 - 4.09 (m, 1H), 3.69 (br d, *J*=12.0 Hz, 2H), 3.40 - 3.37 (m, 6H), 2.90 - 2.41 (m, 4H), 1.92 - 1.81 (m, 6H), 1.70 (br s, 8H), 1.62 - 1.50 (m, 10H)

[1728] ***Step 9.*** To a solution of compound 11 (70 mg, 110.09 μmol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 122.28 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition to saturation solution of $NaHCO_3$ (20 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-[4-[6-(1-adamantyl)-2-hydroxy-8,9-dihydro-7*H*-benzo[7]annulen-5-yl]phenyl]piperidine-4-carbaldehyde (50 mg, 93.43 μmol, 84.86% yield, 90% purity) as a yellow solid which was used in the next step without further purification. LC-MS (ESI+) m/z 482.4 $[M+H]^+$.

[1729] Step 10. To a solution of compound 12 (40 mg, 74.74 μmol, 1 eq) and (3*S*)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (37.41 mg, 74.74 μmol, 1 eq, TsOH) in DCM

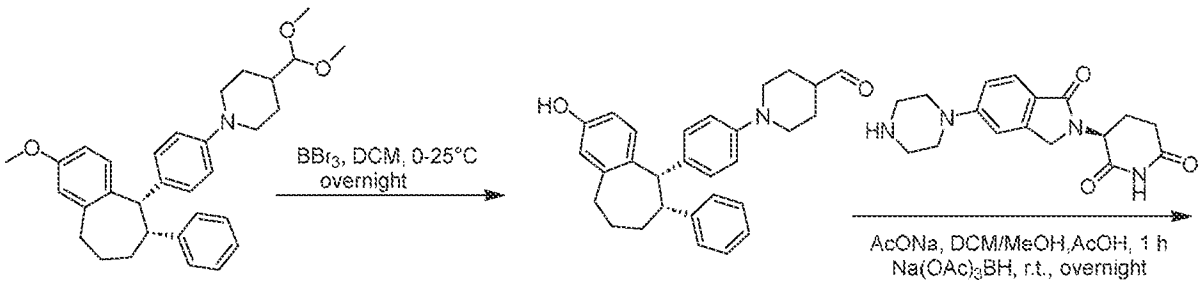
(1.5 mL) and MeOH (1.5 mL), after stirred 30 min was added NaBH(OAc)3 (47.52 mg, 224.22 μmol, 3 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to yield a residue. The residue was purified by preparative HPLC (column: Boston Green ODS 150*30 mm*5 um; mobile phase: [water(FA)-ACN];gradient:30%-60% B over 12 min), followed by lyophilization to yield (3*S*)-3-[5-[4-[[1-[4-[6-(1-adamantyl)-2-hydroxy-8,9-dihydro-7*H*-benzo[7]annulen-5-yl]phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (25.2 mg, 31.55 μmol, 42.22% yield, 100% purity, 0.1FA) as a white solid. LC-MS (ESI+) m/z 794.6 [M+H]+.

[1730] LCMS: calc. for C50H59N5O4: 793.46, found: $[M+H]^+$ 794.6.

[1731] HPLC: 100% purity at 220 nm.

[1732] ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.95 (s, 1H), 9.15 (s, 1H), 8.14 (s, 1H), 7.52 (d, *J*=8.6 Hz, 1H), 7.15 - 7.01 (m, 3H), 6.80 (br s, 2H), 6.55 (s, 2H), 6.46 - 6.37 (m, 2H), 5.05 (dd, *J*=5.2, 13.4 Hz, 1H), 4.38 - 4.29 (m, 1H), 4.25 - 4.15 (m, 1H), 4.04 (s, 1H), 3.66 (br d, *J*=11.3 Hz, 2H), 3.31 (br s, 8H), 2.96 - 2.83 (m, 1H), 2.71 - 2.55 (m, 6H), 2.40 - 2.29 (m, 2H), 2.22 (br d, *J*=6.4 Hz, 2H), 2.00 - 1.93 (m, 2H), 1.81 (br s, 4H), 1.66 (br s, 6H), 1.60 - 1.46 (m, 8H), 1.25 - 1.16 (m, 2H)

Example 110. Synthesis of (S)-3-(5-(4-((1-(4-((5*S,6*R)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-3



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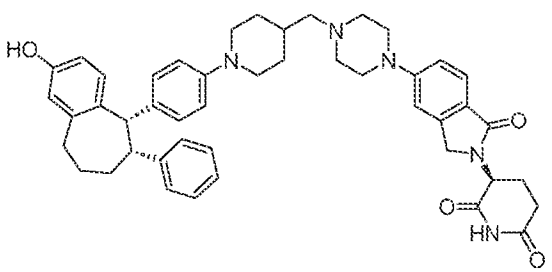


[1733] ***Step 1.*** A mixture of 4-(dimethoxymethyl)-1-(4-((5*S,6*R)-2-methoxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine (60 mg, 0.12 mmol) in DCM (2 mL) at 0 °C was added tribromoborane(0.58 mL, 1M in DCM, 0.58 mmol) with N_2. After addition, the mixture was stirred at 0 °C for 2 h, then the reaction was warmed to 25 °C and was stirred at 25 °C for 16 h. The mixture was added to H_2O (20 mL) at 0 °C and was extracted with CH_2Cl_2 (20 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-((5*S,6*R)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine-4-carbaldehyde (80 mg, 99 % yield) as a brown solid. LC-MS (ESI+) m/z: 444.1$(M+H)^+$.

[1734] ***Step 2.*** A mixture of 1-(4-((5*S,6*R)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine-4-carbaldehyde (80 mg, 0.12 mmol) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, TsOH salt (0.10 g, 0.17 mmol), sodium acetate (47 mg, 0.58 mmol) and acetic acid (21 mg, 20 μL, 0.35 mmol) in DCM (1 mL) and MeOH (1 mL) at 25 °C for 3 h, then Sodium triacetoxyborohydride (49 mg, 0.23 mmol) was added, then the mixture was stirred at 25 °C for 16 h. The reaction was filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep-HPLC (column: Column: Phenomenex C18 75*30mm*3um; mobile phase: [water(FA)-ACN];B% 7%-47%, 8min) to give (S)-3-(5-(4-((1-(4-((5*S,6*R)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (12.5 mg, 15 % yield) as a white solid. LC-MS (ESI^+) m/z: 738.5 $(M+H)^+$.

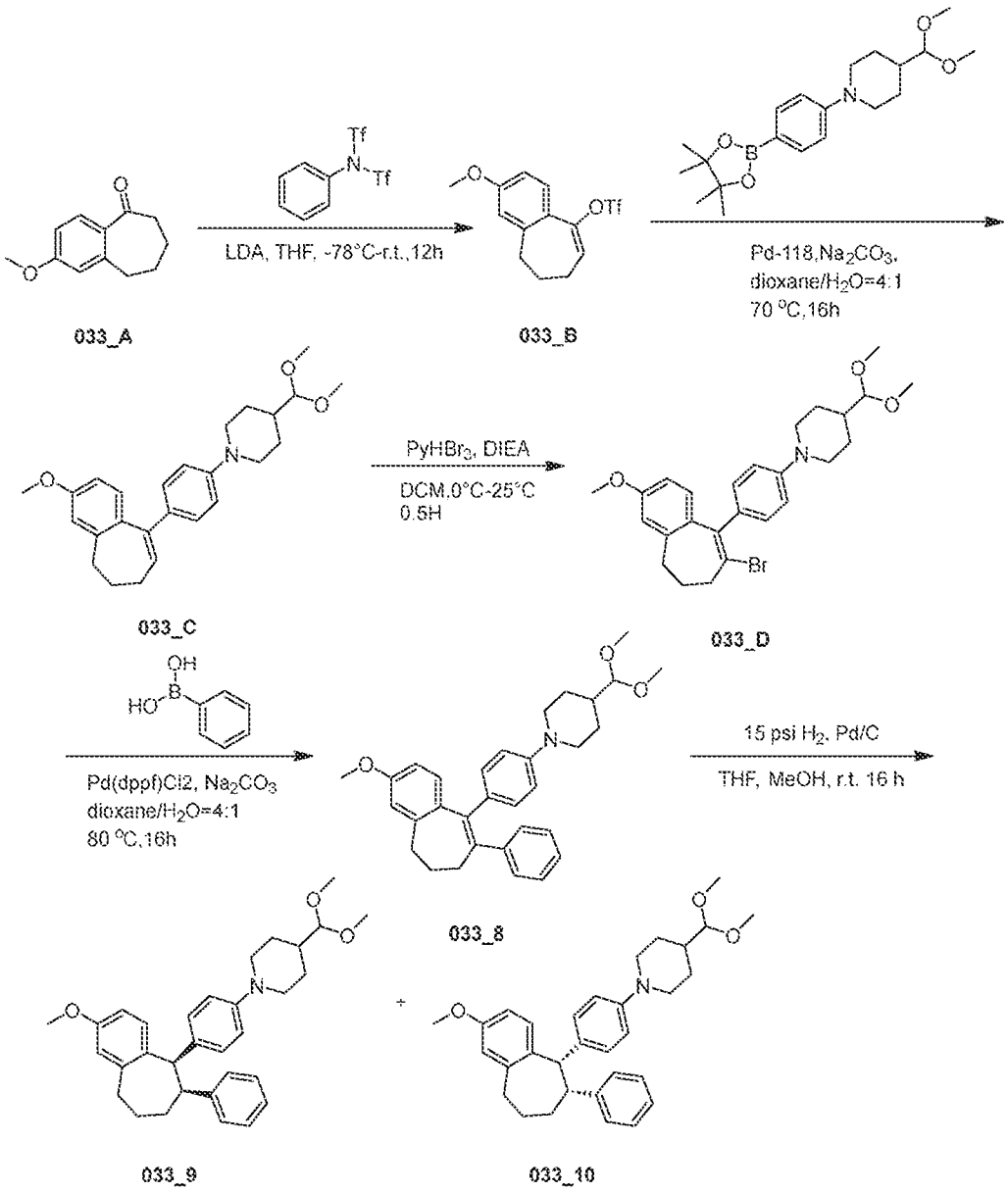
[1735] LCMS: calc. for $C_{46}H_{51}N_5O_4$: 737.39, found: $[M+H]^+$ 738.5.

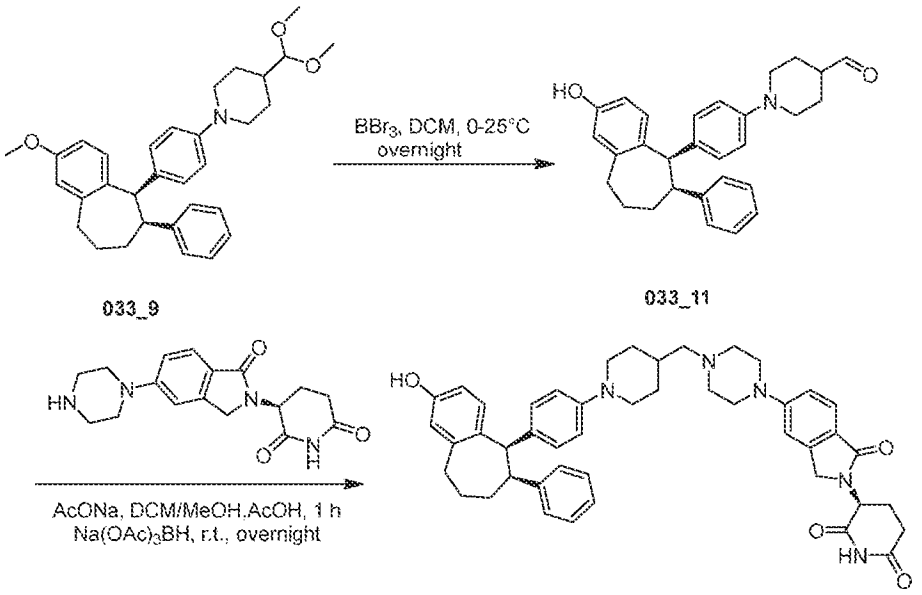
[1736] HPLC: 100% purity at 220 nm.

[1737] ^1H NMR(400 MHz, DMSO-d_6) δ = 10.95 (s, 1H), 9.15 (br s, 1H), 8.16 (s, 1H), 7.52 (br d, *J*=8.6 Hz, 1H), 7.23 - 7.11 (m, 2H), 7.10 - 7.01 (m, 2H), 6.88 (br t, *J*=7.2 Hz, 1H), 6.67 - 6.41 (m, 6H), 6.24 (br d, *J*=8.6 Hz, 2H), 5.05 (br dd, *J*=4.8, 13.1 Hz, 1H), 4.38 - 4.28 (m, 1H), 4.25 - 4.15 (m, 2H), 3.52 (br d, *J*=6.9 Hz, 2H), 3.28 (br s, 6H), 3.07 - 2.80 (m, 5H), 2.61 (br s, 4H), 2.39 (br s, 1H), 2.19 (br d, *J*=6.4 Hz, 2H), 2.15 (br s, 1H), 2.02 - 1.91 (m, 1H), 1.79 - 1.60 (m, 4H), 1.15 (br d, *J*=9.8 Hz, 2H)

[1738] SFC: retention time, 6.005 min; Area, 91.24 %; method: OJ_ETOH_DEA_50_25ML_10CM

Example 111. Synthesis of (S)-3-(5-(4-((1-(4-((5*R,6*S)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-1





[1739] ***Step 1.*** A mixture of 2-methoxy-6,7,8,9-tetrahydrobenzo[7]annulen-5-one (3 g, 15.77 mmol) , LDA (2 M, 11.83 mL) in THF (25 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at -78 °C. Then 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (8.45 g, 23.65 mmol) in THF (25 mL) was added to the mixture at -78 °C for 16 h under N_2 atmosphere. The reaction mixture was added H_2O (200 mL) and extracted with ethyl acetate (150 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether = 0% to 10%) to give the product of (2-methoxy-8,9-dihydro-7H-benzo[7]annulen-5-yl) trifluoromethanesulfonate (4.4 g, 86.57% yield) was obtained as a gray oil. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.41 - 7.35 (m, 1H), 6.96 - 6.91 (m, 2H), 6.22 (t, J=6.0 Hz, 1H), 3.80 (s, 3H), 2.73 - 2.66 (m, 2H), 2.21 (q, J=6.9 Hz, 2H), 2.01 - 1.92 (m, 2H)

[1740] ***Step 2.*** A mixture of (2-methoxy-8,9-dihydro-7H-benzo[7]annulen-5-yl) trifluoromethanesulfonate (2 g, 6.21 mmol) , 4-(dimethoxymethyl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (2.69 g, 7.45 mmol) , Pd-118 (404.4 mg, 620.5 umol) , Na_2CO_3 (1.97 g, 18.62 mmol) in dioxane (16 mL) and H_2O (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 16 h under N_2 atmosphere. The reaction mixture was partitioned between H_2O (200 mL) and EtOAc 300 mL (150 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 30%) to give the product of 4-(dimethoxymethyl)-1-[4-(2-methoxy-8, 9-dihydro-7H-benzo[7]annulen-5-

yl)phenyl]piperidine (970 mg, 34.74% yield) was obtained as a white solid. LC-MS (ESI^+) *m/z*: 408.6 $(M+H)^+$.

[1741] ***Step 3.*** To a mixture of 4-(dimethoxymethyl)-1-(4-(3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (920 mg, 2.04mmol) in DCM (15 mL) and DIPEA (396 mg, 3.07mmol), Pyridinium bromide perbromide (654 mg, 2.04 mmol) were added at 0 °C, then the mixture was stirred at 0 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 30%) to give the product of 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (900 mg, 85.5 % yield) was obtained as a colorless oil.

[1742] ***Step 4.*** The mixture of 1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride (28.9 mg, 44.3μmol), 1-(4-(8-bromo-3-methoxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)-4-(dimethoxymethyl)piperidine (280 mg, 443μmol), phenylboronic acid (64.8 mg, 531μmol) and Sodium carbonate (141 mg, 1.33mmol) in Dioxane (6 mL) and H_2O (1.5 mL) at r.t. N_2 was bubbled into the mixture for 5 min. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was partitioned between H_2O (100 mL) and EtOAc 200 mL (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 20%) to give the product of 4-(dimethoxymethyl)-1-(4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (270 mg, 91.1 % yield) as a yellow solid.

[1743] ***Step 5.*** A mixture of 4-(dimethoxymethyl)-1-(4-(3-methoxy-8-phenyl-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidine (270 mg, 403 μmol) , Pd/C(200 mg, 10% purity, 188 μmol) in MeOH (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 16 h under H_2 (15 psi)atmosphere. The reaction was filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether= 0% to 20%) and was further separated by SFC (condition: column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: [Neu-ETOH];B%: 35%-35%, min) to give 4-(dimethoxymethyl)-1-(4-((5*R,6*S)-2-methoxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine (60 mg, 0.12 mmol 31 % yield) as a white solid and 4-(dimethoxymethyl)-1-(4-((5*S,6*R)-2-methoxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine (60 mg, 0.12 mmol, 29 % yield) as a white solid.

[1744] *Step 6.* The mixture of 4-(dimethoxymethyl)-1-(4-((5*R,6*S)-2-methoxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine (60 mg, 0.12 mmol) in DCM (2 mL) at 0 °C was added BBr_3 (0.62 mL, 1M in DCM, 62 mmol) with N_2. After addition, the mixture was stirred at 0 °C for 2 hour, then the reaction was warmed to 25 °C and was stirred at 25 °C for 16 h. The mixture was added to H_2O (20 mL) at 0 °C and was extracted with CH_2Cl_2 (20 mL * 2). The combined extracts was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give (5*R,6*S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-ol (60 mg, 98 % yield) as a brown solid.

[1745] *Step 7.* A mixture of 1-(4-((5*R,6*S)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidine-4-carbaldehyde (55 mg, 0.12mmol) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione, TsOH salt (0.11 g, 0.18 mmol), Sodium acetate (50 mg, 0.61 mmol) and acetic acid (22 mg, 21 μL, 0.37 mmol) in DCM (1 mL) and MeOH (1 mL) at 25 °C for 3 h, then $Na(OAc)_3BH$ (52 mg, 0.25 mmol) was added, then the mixture was stirred at 25 °C for 16 h. The reaction was filtered and concentrated to dryness in vacuo to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3um; mobile phase: [water(FA)-ACN];B% 8%-48%, 8min) to give the product of (S)-3-(5-(4-((1-(4-((5*R,6*S)-2-hydroxy-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, Formic Acid (11.2 mg, 12 % yield) as a white solid. LC-MS (ESI+) m/z: 738.4 $(M+H)^+$.

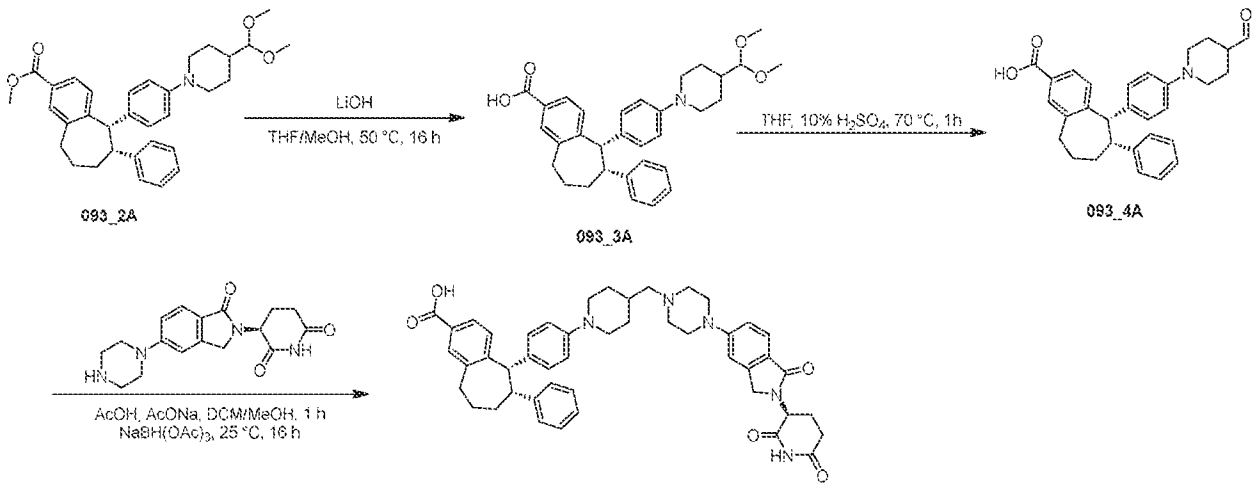
[1746] LCMS: calc. for $C_{46}H_{51}N_5O_4$: 737.39, found: [M+H] + 738.4.

[1747] HPLC: 100% purity at 220 nm.

[1748] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.96 (s, 1H), 9.17 (s, 1H), 8.15 - 8.14 (m, 1H), 7.52 (d, *J*=8.3 Hz, 1H), 7.26 - 7.16 (m, 3H), 7.10 - 7.04 (m, 2H), 6.98 (br d, *J*=7.3 Hz, 2H), 6.69 (br d, *J*=8.5 Hz, 3H), 6.64 - 6.58 (m, 3H), 6.47 (dd, *J*=2.4, 8.4 Hz, 1H), 5.05 (dd, *J*=5.0, 13.3 Hz, 1H), 4.48 (s, 1H), 4.37 - 4.30 (m, 1H), 4.24 - 4.17 (m, 1H), 3.59 (br d, *J*=11.3 Hz, 2H), 3.31 - 3.26 (m, 6H), 2.93 - 2.80 (m, 3H), 2.60 (br s, 6H), 2.43 - 2.36 (m, 1H), 2.23 (br s, 2H), 2.08 (br s, 1H), 2.01 - 1.93 (m, 2H), 1.78 (br d, *J*=11.8 Hz, 3H), 1.64 (br s, 2H), 1.24 - 1.13 (m, 2H)

[1749] SFC: retention time, 6.579 min; Area, 92.97%; method: OJ_ETOH_DEA_50_25ML_10CM.

Example 112. Synthesis of (5S,6R)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid, I-7



[1750] ***Step 1.*** To a solution of methyl (5S,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (530 mg, 1 Eq, 1.03 mmol) in THF (2 mL) and MeOH (2 mL) was added lithium hydroxide (5.2 mL, 2 molar, 10 Eq, 10.3 mmol). The mixture was stirred at 50 °C for 16 hours. The reaction was added aqueous HCl (2 M) to adjust pH=6~7. The resulting mixture was extracted with ethyl acetate (50 mL * 2) and the organic layers was combined. The organic was washed with brine (20 mL * 2), dried over anhydrous sodium sulfate and concentrated under vacuum to give (5S,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (400 mg, 756 μmol, 62.9 %, 94.396% purity)as a yellow oil.

[1751] ***Step 2.*** To a solution of (5S,6R)-5-[4-(4-formyl-1-piperidyl)phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (54 mg, 119.06 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione(78 mg, 238.11 umol, 2eq) in DCM (1 mL) and MeOH (1 mL)was added sodium acetate (49 mg, 595.28 umol, 5 eq) and acetic acid (14.3 mg, 238.11 umol, 14 uL, 2 eq). The mixture was stirred at 20 °C for 1 hr. Then the sodium triacetoxyboranuide (50 mg, 238.11 umol, 2 eq) added to the mixture and stirred at 20 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];B%: 22%-52%,7min). Compound (5S,6R)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-phenyl-

6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (12 mg, 15.67 umol, 13.16% yield, 100% purity) was obtained as a white solid.

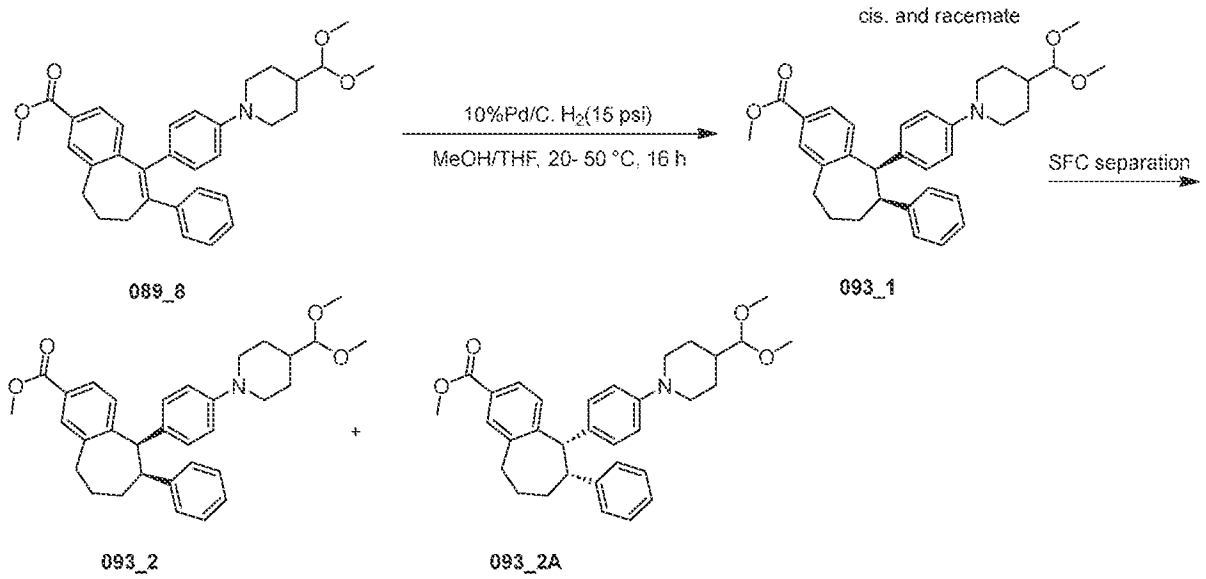
[1752] LCMS: calc. for $C_{47}H_{51}N_5O_5$:765.96, found: $[M+H]^+$766.4

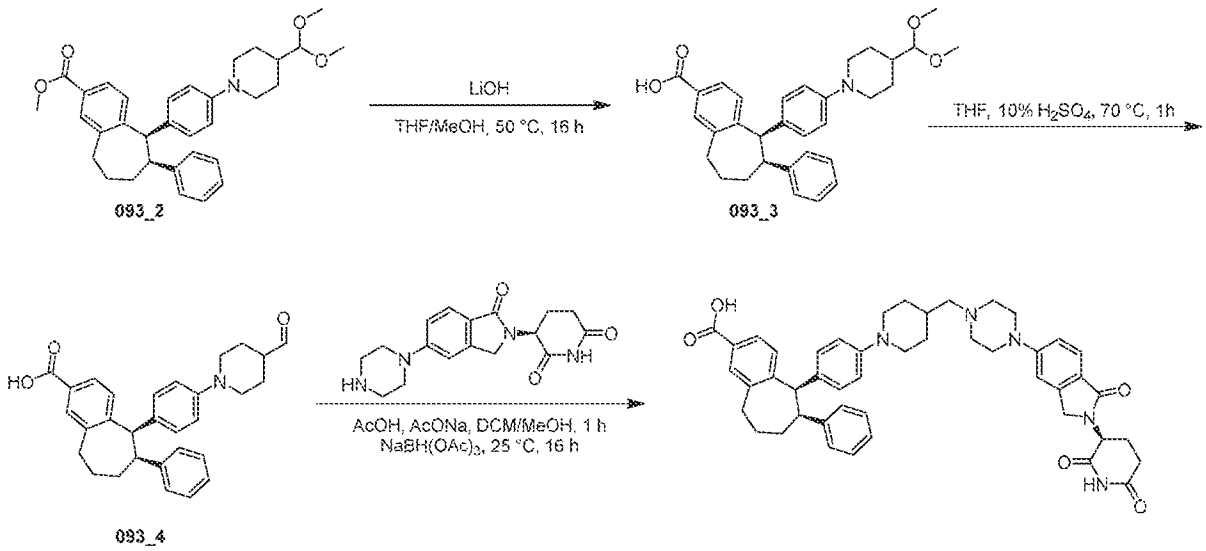
[1753] HPLC: 100 % purity at 220 nm.

[1754] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.95 (br s, 1H), 8.15 (br d, J = 1.8 Hz, 0.132H), 7.80 (br s, 1H), 7.66 (br d, J = 6.0 Hz, 1H), 7.51 (br d, J = 7.5 Hz, 1H),7.23 (br d, J = 6.5 Hz, 3H), 7.06 (br s, 4H), 6.99 (br s, 2H), 6.71 (br d, J = 7.3 Hz, 2H), 6.62 (br d, J = 6.8 Hz, 2H), 5.04 (br d, J = 15.3 Hz, 1H), 4.68 (br s,1H), 4.36 - 4.29 (m, 1H), 4.22 (br s, 1H), 3.61 (br s, 1H), 3.28 (br s, 8H), 3.15 - 2.79 (m, 6H), 2.59 (br s, 3H), 2.19 (br d, J = 3.8 Hz, 2H), 2.14 (br d, J = 12.8Hz, 2H), 1.98 (br d, J = 19.8 Hz, 2H), 1.77 (br d, J = 11.3 Hz, 2H), 1.67 (br d, J = 6.3 Hz, 2H), 1.16 (br d, J = 9.5 Hz, 2H)

[1755] SFC: retention time, 2.941 min; Area, 100%; Method: IG_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

Example 113. Synthesis of (5R,6S)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid, I-8





[1756] ***Step 1.*** To a solution of methyl 5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-phenyl-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (1.54 g, 2.17 mmol, 72.2% purity, 1 eq) in MeOH(5 mL) and THF(5 mL) was added Pd/C (1.61 g, 1.51 mmol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 50 °C for 16 hrs. The mixture was filtered by and the cake was rinsed with THF (4 * 20 mL), the filtrate was concentrated to dryness in vacuum to give a yellow solid. The yellow solid was subjected by SFC(condition: column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O IPA];B%: 40%-40%,min) Column: Chiral Pak AD-3 150×4.6mm I.D., 3um Mobile phase: A: CO_2 B:IPA (0.05% DEA) Isocratic: 40% B Flow rate: 2.5mL/min Column temp.:40 ABPR: 100 bar. The pure fractions were collected and concentrated to dryness in vacuum to give a white solid of methyl (5R,6S)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (600 mg, 1.17 mmol, 53.72% yield, 100% purity) and a white solid of methyl (5S,6R)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (530 mg, 1.03 mmol, 47.41% yield, 99.9% purity).

[1757] LCMS of 093_2: calc. for $C_{33}H_{39}NO_4$:513.68, found: $[M+H]^+$514.3

[1758] SFC of 093_2: retention time, 2.034 min; Area, 100%; Method: AD-3_IPA (DEA) _40_25ML

[1759] LCMS of 093_2A: calc. for $C_{33}H_{39}NO_4$:513.68, found: $[M+H]^+$514.3

[1760] SFC of 093_2A: retention time, 3.567 min; Area, 99.9%; Method: AD-3_IPA (DEA)_40_25ML

[1761] ***Step 2.*** To a solution of methyl (5R,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylate (600 mg, 1 Eq, 1.17 mmol) in THF(2 mL) and MeOH(2 mL) was added lithium hydroxide (280 mg, 5.8 mL, 2 molar, 10 Eq, 11.7 mmol) .The mixture was stirred at 50 °C for 16 hrs. TLC (petroleum ether/ethyl acetate=0:1, R_f=0.5) showed new spot was formed. The reaction was concentrated to dryness in vacuum to give (5R,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (600 mg, 1.2 mmol) as a yellow oil.

[1762] ***Step 3.*** To a solution of (5R,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5Hbenzo[7]annulene-2-carboxylic acid (200 mg, 1 Eq, 400 μmol) in THF (2 mL) was added 10% H_2SO_4 (3.93 g, 2.1 mL,10% Wt, 10 Eq, 4 mmol) at 0°C. The mixture was stirred at 70 °C for 16 hrs. TLC (petroleum ether/ethyl acetate=1/1, R_f=0.3) showed one new spot was formed. The reaction mixture was cooled to room temperature and diluted with water (10 mL). The reaction was added saturated $NaHCO_3$ to adjust the pH to 7. The resulting mixture was extracted with ethyl acetate (20 mL * 2) and the organic layers was combined. The organic was washed with brine (20 mL * 2), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. compound(5R,6S)-5-(4-(4-formylpiperidin-1-yl)phenyl)-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (120 mg, 261 μmol, 65.2 %, 98.62% Purity) was obtained as a yellow solid.

[1763] ***Step 4.*** To a solution of (5R, 6S)-5-[4-(4-formyl-1-piperidyl)phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (47 mg, 103.62 umol, 1 eq), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (68 mg, 207.24 umol, 2 eq) in DCM (1 mL) and MeOH (1 mL) was added sodium acetate (43 mg, 518.11 umol, 5eq) and acetic acid (207 umol, 12 uL, 2 eq). The mixture was stirred at 20 °C for 1 hr. Then the sodium triacetoxyboranuide (44 mg, 207.24 umol, 2 eq) added to the mixture and stirred at 20 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN];B%: 22%-52%,7min). Compound (5R,6S)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-6-phenyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-carboxylic acid (10 mg, 13.06 umol, 12.6% yield, 100% purity) was obtained as a white solid.

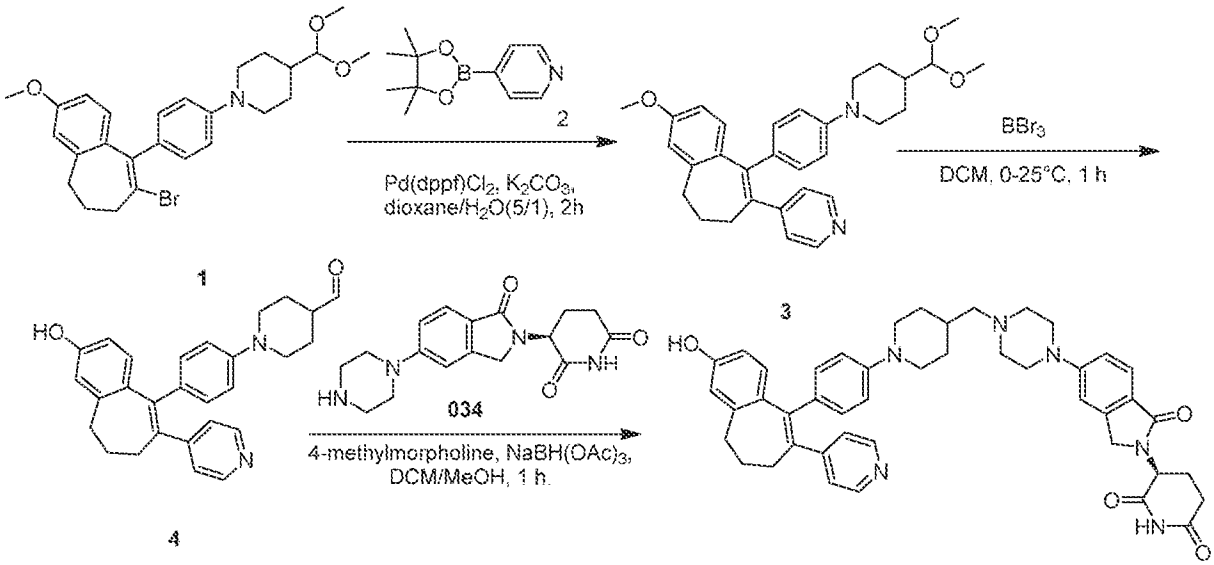
[1764] LCMS: calc. for $C_{47}H_{51}N_5O_5$:765.96, found: $[M+H]^+$766.4

[1765] HPLC: 100 % purity at 220 nm.

[1766] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.96 (br s, 1H), 8.16 (br s, 0.328H), 7.81 (br s, 1H), 7.67 (br d, J = 6.0 Hz, 1H), 7.52 (br d, J = 7.8 Hz, 1H), 7.23 (br d, J = 7.0 Hz, 3H), 7.07 (br s, 3H), 7.00 (br s, 2H), 6.72 (br d, J = 7.5 Hz, 2H), 6.63 (br d, J = 7.5 Hz, 2H), 5.11 - 5.01 (m, 1H), 4.68 (br s, 1H), 4.31 (br s, 1H), 4.22 (br s, 1H), 3.61 - 3.58 (m, 1H), 3.29 (br d, J = 1.3 Hz, 8H), 3.19 - 2.73 (m, 6H), 2.63 - 2.56 (m, 4H), 2.20 (br d, J = 5.0 Hz, 2H), 2.15 - 2.09 (m, 1H), 1.97 (br dd, J = 4.0, 7.3 Hz, 2H), 1.77 (br d, J = 10.5 Hz, 2H), 1.71 - 1.61 (m, 2H), 1.21 - 1.11 (m, 2H)

[1767] SFC: retention time, 2.725 min; Area, 100%; Method: IG_MeOH_DEA_MeCN_50_1ML_10MIN_10CM

Example 114. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-4-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-35, I-126



[1768] ***Step 1.*** To a solution of compound 1 (150 mg, 308.36 μmol, 1 *eq*) and compound 2 (69.56 mg, 339.20 μmol, 1.1 *eq*) in Dioxane/H_2O (3 mL) was added K_2CO_3 (127.86 mg, 925.09 μmol, 3 *eq*) and $Pd(dppf)Cl_2$ (40.19 mg, 61.67 μmol, 0.2 *eq*) at 20 °C under N_2. The reaction mixture was stirred at 90 °C for 2h. LCMS showed that the material was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 3/1 to 1/1, TLC: PE/EtOAc = 1/1,

Rf= 0.34) to give compound 3 (100 mg, 169.20 μmol, 54.87% yield) as a yellow solid. LC-MS (ESI+) *m/z*: 485.5 $(M+H)^+$.

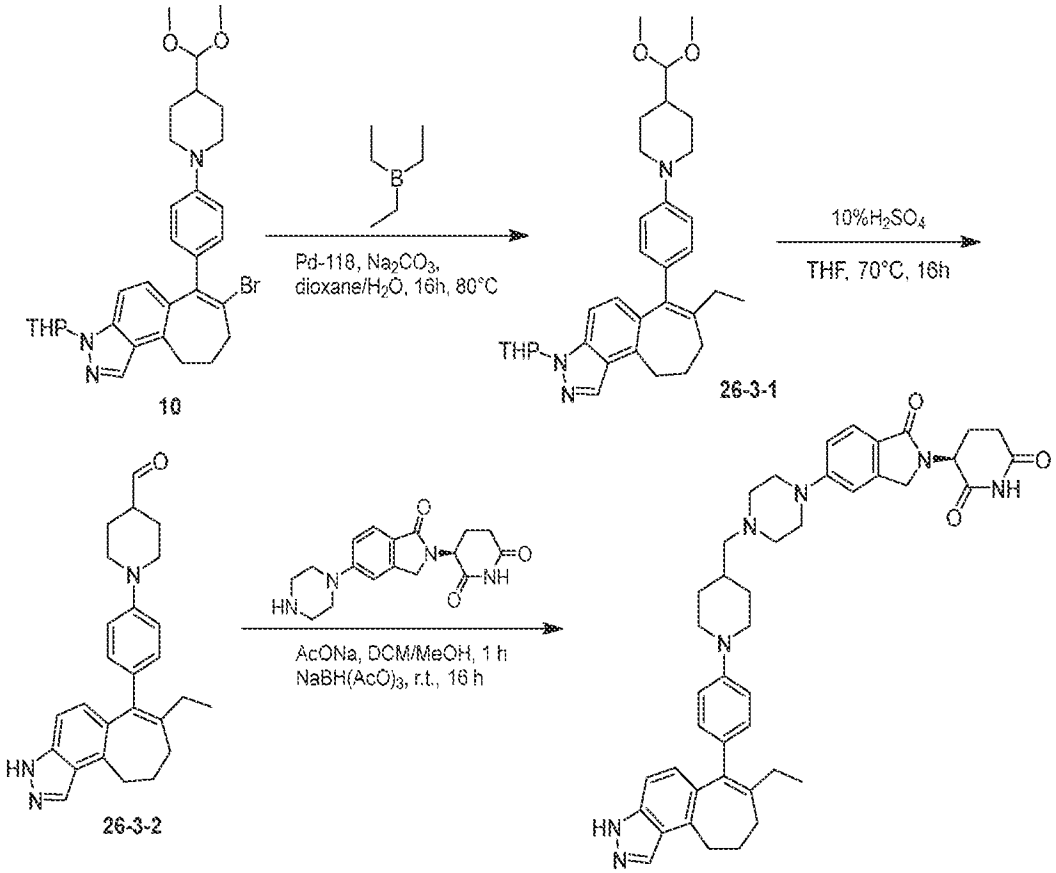
[1769] ***Step 2.*** To a solution of compound 3 (100 mg, 206.34 μmol, 1 *eq*) in DCM (4 mL) was added BBr_3 (51.69 mg, 206.34 μmol, 19.88 μL, 1 *eq*) at 0 °C. The reaction mixture was stirred at 20 °C for 1h. Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give compound 4 (100 mg, 143.69 μmol, 69.63% yield) as a red solid. LC-MS (ESI+) *m/z*: 425.4 $(M+H)^+$.

[1770] ***Step 3.*** To a solution of compound 4 (100 mg, 235.55 μmol, 1 *eq*) in DCM/MeOH (2 mL) was added 4-methylmorpholine (71.48 mg, 706.66 μmol, 77.69 μL, 3 *eq*) and compound 034 (77.35 mg, 235.55 μmol, 1 *eq*) in DCM/MeOH (2 mL). After stirring at 20 °C for 20 min, the mixture is adding $NaBH_3CN$ (29.60 mg, 471.11 μmol, 2 *eq*) and stirring at 20 °C for 1 h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 150*25mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 33%-63%,8min) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-4-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (12 mg, 15.55 μmol, 6.60% yield) as a yellow solid.

[1771] LC-MS (ESI+) *m/z:* 737.3 $(M+H)^+$.

[1772] ^1H NMR: (400 MHz, METHANOL-d4) δ = 8.30 - 8.21 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.22 - 7.16 (m, 2H), 7.11 - 7.04 (m, 2H), 6.80 - 6.70 (m, 5H), 6.69 - 6.64 (m, 1H), 6.61 - 6.55 (m, 1H), 5.10 (dd, *J* = 5.2, 13.4 Hz, 1H), 4.47 - 4.32 (m, 2H), 3.65 (br d, *J* = 12.8 Hz, 2H), 3.46 - 3.34 (m, 4H), 2.92 - 2.85 (m, 1H), 2.82 - 2.70 (m, 3H), 2.69 - 2.58 (m, 6H), 2.46 (br dd, *J* = 4.8, 13.4 Hz, 1H), 2.40 (br t, *J* = 7.2 Hz, 2H), 2.30 (br d, *J* = 6.8 Hz, 2H), 2.17 - 2.08 (m, 3H), 1.95 - 1.82 (m, 2H), 1.81 - 1.67 (m, 1H), 1.34 - 1.29 (m, 2H)

Example 115. Synthesis of (3S)-3-[5-[4-[[1-[4-(7-ethyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-73



[1773] ***Step 1.*** A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (300 mg, 516.8 μmol, 1 *eq*) , triethylborane (151.9 mg, 1.55 mmol, 3.00 *eq*), Pd-118 (33.68 mg, 51.7 μmol, 0.1 *eq*), Na_2CO_3 (164.31 mg, 1.55 mmol, 3 *eq*) in dioxane (5 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The reaction mixture was diluted with 20 mL H_2O and extracted with ethyl acetate 30 mL (15 mL * 2). The combined organic layers were washed with brine 20 mL (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1). The residue was further purified by flash silica gel chromatography (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN];B%: 55%-85%,7min). Compound 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-7-ethyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (57

mg, 107.61 μmol, 20.82% yield) was obtained as a yellow oil. LC-MS (ESI+) m/z: 530.4 $(M+H)^+$

[1774] ***Step 2.*** To a solution of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-7-ethyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (57 mg, 107.61 μmol, 1 eq) in THF (4 mL) was added 10% H_2SO_4 (4 mL). The mixture was stirred at 70 °C for 16 hr. TLC (petroleum ether/ethyl acetate=5:1, R_f=0.4) showed new spot was formed. The reaction mixture was quenched by addition 20 mL saturated aqueous $NaHCO_3$ aqueous solution at 25°C, and then extracted with EA 40 mL (20 mL * 2). The combined organic layers were washed with brine 20 mL (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound 1-[4-(7-ethyl-3, 8, 9, 10-tetrahydrocyclohepta[e]indazol-6-yl) phenyl] piperidine-4-carbaldehyde (30 mg, 41.30 μmol, 38.38% yield, 55% purity) was obtained as a yellow oil.LC-MS (ESI+) m/z: 400.1 $(M+H)^+$.

[1775] ***Step 3.*** To a solution of 1-[4-(7-ethyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (30 mg, 75.09 μmol, 1 eq) and (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (37.59 mg, 75.09 μmol, 1 eq, $PhSO_3H$ salt) in DCM (4 mL) and MeOH (4 mL) was added sodium acetate (18.48 mg, 225.27 μmol, 3 eq). The mixture was stirred at 25 °C for 0.5 hr. After this, the mixture was added sodium triacetoxyboranuide (31.83 mg, 150.18 μmol, 2 eq) and acetic acid (13.53 mg, 225.27 μmol, 12.90 μL, 3 eq). Finally, the mixture was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O 10 mL and extracted with DCM (15 mL *2). The combined organic layers were washed with brine 10 mL (5 mL *2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];gradient:18%-48% B over 7 min) to give Compound (3S)-3-[5-[4-[[1-[4-(7-ethyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (5.5 mg, 7.73 μmol, 10.29% yield) was obtained as a white solid.

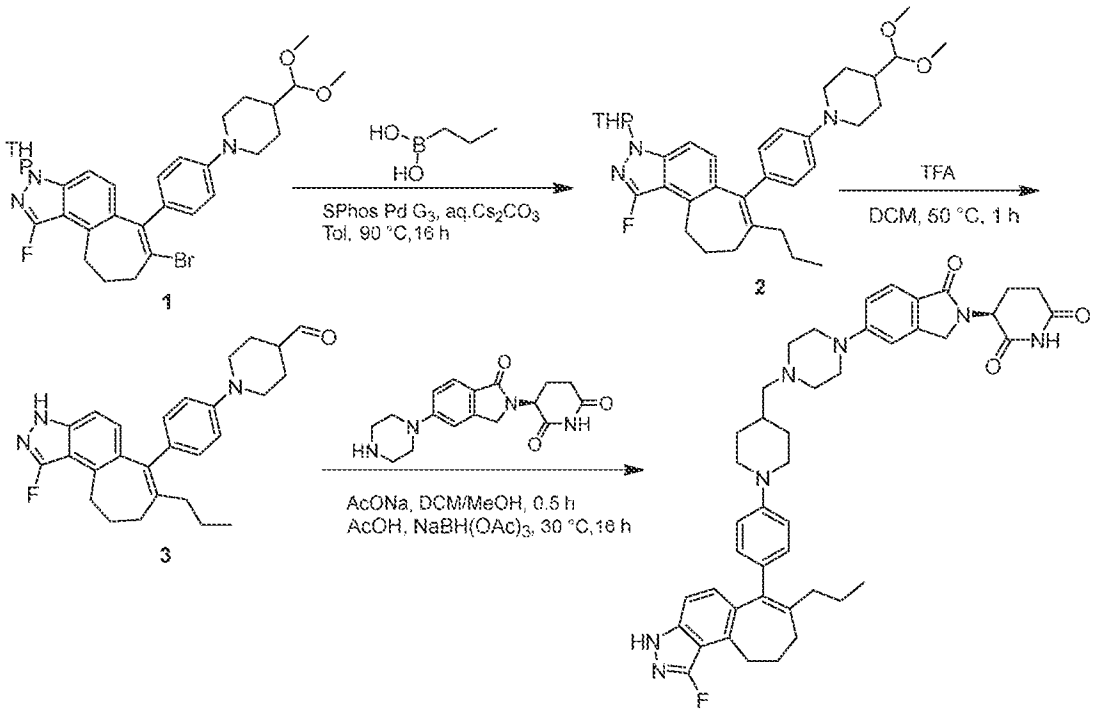
[1776] LC-MS (ESI^+) *m/z*: 712.3 $(M+H)^+$.

[1777] HPLC: 93.164%, purity at 220 nm.

[1778] SFC: Rt: 3.562 min; Area, 98.566%; method: ID_MeOH_DEA_MeCN_50_1ML_15MIN_10CM.

[1779] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.93 (s, 1 H) 10.95 (s, 1 H) 8.26 (s, 0.115 H) 8.18 (s, 1 H) 7.49 - 7.57 (m, 1 H) 7.21 (d, *J*=8.34 Hz, 1 H) 7.03 - 7.12 (m, 2 H) 6.84 - 6.95 (m, 4 H) 6.68 (d, J=8.58 Hz, 1 H) 4.99 - 5.13 (m, 1 H) 4.17 - 4.37 (m, 2 H) 3.65 - 3.73 (m, 2 H) 3.28 - 3.32 (m, 8 H) 2.86 - 3.00 (m, 3 H) 2.66 - 2.70 (m, 2 H) 2.58 - 2.64 (m, 2 H) 2.32 - 2.40 (m, 2 H) 2.28 (br s, 1 H) 2.25 (br t, *J*=7.33 Hz, 4 H) 1.94 - 2.00 (m, 1 H) 1.91 (br t, *J*=7.03 Hz, 2 H) 1.79 - 1.87 (m, 2 H) 1.19 - 1.30 (m, 2 H) 1.08 (t, *J*=7.45 Hz, 3 H)

Example 116. Synthesis of (3S)-3-[5-[4-[[1-[4-(1-fluoro-7-propyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione, I-124



[1780] ***Step 1.*** A mixture of 7-bromo-6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (200 mg, 334.14 μmol, 1 eq), propylboronic acid (58 mg, 668 μmol, 2 eq), Sphos Pd G_3(48 mg, 66 μmol, 0.2 eq), dicesium carbonate (326 mg, 1 mmol, 3 eq) was added in toluene (5 mL) and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 h under N_2 atmosphere. The reaction was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the combined organic layer was washed with saturated salt water (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/Petroleum ethergradient @ 30 mL/min) to give compound 6-[4-[4-(dimethoxymethyl)-1-

piperidyl]phenyl]-1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (180 mg, 320 μmol) was obtained as a yellow oil. LC-MS (ESI+) m/z: 562.0 $(M+H)^+$

[1781] ***Step 2.*** A mixture of 6-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazole (100 mg, 178 μmol, 1 eq) was added in DCM (8 mL) and TFA (2 mL) and purged with N_2 for 3 times, the mixture was stirred at 50 °C for 1 h under N_2 atmosphere. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the combined organic layer was washed with saturated salt water (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound 1-[4-(1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (80 mg, 124 μmol) was obtained as a white solid.

[1782] ***Step 3.*** A mixture of (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (81 mg, 222 μmol, 1.2 eq, HCl salt), 1-[4-(1-fluoro-7-propyl-3-tetrahydropyran-2-yl-9,10-dihydro-8H-cyclohepta[e]indazol-6-yl)phenyl]piperidine-4-carbaldehyde (80 mg, 155 μmol, 1 eq), AcONa (45 mg, 556 μmol, 3 eq) was added in the DCM (2 mL) and MeOH (2 mL), the mixture was stirred at 30 °C for 0.5 h, and then AcOH (33mg, 556 μmol, 31 μL, 3 eq), $NaBH(OAc)_3$ (78 mg, 370 μmol, 2 eq) was added in the mixture and was stirred at 30 °C for 16 h. the reaction was treated with H_2O (50 mL) and was extracted with ethyl acetate (100 mL), the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water(FA)-ACN];gradient:23%-53% B over 7 min) to give (3S)-3-[5-[4-[[1-[4-(1-fluoro-7-propyl-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl]-4-piperidyl]methyl]piperazin-1-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione (27 mg, 36 μmol) was obtained as a white solid.

[1783] LC-MS (ESI+) m/z: 744.4 $(M+H)^+$

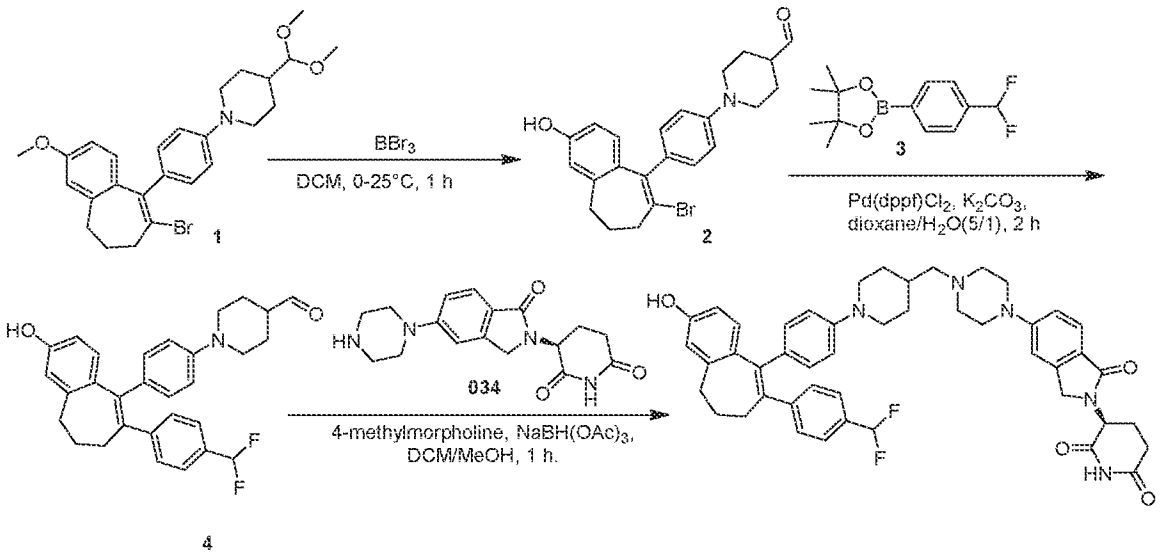
[1784] HPLC: 100% purity at 220 nm

[1785] SFC: Rt: 3.310 min; Area: 88%; Method: IC_MeOH_DEA_MeCN_50_1ML_15MIN_10CM

[1786] ^1H NMR (400 MHz, DMSO-d_6) δ= 12.41 (s, 1H), 10.95 (s, 1H), 8.16 (s, 0.237H), 7.53 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 2.6, 8.8 Hz, 1H), 7.10 - 7.04 (m, 2H), 6.89 (s, 4H), 6.75 (d, J =

8.8 Hz, 1H), 5.06 (dd, *J* = 5.1, 13.2 Hz, 1H), 4.34 (d, *J* = 16.8 Hz, 1H), 4.26 - 4.15 (m, 1H), 3.70 (br d, *J* = 12.3 Hz, 2H), 3.25(brs, 3H), 3.03 - 2.83 (m, 3H), 2.72 - 2.55 (m, 4H), 2.43 - 2.31 (m, 2H), 2.31 - 2.19 (m, 6H), 2.03 - 1.79 (m, 6H), 1.78 - 1.65 (m, 1H), 1.58 - 1.43 (m, 3H), 1.33 - 1.15 (m, 3H), 0.87 (t, *J* = 7.3 Hz, 3H).

Example 117. Synthesis of (S)-3-(5-(4-((1-(4-(8-(4-(difluoromethyl)phenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-125



[1787] ***Step 1.*** To a solution of compound 1 (150 mg, 308.36 μmol, 1 eq) in DCM (4 mL) was added BBr_3 (77.25 mg, 308.36 μmol, 29.71 μL, 1 eq) at 0 °C . The reaction mixture stirring at 20 °C for 1h. Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40mL x 3). The combined organic layers were washed with brine (100mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give compound 2 (154 mg, 258.26 μmol, 83.75% yield) as a red solid. LC-MS (ESI^+) *m/z*: 428.1 $(M+H)^+$.

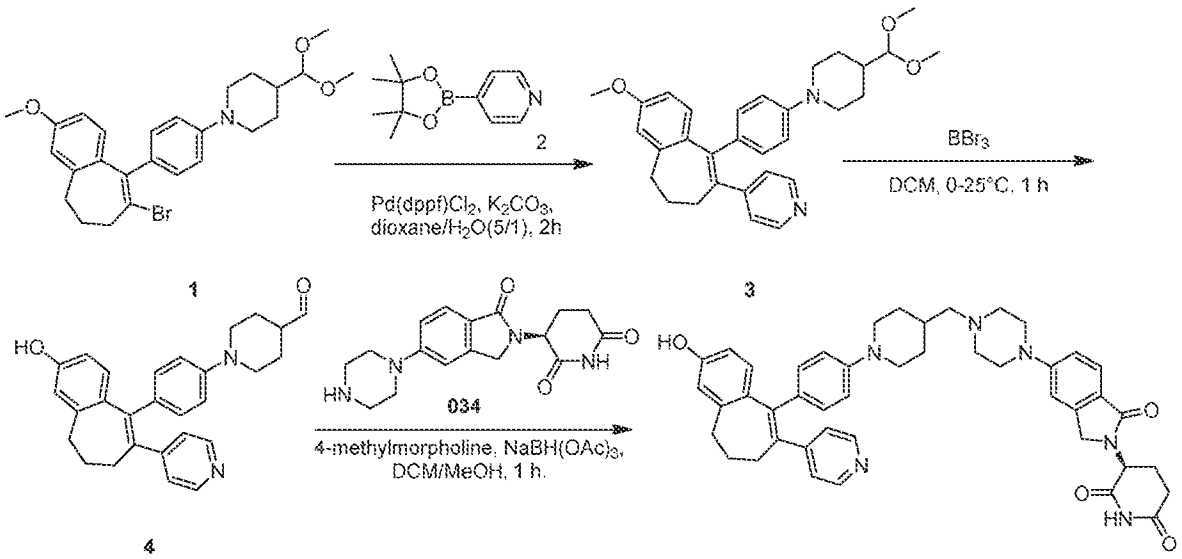
[1788] ***Step 2.*** To a solution of compound 2 (150 mg, 351.83 μmol, 1 *eq*) and compound 3 (89.39 mg, 351.83 μmol, 1 *eq*) in Dioxane/H_2O (4 mL) was added $Pd(dppf)Cl_2$ (25.74 mg, 35.18 μmol, 0.1 *eq*) and K_2CO_3 (97.25 mg, 703.66 μmol, 2 *eq*) under N_2. The mixture was stirred at 90 °C for 2 h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40mL x 3). The combined organic layers were washed with brine (100mL), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give compound 4 (92 mg, 101.02 μmol, 28.71% yield) as a yellow solid. LC-MS (ESI^+) m/z: 474.3 $(M+H)^+$.

[1789] ***Step 3.*** To a solution of compound 4 (92 mg, 194.28 μmol, 1 *eq*) in DCM/MeOH (2 mL) was added 4-methylmorpholine (39.30 mg, 388.55 μmol, 42.72 μL, 2 *eq*) and compound 034 (63.79 mg, 194.28 umol, 1 *eq*) in DCM/MeOH (2 mL). After stirring at 20 °C for 20 min, the mixture is adding $NaBH_3CN$ (24.42 mg, 388.55 μmol, 2 *eq*) and stirring at 20 °C for 1h. LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40mL x 3). The combined organic layers were washed with brine (100mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters xbridge 150*25mm 10um; mobile phase: [water (NH4HCO3)-ACN];B%: 50%-80%,9min) to give (S)-3-(5-(4-((1-(4-(8-(4-(difluoromethyl)phenyl)-3-hydroxy-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (18.7 mg, 23.16 μmol, 11.92% yield) as a pink solid. LC-MS (ESI+) m/z: 786.3. $(M+H)^+$.

[1790] ^1H NMR: (400 MHz, METHANOL-d4) δ 7.63 (d, J = 8.4 Hz, 1H), 7.28 (q, J = 8.4 Hz, 4H), 7.15 - 6.99 (m, 2H), 6.82 - 6.63 (m, 7H), 6.60 - 6.54 (m, 1H), 5.10 (dd, J = 5.2, 13.2 Hz, 1H), 4.48 - 4.32 (m, 2H), 3.61 (br d, J = 12.4 Hz, 2H), 3.38 - 3.35 (m, 4H), 2.95 - 2.84 (m, 1H), 2.82 - 2.71 (m, 3H), 2.69 - 2.57 (m, 6H), 2.46 (br dd, J = 5.0, 13.3 Hz, 1H), 2.39 (br t, J = 6.8 Hz, 2H), 2.30 (br d, J = 7.2 Hz, 2H), 2.19 - 2.07 (m, 3H), 1.88 (br d, J = 11.6 Hz, 2H), 1.79 - 1.66 (m, 1H), 1.35 - 1.29 (m, 2H)

Example 118. Synthesis of (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-4-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-126



[1791] ***Step 1.*** To a solution of compound 1 (150 mg, 308.36 μmol, 1 *eq*) and compound 2 (69.56 mg, 339.20 μmol, 1.1 *eq*) in Dioxane/H_2O (3 mL) was added K_2CO_3 (127.86 mg, 925.09 μmol, 3 *eq*) and $Pd(dppf)Cl_2$ (40.19 mg, 61.67 μmol, 0.2 *eq*) at 20 °C under N_2. The reaction mixture was stirred at 90 °C for 2h. LCMS showed that the material was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 3/1 to 1/1, TLC: PE/EtOAc = 1/1, Rf= 0.34) to give compound 3 (100 mg, 169.20 μmol, 54.87% yield) as a yellow solid. LC-MS (ESI+) *m/z*: 485.5 $(M+H)^+$.

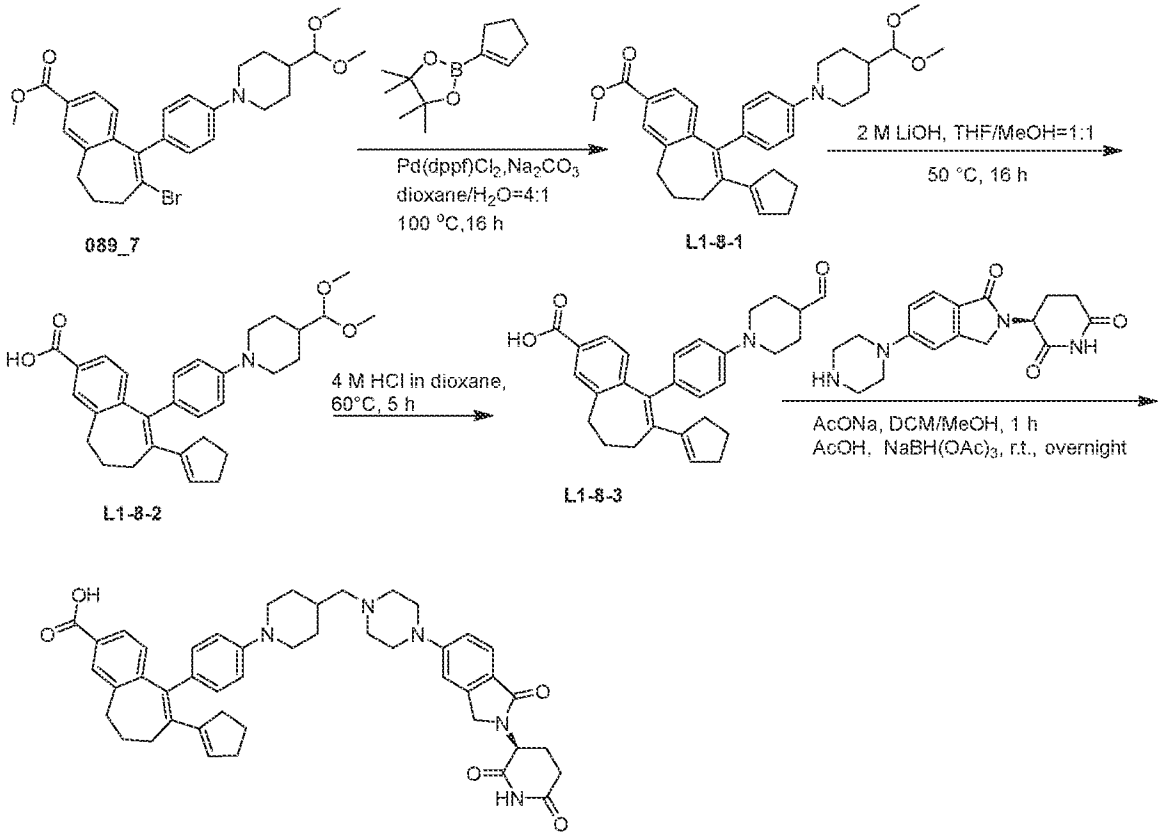
[1792] ***Step 2.*** To a solution of compound 3 (100 mg, 206.34 μmol, 1 *eq*) in DCM (4 mL) was added BBr_3 (51.69 mg, 206.34 μmol, 19.88 μL, 1 *eq*) at 0 °C. The reaction mixture was stirred at 20 °C for 1h. Then, it was dropwised H_2O (4ml) at 0 °C and stirred at 20 °C for 10 min. LCMS showed that the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give compound 4 (100 mg, 143.69 μmol, 69.63% yield) as a red solid. LC-MS (ESI+) *m/z*: 425.4 $(M+H)^+$.

[1793] ***Step 3.*** To a solution of compound 4 (100 mg, 235.55 μmol, 1 *eq*) in DCM/MeOH (2 mL) was added 4-methylmorpholine (71.48 mg, 706.66 μmol, 77.69 μL, 3 *eq*) and compound 034 (77.35 mg, 235.55 μmol, 1 *eq*) in DCM/MeOH (2 mL). After stirring at 20 °C for 20 min, the mixture is adding $NaBH_3CN$ (29.60 mg, 471.11 μmol, 2 *eq*) and stirring at 20 °C for 1 h.

LCMS showed that the material was consumed and the desired MS was found. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 150*25mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 33%-63%,8min) to give (S)-3-(5-(4-((1-(4-(3-hydroxy-8-(pyridin-4-yl)-6,7-dihydro-5H-benzo[7]annulen-9-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (12 mg, 15.55 μmol, 6.60% yield) as a yellow solid. LC-MS (ESI+) *m/z:* 737.3 $(M+H)^+$.

[1794] ^{1}H NMR: (400 MHz, METHANOL-d4) δ = 8.30 - 8.21 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.22 - 7.16 (m, 2H), 7.11 - 7.04 (m, 2H), 6.80 - 6.70 (m, 5H), 6.69 - 6.64 (m, 1H), 6.61 - 6.55 (m, 1H), 5.10 (dd, *J* = 5.2, 13.4 Hz, 1H), 4.47 - 4.32 (m, 2H), 3.65 (br d, *J* = 12.8 Hz, 2H), 3.46 - 3.34 (m, 4H), 2.92 - 2.85 (m, 1H), 2.82 - 2.70 (m, 3H), 2.69 - 2.58 (m, 6H), 2.46 (br dd, *J* = 4.8, 13.4 Hz, 1H), 2.40 (br t, *J* = 7.2 Hz, 2H), 2.30 (br d, *J* = 6.8 Hz, 2H), 2.17 - 2.08 (m, 3H), 1.95 - 1.82 (m, 2H), 1.81 - 1.67 (m, 1H), 1.34 - 1.29 (m, 2H)

Example 119. Synthesis of 6-(cyclopenten-1-yl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, I-127



[1795] *Step 1.* A mixture of methyl 6-bromo-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate(400 mg, 777.53 umol, 1 eq), 2-(cyclopenten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (190 mg, 978.99 umol, 1.26 eq) , $Pd(dppf)Cl_2$(64 mg, 78.37 umol, 0.1 eq) and Na_2CO_3(250mg, 2.36 mmol, 3.03 eq) in mixture of dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with 30 mL H_2O and extracted with EtOAc 100 mL (50 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound methyl 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (120 mg, 153.85 umol, 19.79% yield, 64.316% purity) was obtained as a yellow oil. TLC: petroleum ether: ethyl acetate=5:1, R_f =0.5; LC-MS (ESI^+) m/z: 502.4 $(M+H)^+$

[1796] *Step 2.* To a solution of methyl 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylate (120 mg, 239.21 umol, 1 eq) in mixture of MeOH (2 mL)and THF (2 mL) was added LiOH (2 M, 1.20 mL, 10eq).The mixture was stirred at 50 °C for 16 hr . The reaction mixture was poured into 20 mL of ice-water carefully and acidified with 1M HCl to pH=4. The resulting solution was extracted with ethyl acetate 60 mL (30 mL ×2).dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue as a yellow solid. This reaction was used to next step without purification. Compound 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (128 mg, 174.60 umol, 72.99% yield, 66.514% purity) was obtained as a yellow solid. LC-MS (ESI^+) m/z: 488.3 $(M+H)^+$

[1797] *Step 3.* To a solution of 6-(cyclopenten-1-yl)-5-[4-[4-(dimethoxymethyl)-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (100 mg, 205.07 umol, 1 eq) in HCl/dioxane (3 mL) .The mixture was stirred at 60 °C for 5 hr .This reaction mixture was concentrated under reduced pressure to give a residue as a brown solid. This reaction was used to next step without purification. Compound 6-(cyclopenten-1-yl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (100 mg, crude) was obtained as a brown solid. LC-MS (ESI^+) m/z: 542.1 $(M+H)^+$

[1798] ***Step 4.*** To a solution of 6-(cyclopenten-1-yl)-5-[4-(4-formyl-1-piperidyl)phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (140 mg, 317 umol, 1 *eq*), (3S)-3-(1-oxo-5-piperazin-1-yl-isoindolin-2-yl)piperidine-2,6-dione (240 mg, 479.46 umol, 1.51 *eq*, p-TSA salt) , AcONa (80 mg, 975.25 umol, 3.08 *eq*) and AcOH (20 mg, 333.04 umol, 19.05 uL, 1.05 *eq*) in DCM (3 mL) and MeOH (3 mL) at 25°C over 1hr, and then $NaBH(OAc)_3$ (100 mg, 471.83 umol, 1.49 *eq*) was added dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 16 hr. The reaction mixture was concentrated to dryness in vacuo. The residue was purified twice by prep-HPLC. First： The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN];B%: 28%-58%,15min). Second： The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um;mobile phase: [water(NH4HCO3)-ACN];B%: 32%-62%,9min). Compound 6-(cyclopenten-1-yl)-5-[4-[4-[[4-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-5-yl]piperazin-1-yl]methyl]-1-piperidyl]phenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (7 mg, 9.17 umol, 2.89% yield, 98.80% purity) was obtained as a yellow solid.

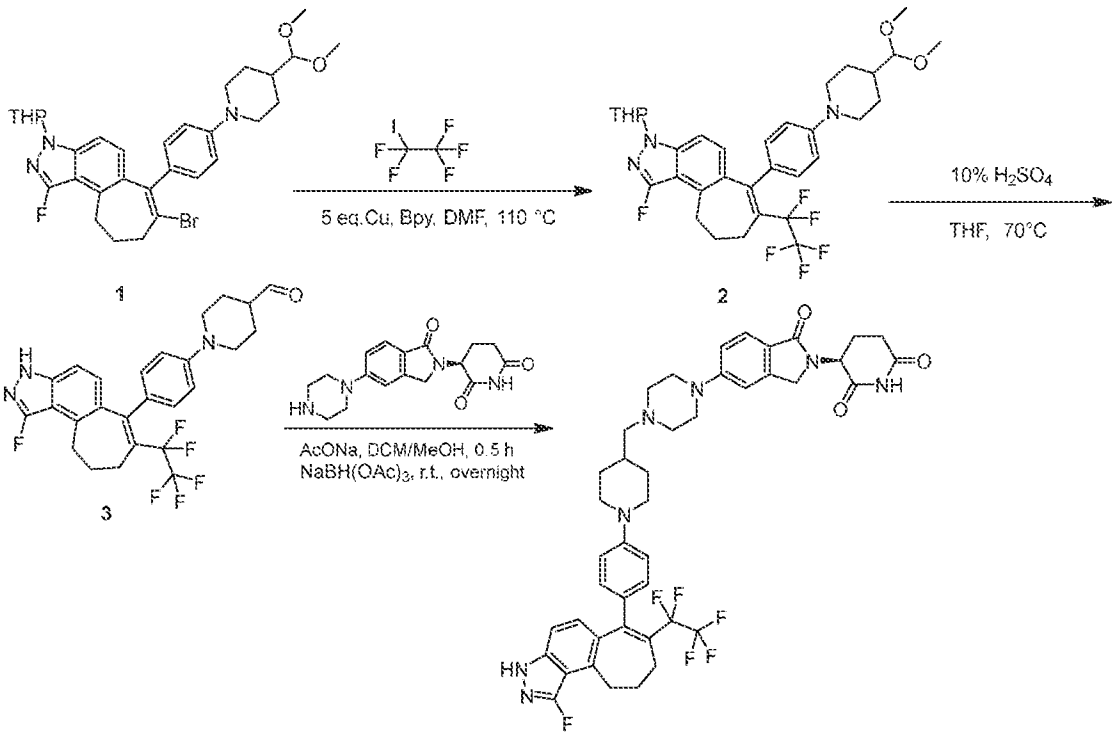
[1799] LC-MS (ESI^+) m/z: 754.3$(M+H)^+$

[1800] HPLC: 99.874% purity at 220 nm

[1801] SFC: Rt: 1.378 min; Area, 74.754%; Rt: 0.763 min; Area, 25.246 %; method: AS-3-EtOH+ACN(DEA)-50-3mL-35T

[1802] ^1H NMR (400 MHz, DMSO-d_6) δ = 10.97 (s, 1H), 7.82 - 7.78 (m, 1H), 7.63 (br d, J = 1.9 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.09 - 7.04 (m, 2H), 6.85 - 6.83 (m,3H), 5.86 - 5.81 (m, 1H), 5.08 - 4.98 (m, 1H), 4.39 - 4.29 (m, 1H), 4.24 - 4.15 (m, 1H), 3.70 (br d, J = 12.8 Hz, 2H), 2.69 - 2.65 (m, 6H), 2.37 - 2.31 (m, 3H),2.30 - 2.19 (m, 6H), 2.17 - 2.03 (m, 6H), 2.00 - 1.91 (m, 4H), 1.89 - 1.78 (m, 3H), 1.75 - 1.62 (m, 4H), 1.28 - 1.17 (m, 3H)

Example 120. Synthesis of (S)-3-(5-(4-((1-(4-(1-fluoro-7-(perfluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione, I-128



[1803] ***Step 1.*** A solution of 1,1,1,2,2-pentafluoro-2-iodoethane (49 µL. 5 Eq, 417.7 µmol), 2,2'-Bipyridine (13 mg, 1 Eq, 83.53 µmol)7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (50 mg, 1 Eq, 83.53 µmol) and Copper (27 mg, 5 Eq, 417.7 µmol) in DMF (3 mL) was stirred at 110 °C for 16 hour under N_2. TLC (petroleum ether: ethyl acetate=3:1, R_f=0.6, UV) showed one main new spot was observed. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL*3). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4 and concentrated in vacuo to give a white solid. The white solid was subjected to column chromatography over silica gel (gradient elution: 0 – 70% ethyl acetate).The desired fractions were collected, and concentrated to dryness in vacuo to give 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(perfluoroethyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (30 mg, 45 µmol, 95.21% purity) as a yellow solid. which confirmed by LC-MS (ESI^+) m/z: 638.2 $(M+H)^+$.

[1804] ***Step 2.*** To a solution of 6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-7-(perfluoroethyl)-3-(tetrahydro-2H-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (30 mg, 1 Eq, 47 µmol) in THF (1 mL) and 10% H_2SO_4 (3 mL) was stirred at 70 °C for 12 hour. LCMS

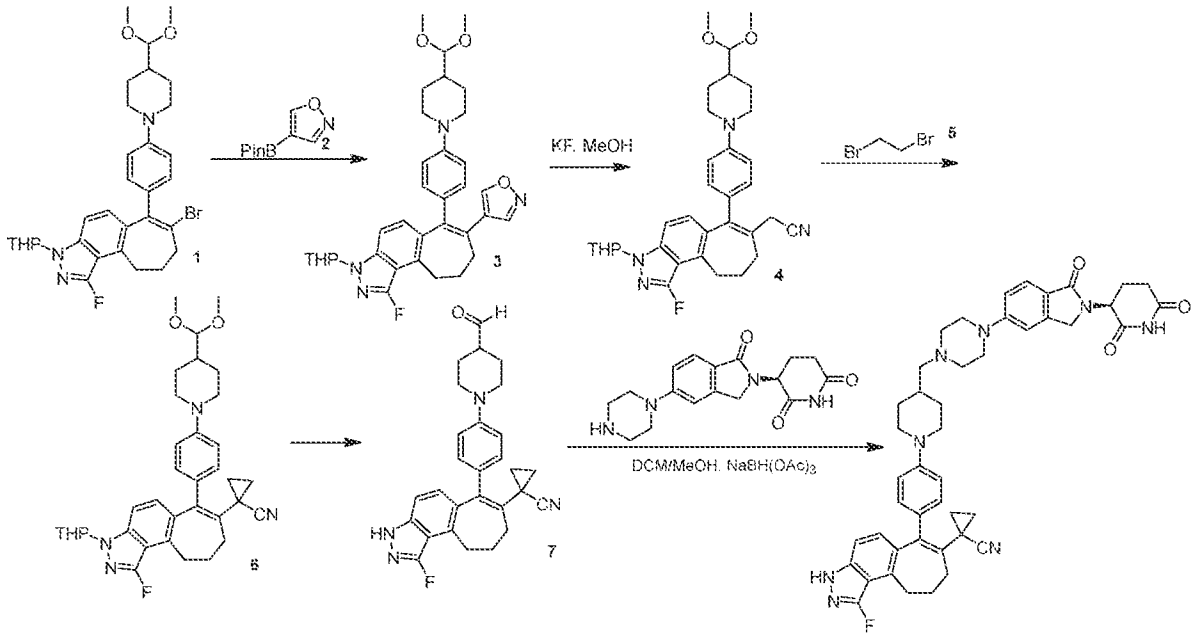
showed 83.93% desired MS. The reaction was adjust to pH=~8 with saturated aq.$NaHCO_3$ (15 mL). Then the mixture was added water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo to give 1-(4-(1-fluoro-7-(perfluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (20 mg, 33 μmol, 83.93% purity) as a yellow oil. LC-MS (ESI^+) m/z: 508.2 $(M+H)^+$.

[1805] ***Step 3.*** To solution of 1-(4-(1-fluoro-7-(perfluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidine-4-carbaldehyde (20 mg, 1 Eq, 39 μmol) , (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (13 mg, 1 Eq, 39 μmol) and sodium acetate (19 mg, 6 Eq, 0.24 mmol) in DCM (1 mL) and MeOH (1 mL) was stirred at 25 °C for 0.5 h, Then acetic acid (5 μL, 2 Eq, 79 μmol) and sodium triacetoxyhydroborate (17 mg, 2 Eq, 79 μmol) was added. The mixture was stirred at 25 °C for 16 hour. The reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (30 mL*2). The organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 28%-58%, 6 min) to give (S)-3-(5-(4-((1-(4-(1-fluoro-7-(perfluoroethyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-6-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2.5 mg, 98.99% purity) as a white solid. LCMS: calc. for $C_{43}H_{43}F_6N_7O_3$: 819.33, found: $[M+H]^+$ 820.4.

[1806] HPLC: 98.99% purity at 220 nm.

[1807] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.64 (s, 1H), 10.96 (s, 1H), 9.64 - 9.55 (m, 0.346H), 7.64 - 7.48 (m, 1H), 7.28 - 7.22 (m, 1H), 7.21 - 7.13 (m, 1H), 7.07 (br s, 1H), 6.91 (br d, J = 15.6 Hz, 4H), 6.80 (d, J = 8.8 Hz, 1H), 5.10 - 5.01 (m, 1H), 4.39 - 4.29 (m, 1H), 4.28 - 4.17 (m, 1H), 4.07 - 3.94 (m, 1H), 3.80 - 3.67 (m, 2H), 3.30 - 3.11 (m, 8H), 3.09 - 3.00 (m, 2H), 2.94 - 2.86 (m, 1H), 2.74 - 2.65 (m, 2H), 2.59 (br d, J = 16.8 Hz, 2H), 2.39 - 2.29 (m, 3H), 2.22 (br d, J = 2.0 Hz, 1H), 2.07 (br s, 2H), 2.03 - 1.93 (m, 2H), 1.91 - 1.80 (m, 2H), 1.23 (br s, 2H) SFC: retention time, 2.780 min; Area, 92.716%; method: ID_MeOH_DEA_MeCN_50_1ML_10MIN_10CM.

Example 121. Synthesis of (*S*)-1-(6-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)cyclopropane-1-carbonitrile, I-129



[1808] *Step 1.* To a solution of 7-bromo-6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazole (400 mg, 1 eq, 668 μmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (195 mg, 1.5 eq, 1.00 mmol)in 1,4-Dioxane (4 mL) and H_2O (1 mL) was added sodium carbonate (177 mg, 2.5 eq, 1.67 mmol)and $PdCl_2$(dppf) (48.9 mg, 0.1 eq, 66.8 μmol). The mixture was stirred under N_2 at 85 °C for 12 h. The reaction mixture was quenched by addition of water (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.49) to yield 4-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)isoxazole (180 mg, 0.28 mmol, 41 %, 90% Purity) as a yellow solid. LC-MS (ESI^+) *m/z*: 587.2 $(M+H)^+$.

[1809] ^1H NMR (500MHz, $CDCl_3$) δ = 8.18 (s, 1H), 7.69 (s, 1H), 7.20 (dd, *J*=2.1, 8.9 Hz, 1H), 7.00 - 6.93 (m, 3H), 6.87 - 6.84 (m, 2H), 5.54 (d, *J*=9.3 Hz, 1H), 4.02 (d, *J*=9.6 Hz, 1H), 3.80 - 3.69 (m, 3H), 3.39 (s, 6H), 3.09 (br t, *J*=6.7 Hz, 2H), 2.74 - 2.65 (m, 2H), 2.49 (d, *J*=11.4 Hz, 1H), 2.38 - 2.32 (m, 3H), 2.17 - 2.13 (m, 1H), 1.94 - 1.89 (m, 6H), 1.78 - 1.70 (m, 3H), 1.51 - 1.44 (m, 2H).

[1810] *Step 2.* To a solution of 4-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)isoxazole (220 mg, 85% Wt, 1 eq, 319 μmol) in MeOH (10 mL) was added Potassium fluoride (111 mg, 44.8 μL, 6 eq, 1.91 mmol) .The mixture was stirred at 90 °C for 12 h. The reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)acetonitrile (150 mg, 0.21 mmol, 66 %, 78% Purity) as a yellow solid which was used in the next step without further purification. LC-MS (ESI+) m/z: 559.2 (M+H)+.

[1811] *Step 3.* To a solution of 2-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)acetonitrile (140 mg, 78% wt, 1 eq, 195 μmol) in NaOH (2 g, 3e+2 eq, 0.05 mol) in H_2O (2 mL) was added 1,2-dibromoethane (110 mg, 3 eq, 586 μmol) in THF (0.5 mL). The mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched by addition of water (10 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column:YMC-Actus Triart C18 150*30mm*5um;mobile phase: [water(TFA)-CAN];B%: 48%-68%,11.5min), followed by lyophilization to yield 1-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)cyclopropane-1-carbonitrile (30 mg, 49 μmol, 25 %, 95% Purity) as a yellow solid. LC-MS (ESI+) m/z: 585.2 (M+H)+

[1812] ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.49 (d, *J*=8.7 Hz, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 7.23 (dd, *J*=1.8, 8.9 Hz, 1H), 6.75 (d, *J*=8.9 Hz, 1H), 5.54 (d, *J*=9.2 Hz, 1H), 4.16 (d, *J*=6.9 Hz, 1H), 4.01 (d, *J*=10.7 Hz, 1H), 3.84 (d, *J*=12.1 Hz, 2H), 3.76 - 3.47 (m, 2H), 3.45 - 3.38 (m, 6H), 3.18 (t, *J*=10.8 Hz, 2H), 2.91 (t, *J*=6.9 Hz, 2H), 2.42 - 2.36 (m, 3H), 2.30 (d, *J*=6.9 Hz, 2H), 2.13 - 1.97 (m, 6H), 1.75 - 1.62 (m, 3H), 1.35 - 1.30 (m, 2H), 0.90 - 0.82 (m, 2H)

[1813] *Step 4.* To a solution of 1-(6-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)-1-fluoro-3-(tetrahydro-2*H*-pyran-2-yl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)cyclopropane-1-carbonitrile (20 mg, 95% Wt, 1 eq, 32 μmol) in THF (0.5 mL) was added sulfuric acid (32 mg, 0.5 mL, 10% wt, 1 eq, 32 μmol). The mixture was stirred at 60 °C for 12 h. The reaction mixture was quenched by addition of saturation solution ($NaHCO_3$, 10 mL), extracted with EtOAc (10

mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-(1-fluoro-6-(4-(4-formylpiperidin-1-yl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)cyclopropane-1-carbonitrile (10 mg, 15 μmol, 47 %, 70% Purity) as a white solid which was used in the next step without further purification. LC-MS (ESI^+) *m/z*: 455.1 $(M+H)^+$.

[1814] ***Step 5.*** To a solution of 1-(1-fluoro-6-(4-(4-formylpiperidin-1-yl)phenyl)-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)cyclopropane-1-carbonitrile (10 mg, 70% wt, 1 eq, 15 μmol) and (*S*)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (10 mg, 2 eq, 31 μmol) in DCM (0.5 mL) and MeOH (0.5 mL), after stirred 30 min was added Sodium triacetoxyborohydride (9.8 mg, 6.8 μL, 3 eq, 46 μmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated to yield a residue. The residue was purified by preparative HPLC (column:Phenomenex Gemini NX 150×30mm,5μm;mobile phase: [water(NH4HCO3)-CAN];B%: 49%-79%,11min), followed by lyophilization to yield (*S*)-1-(6-(4-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-1-fluoro-3,8,9,10-tetrahydrocyclohepta[e]indazol-7-yl)cyclopropane-1-carbonitrile (2 mg, 3 μmol, 20 %, 100% Purity) as a white solid. LC-MS (ESI^+) *m/z*: 767.3$(M+H)^+$.

[1815] LCMS: calc. for C45H47FN8O3: 766.38, found: $[M+H]^+$767.3.

[1816] HPLC: 100% purity at 220 nm.

[1817] ^1H NMR (400MHz, DMSO-d_6) δ = 12.56 (s, 1H), 11.13 - 10.77 (m, 1H), 7.52 (d, *J*=8.2 Hz, 1H), 7.21 (d, *J*=8.6 Hz, 1H), 7.10 - 7.03 (m, 2H), 6.96 (s, 4H), 6.74 (d, *J*=8.7 Hz, 1H), 5.05 (dd, *J*=4.8, 13.5 Hz, 1H), 4.39 - 4.27 (m, 1H), 4.24 - 4.14 (m, 1H), 3.77 (d, *J*=11.4 Hz, 2H), 3.33 - 3.30 (m, 8H), 2.98 - 2.79 (m, 3H), 2.73 - 2.66 (m, 2H), 2.39 - 2.32 (m, 3H), 2.23 (d, *J*=6.8 Hz, 2H), 2.16 - 2.08 (m, 2H), 2.02 - 1.94 (m, 2H), 1.83 (d, *J*=11.3 Hz, 2H), 1.73 (s, 1H), 1.30 (s, 1H), 1.23 (s, 3H), 0.90 - 0.85 (m, 2H)

Example A1 – Nano Glo HiBiT Lytic Degradation Assay

[1818] Selected compounds of the present disclosure were tested in a Nano Glo HiBiT Lytic Degradation Assay to measure the level of ERα protein degradation in MCF7 cells.

Table 2. Materials Used.

Materials	Vendor	Catalog number
Eagle's Minimum Essential Medium (EMEM)	Corning	10009CV
Fetal Bovine Serum (FBS)	VWR	89510-194
Human Recombinant Insulin	Gibco	12585-014
384-Well, Cell Culture-Treated, Flat-Bottom Microplate	Corning	3570
Nano Glo HiBiT Lytic Detection System	Promega	N3050
ESR1_HiBiT KI MCF7 cells	Promega	CS302392

Table 3. Instruments Used.

Instrument	Vendor
Vi-Cell	Beckman Coulter
MultiFlo Multimode Dispenser	BioTek
Echo Acoustic Liquid Handler	Beckman Coulter
EnVision 2105 Multimode Plate Reader	Perkin Elmer

Table 4. Cell Line Information.

Cell line	Growth Media
ESR1_HiBiT KI MCF7	EMEM + 10% FBS + 0.01 mg/mL human recombinant insulin

[1819] Cell culture: ESR1_HiBiT KI MCF7 cells were maintained in growth media without antibiotics. Cells were maintained in exponential growth phase, between 40% and 90% confluency.

[1820] Cell seeding: Cells were counted using a Vi-Cell and seeded in a 384-well flat-bottom microplate (cell culture-treated) at 4000 cells/well in in 25 µL of growth medium using a BioTek MultiFlo Multimode Dispenser. Plates were incubated for 24h at 37°C, 5% CO_2, >95% relative humidity.

[1821] Compound preparation: Compounds were screened as 14-point dose response curves 1:3 dilutions. DMSO is used as the vehicle control and all wells were normalized to the same final DMSO concentration (0.1% v/v). Compounds were dosed using an Echo Acoustic Liquid Handler, 25 nL of 1000X (10mM top concentration) DMSO stock/well. Cells were incubated with compounds for 6 hours at 37°C, 5% CO_2, >95% relative humidity. Each compound was run in duplicate.

[1822] Nano Glo HiBiT Lytic Degradation Assay: HiBiT-tagged ERα protein levels were quantified using a Nano Glo HiBiT Lytic Degradation Assay following the manufacturer's protocol. Briefly, the Nano-Glo® HiBiT Lytic Reagent was prepared by diluting the LgBiT Protein reagent (1:100) and the Nano-Glo® HiBiT Lytic Substrate (1:50) into Nano-Glo® HiBiT Lytic Buffer at room temperature. The 384-well microplate were equilibrated to room temperature and 25 µL of Nano-Glo® HiBiT Lytic Reagent was added to each well. Samples were mixed by placing the 384-well microplate on an orbital shaker for 10 minutes. Luminescence was measured using an EnVision 2105 Multimode Plate Reader.

[1823] Data processing and analysis: Background signal (wells containing growth medium without cells) was subtracted from individual relative light units (RLU) values and the resulting values were normalized to the DMSO control well values. Dose responses were analyzed with Genedata Screener® using a bell-shape curve fit and the concentrations corresponding to the half-maximal effect of the first Hill model were used as DC_{50} values.

[1824] Results of the Nano Glo HiBiT Lytic Degradation Assay are presented in **Table 5**.

Table 5. HiBit assay results.

Compound No.	MCF7 ESR1 HiBiT - (DC_{50}, µM)
I-1	0.11
I-2	0.00098
I-3	>10
I-4	0.01
I-5	0.003
I-6	0.004
I-7	1.1

I-8	>10
I-9	0.37
I-10	0.001
I-11	1.1
I-12	0.00002
I-13	0.00028
I-14	0.003
I-15	0.004
I-16	0.00113
I-23	10
I-25	0.003
I-29	0.002
I-31	10
I-33	0.00061
I-38	0.00036
I-40	0.00122
I-41	0.00025
I-43	0.00075
I-44	0.011
I-45	0.002
I-46	0.002
I-47	0.005
I-48	0.0013
I-49	0.004
I-50	10

I-51	0.00055
I-52	0.01
I-53	0.002
I-54	0.0003
I-55	0.00068
I-56	0.003
I-57	0.00074

Table 6. HiBit assay results.

Compound No.	MCF7 ESR1 HiBiT – 2759 (DC_{50}, μM)
I-1	0.11
I-2	0.00051
I-3	10
I-4	0.01
I-5	0.003
I-6	0.002
I-7	1.1
I-8	10
I-9	0.37
I-10	0.001
I-11	1.1
I-12	0.00002
I-13	0.00028
I-14	0.003
I-15	0.004
I-16	0.00113
I-18	0.245
I-20	0.006

I-22	0.283
I-23	10
I-24	10
I-25	0.003
I-26	0.173
I-27	10
I-28	0.00118
I-29	0.00149
I-30	0.016
I-31	
I-32	0.004
I-33	0.00055
I-34	0.00085
I-36	0.00013
I-38	
I-39	0.00032
I-40	0.00122
I-41	0.00046
I-43	0.00075
I-44	0.011
I-45	0.002
I-46	0.002
I-47	0.005
I-48	0.0013
I-49	0.004
I-50	10
I-51	0.00055
I-52	0.008
I-53	0.002
I-54	0.0003
I-55	0.00089
I-56	0.005

I-57	0.00164
I-58	0.0039
I-59	0.145
I-60	0.003
I-61	0.011
I-62	0.0011
I-65	0.003
I-66	0.00092
I-67	0.001
I-68	0.00046
I-69	0.002
I-70	0.002
I-72	0.003
I-73	0.003
I-74	0.011
I-75	0.012
I-76	0.011
I-77	0.005
I-78	0.00062
I-79	0.001
I-80	0.00029
I-81	0.00028
I-82	
I-83	
I-84	0.002
I-85	0.001
I-86	0.00061
I-87	0.0001
I-88	0.00025
I-89	0.00108
I-90	0.00031
I-91	0.00045

I-92	0.005
I-93	0.006
I-94	
I-95	0.001
I-96	0.003
I-97	0.004
I-98	0.0008
I-99	0.006
I-100	
I-101	
I-102	0.007
I-103	0.004
I-104	0.004
I-105	0.004
I-106	0.009
I-107	0.018
I-108	0.01
I-109	0.002
I-110	0.002
I-111	0.022
I-112	0.005
I-113	0.007
I-114	0.00096
I-115	0.005
I-116	0.005
I-117	0.003
I-118	
I-119	0.00023
I-120	0.005
I-121	0.00092
I-122	0.00067
I-123	0.02561

I-124	0.003
I-125	0.0004
I-126	0.00069
I-127	0.009

INCORPORATION BY REFERENCE

[1825] All publications and patents mentioned herein are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

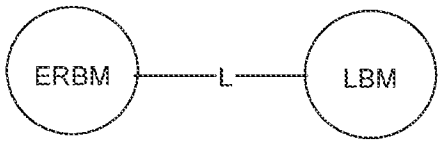
[1826] While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the present disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[1827] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

CLAIMS

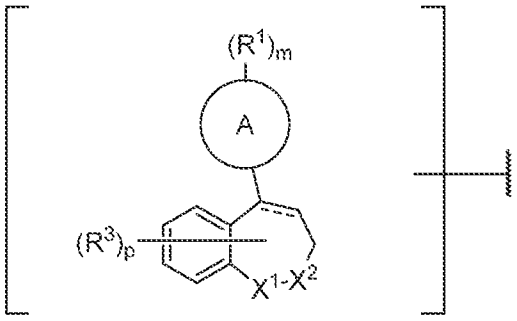
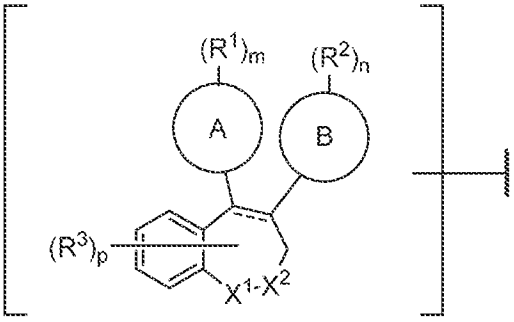
What is claimed is:

1. A compound of formula **I-c**:



I-c

or a pharmaceutically acceptable salt thereof, wherein:

ERBM is selected from  and  , wherein ⊣ indicates the site of attachment of the -L-LBM moiety to a modifiable carbon, oxygen, nitrogen, or sulfur atom of the ERBM moiety and ≈ indicates a single or double bond;

each of X^1 and X^2 is independently –CH_2–, –$CH(R^{A1})$–, –$C(R^{A1})_2$–, –O–, –S–, –S(O)–, –$S(O)_2$–, or –$N(R^{A2})$–;

each instance of R^1, R^2, R^4, R^5, R^{A1}, and R^{A2} is independently R^A or R^B, and is substituted by 0-4 instances of R^C;

each instance of R^3 is independently R^A or R^B, and is substituted by 0-4 instances of R^C, or two R^3 groups are optionally taken together to form a 5-8 membered partially unsaturated or aryl fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A is independently oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –S(O)(NCN)R, –S(NCN)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)C(NR)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$, –$P(O)R_2$, –P(O)(R)OR, or –$B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

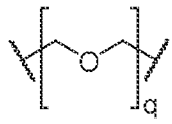
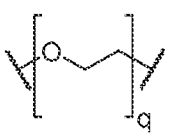
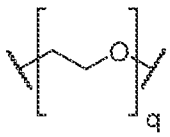
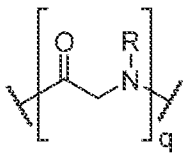
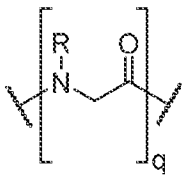
each instance of R^C is independently oxo, deuterium, halogen, –CN, –NO_2, –OR, –SF_5, –SR, –NR_2, –$S(O)_2R$, –$S(O)_2NR_2$, –$S(O)_2F$, –S(O)R, –$S(O)NR_2$, –S(O)(NR)R, –C(O)R, –C(O)OR, –$C(O)NR_2$, –C(O)N(R)OR, –OC(O)R, –$OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, –$N(R)C(O)NR_2$, –$N(R)C(NR)NR_2$, –$N(R)S(O)_2NR_2$, –$N(R)S(O)_2R$, –$P(O)R_2$, –P(O)(R)OR, -$B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl

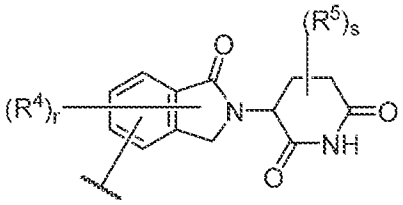
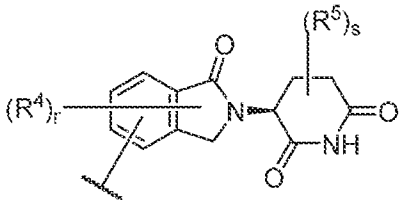
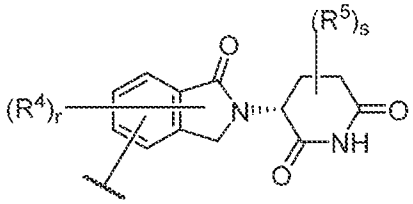
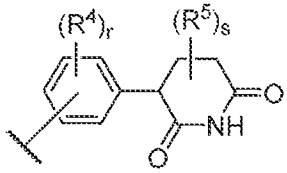
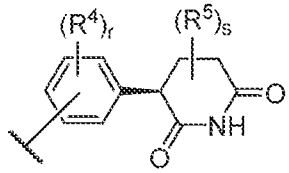
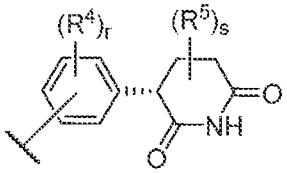
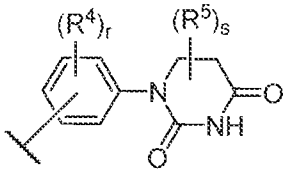
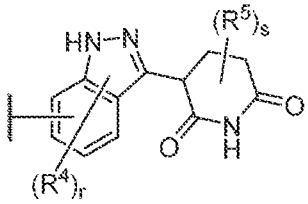
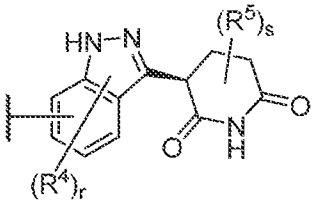
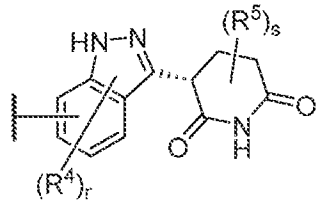
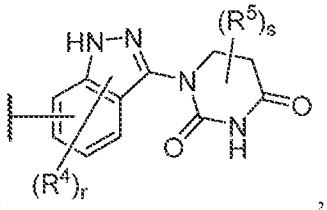
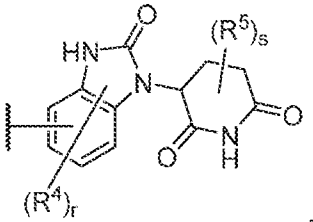
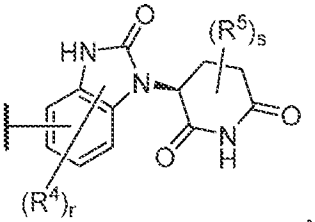
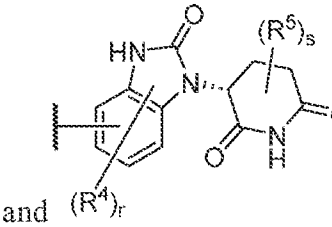
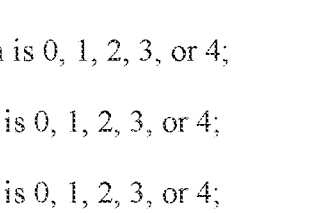
ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Ring A and Ring B are each independently phenyl; naphthyl; benzocyclobutenyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, –$C(R)_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –$S(O)_2$–, –$NRS(O)_2$–, –$S(O)_2NR$–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  ,  ,  ,  , or  , wherein:

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

LBM is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , and ;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

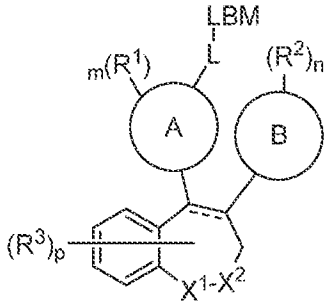
each of q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

r is 0, 1, 2, 3, or 4; and

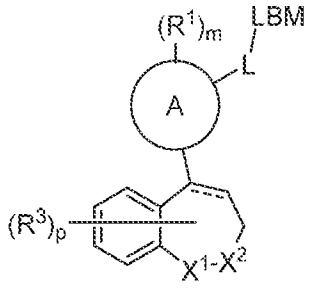
s is 0, 1, 2, 3, or 4;

provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

2. The compound of claim 1, wherein the compound is a compound of formula **I-d** or **I-e**

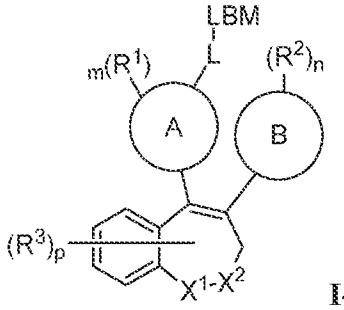


I-d

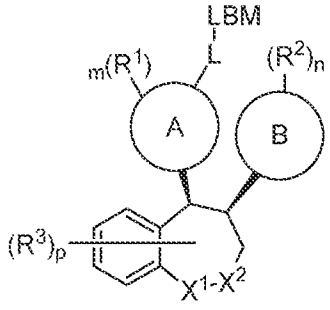


I-e or a pharmaceutically acceptable salt thereof.

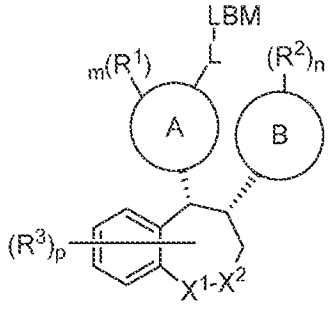
3. The compound of claim 1, wherein the compound is a compound of formula **I-f**, **I-g**, **I-h**, **I-i**, **I-j** or **I-k**:



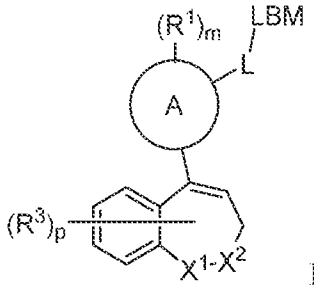
I-f



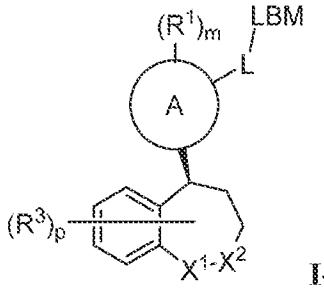
I-g



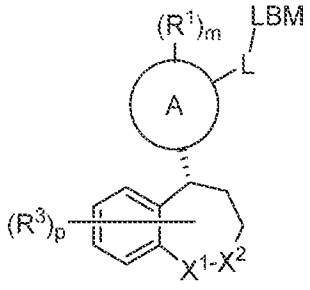
I-h



I-i

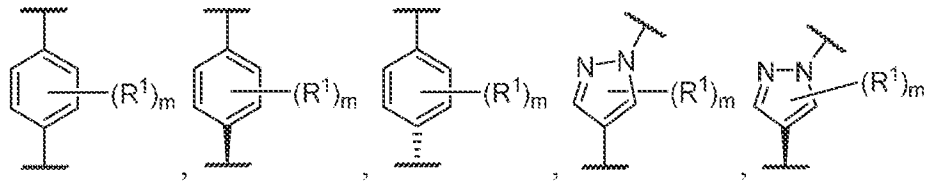


I-j

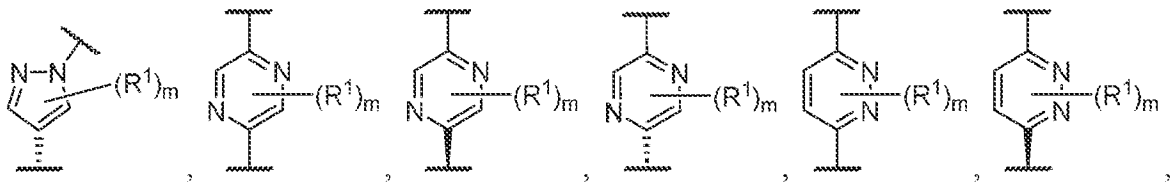
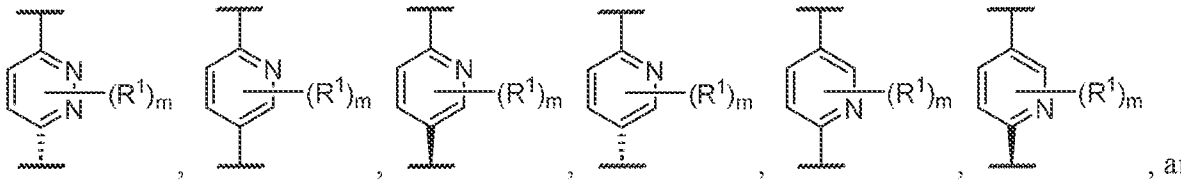
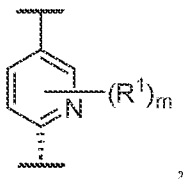


I-k or a pharmaceutically acceptable salt thereof.

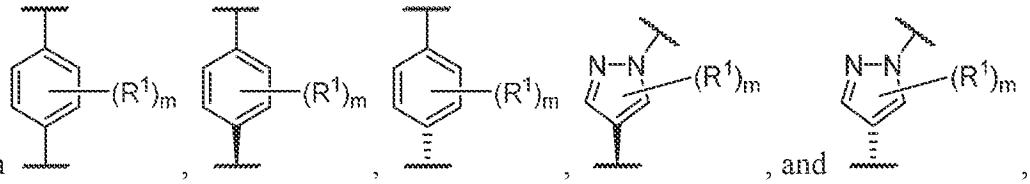
4. The compound of any one of claims 1-3, wherein Ring A together with its R^1 substituents is selected from

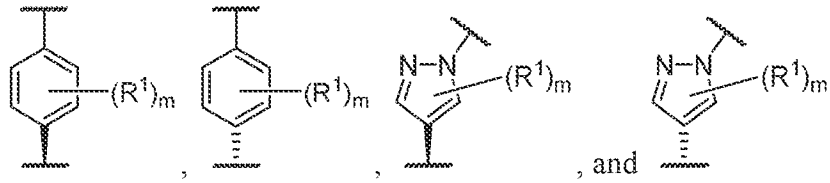


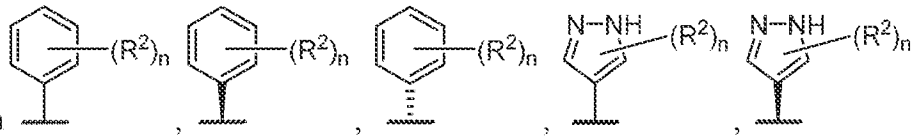
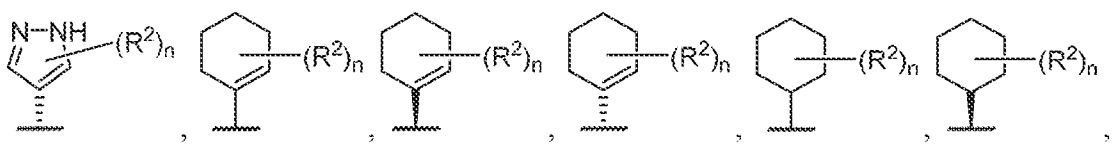
,

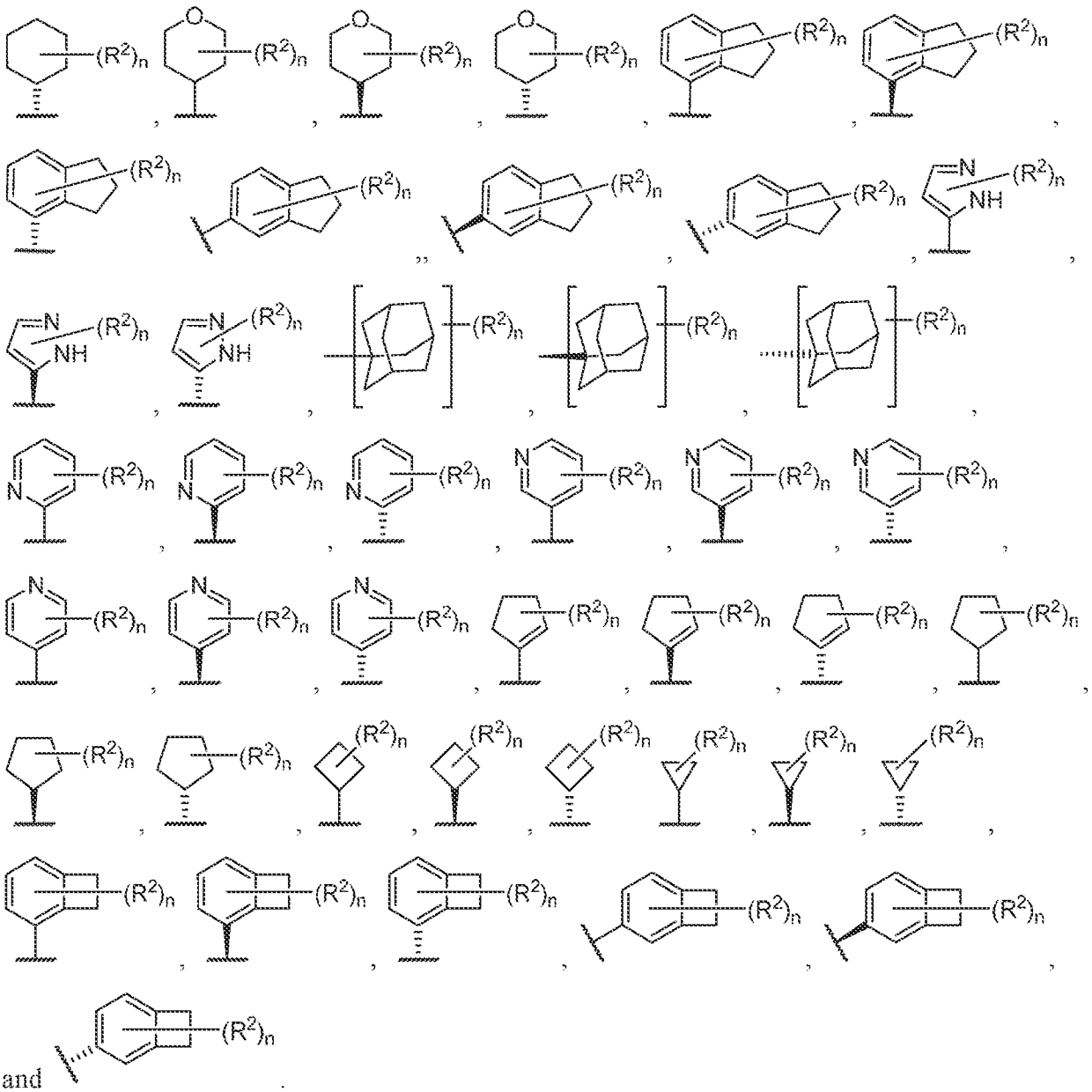



, and

, wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

5. The compound of any one of claims 1-3, wherein Ring A together with its R^1 substituents is selected from  , and , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

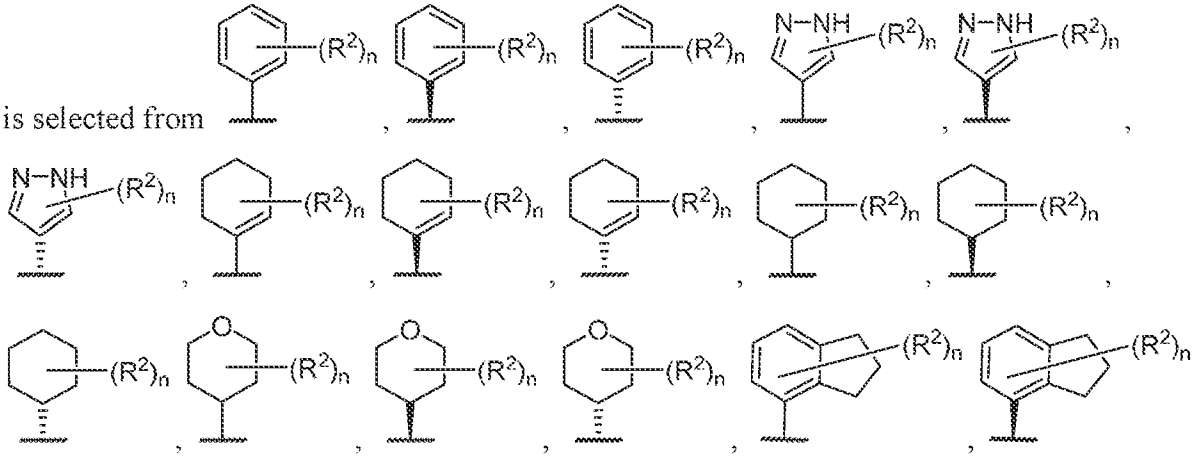
6. The compound of any one of claims 1-3, wherein Ring A together with its R^1 substituents is selected from  , and , wherein the top attachment point connects to L and the bottom attachment point connects to the seven-member ring of the ERBM moiety.

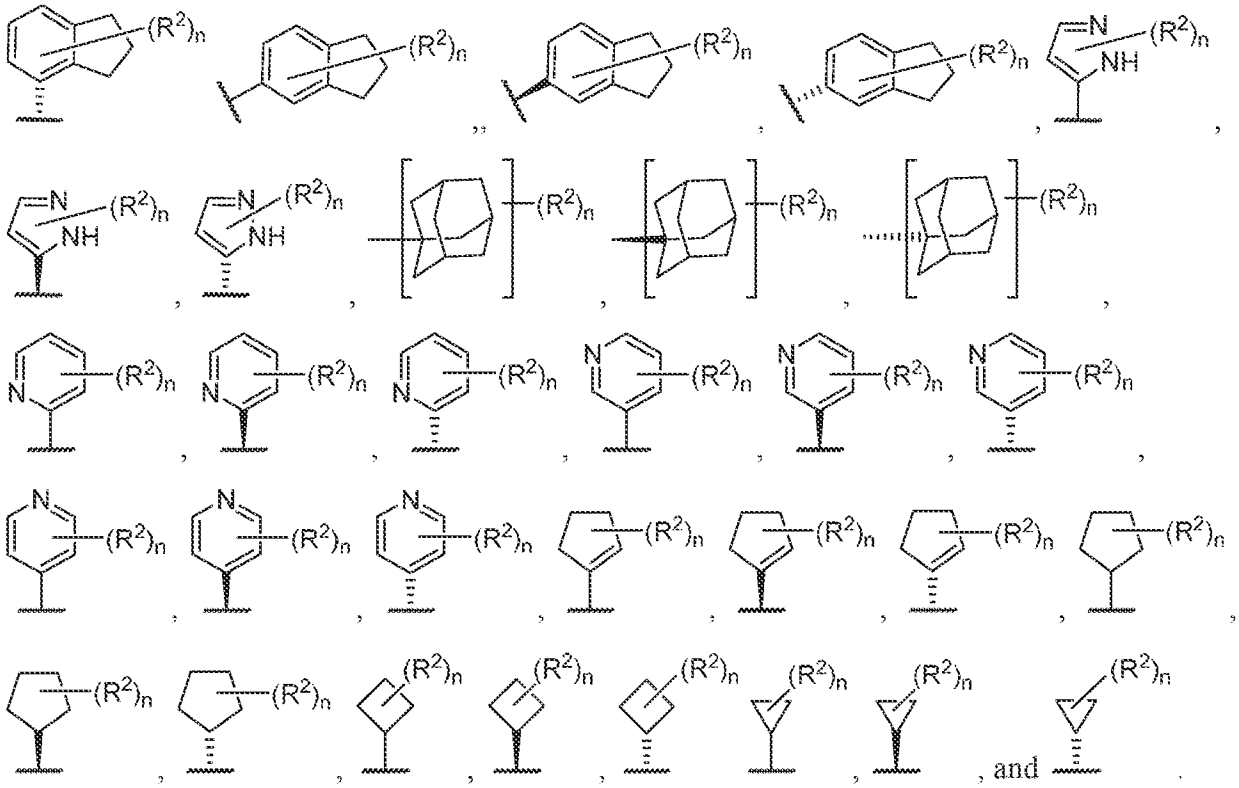
7. The compound of any one of claims 1-6, wherein Ring B together with its R^2 substituents is selected from 




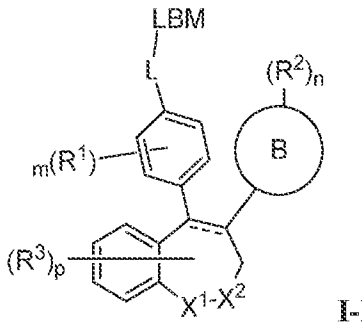
and

8. The compound of any one of claims 1-6, wherein Ring B together with its R^2 substituents is selected from

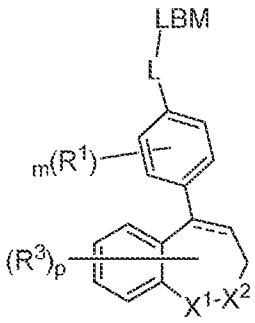




9. The compound of claim 1, wherein the compound is a compound of formula **I-l** or **I-m**

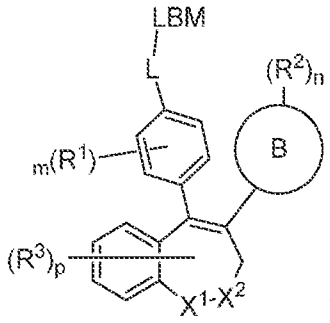


I-l

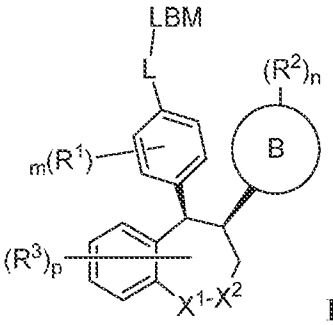


I-m, or a pharmaceutically acceptable salt thereof.

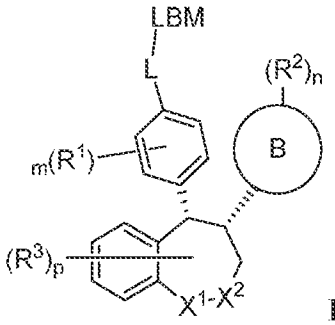
10. The compound of claim 1, wherein the compound is a compound of formula **I-n**, **I-o**, **I-p**, **I-q**, **I-r** or **I-s**:



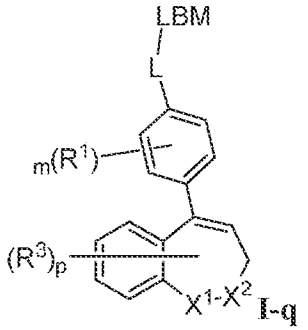
I-n



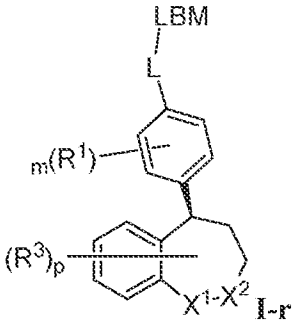
I-o



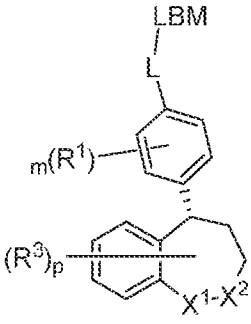
I-p



I-q



I-r

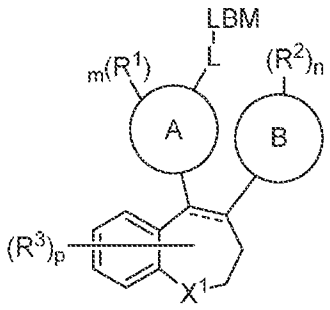


I-s, or a pharmaceutically acceptable salt thereof.

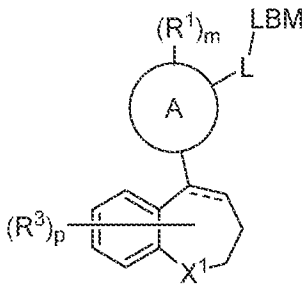
11. The compound of any one of claims 1-10, wherein X^2 is selected from $–CH_2–$ and –O–.

12. The compound of any one of claims 1-10, wherein X^2 is $–CH_2–$.

13. The compound of claim 1, wherein the compound is a compound of formula **II-1** or **II-2**

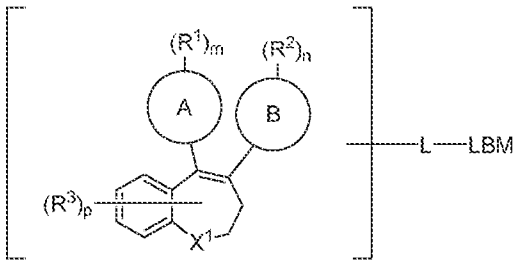


II-1

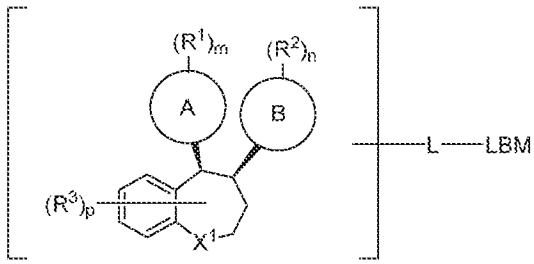


II-2, or a pharmaceutically acceptable salt thereof.

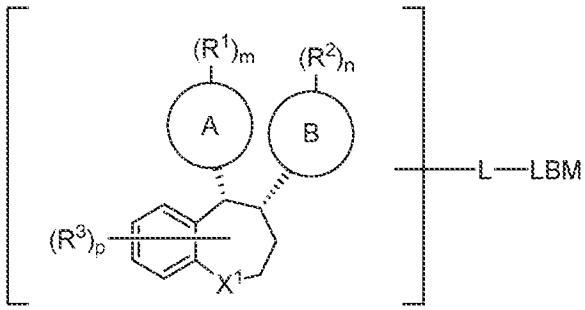
14. The compound of claim 1, wherein the compound is a compound of one of formulas **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, or **II-f**:



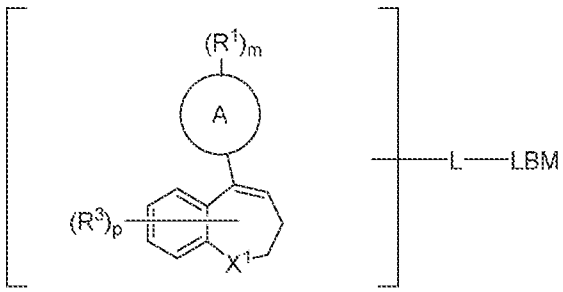
II-a



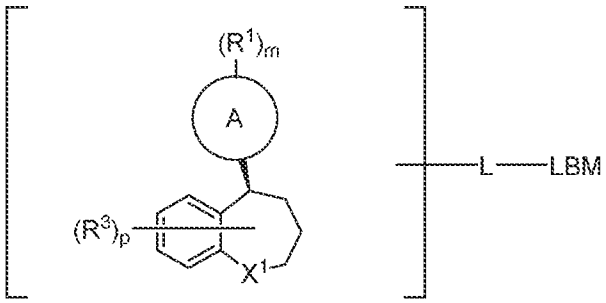
II-b



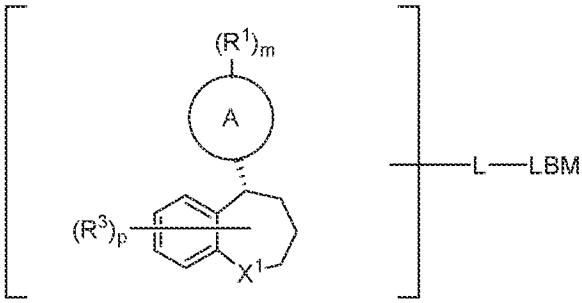
II-c



II-d



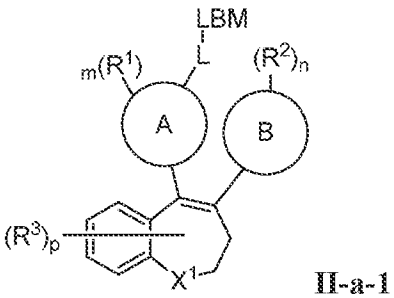
II-e



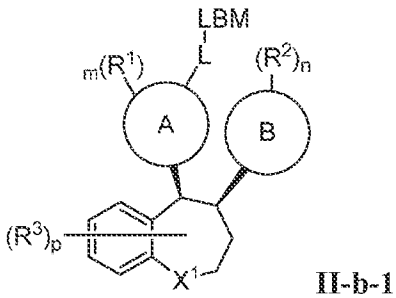
II-f

or a pharmaceutically acceptable salt thereof.

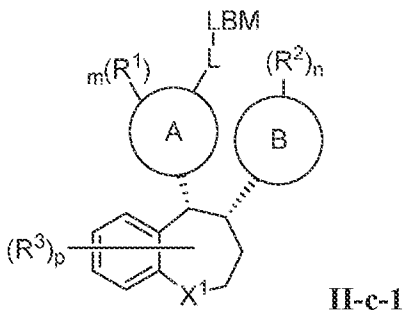
15. The compound of claim 1, wherein the compound is a compound of one of formulas **II-a-1**, **II-b-1**, **II-c-1**, **II-d-1**, **II-e-1**, or **II-f-1**:



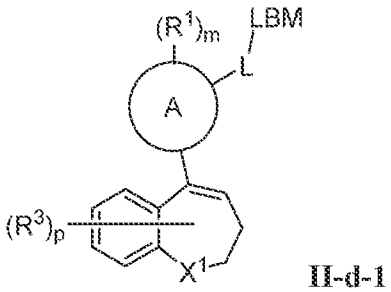
II-a-1



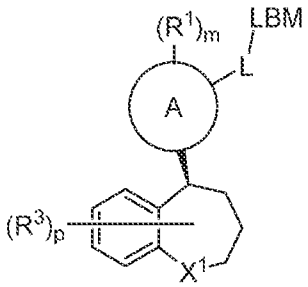
II-b-1



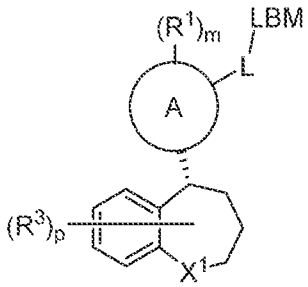
II-c-1



II-d-1



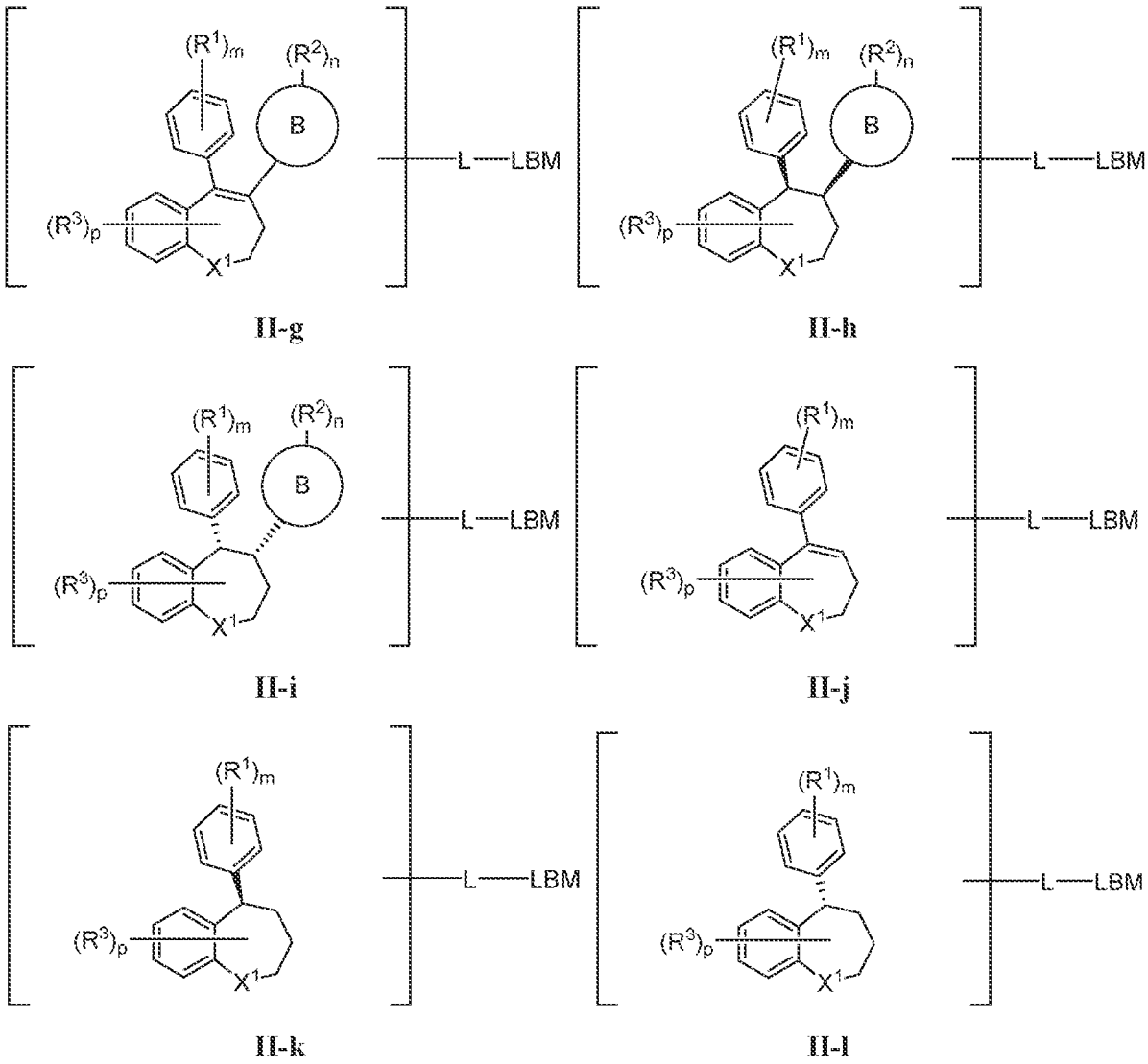
II-e-1



II-f-1

or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1, wherein the compound is a compound of one of formulas **II-g**, **II-h**, **II-i**, **II-j**, **II-k**, or **II-l**:



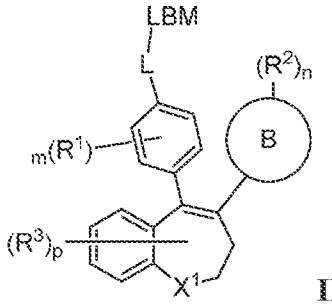
II-g **II-h**

II-i **II-j**

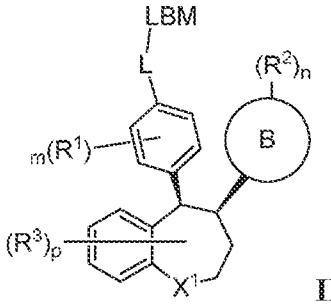
II-k **II-l**

, or a pharmaceutically acceptable salt thereof.

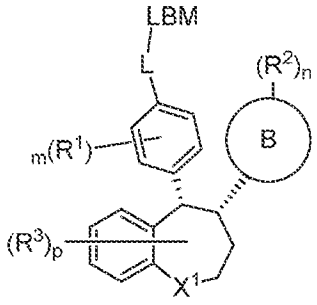
17. The compound of claim 1, wherein the compound is a compound of one of formulas **II-g-1**, **II-h-1**, **II-i-1**, **II-j-1**, **II-k-1**, or **II-l-1**:



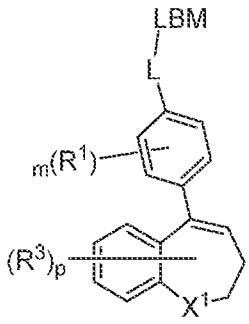
II-g-1



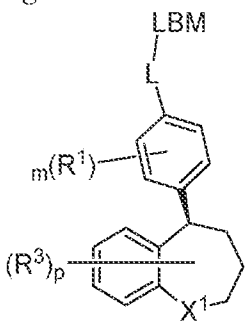
II-h-1



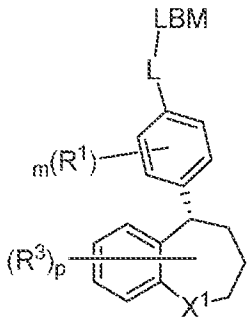
II-i-1



II-j-1



II-k-1



II-l-1, or a pharmaceutically acceptable salt thereof.

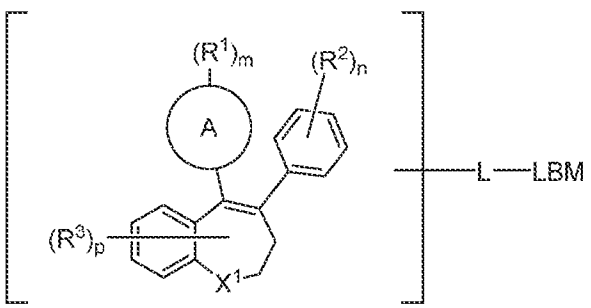
18. The compound of any one of claims 1-17, wherein X^1 is selected from $–CH_2–$, $–CH(R^{A1})–$, $–C(R^{A1})_2–$, –O–, –S–, $–S(O)_2–$, and $–N(R^{A2})–$, provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

19. The compound of any one of claims 1-17, wherein X^1 is selected from $–CH_2–$ and –O– provided that X^1 and X^2 cannot both be heteroatoms simultaneously.

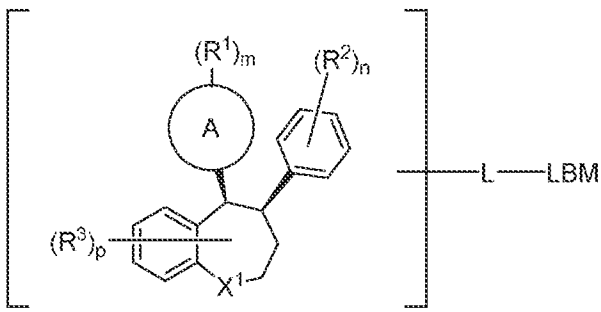
20. The compound of any one of claims 1-17, wherein X^1 is $–CH_2–$.

21. The compound of any one of claims 1-17, wherein X^1 is –O– provided that X^2 is not a heteroatom.

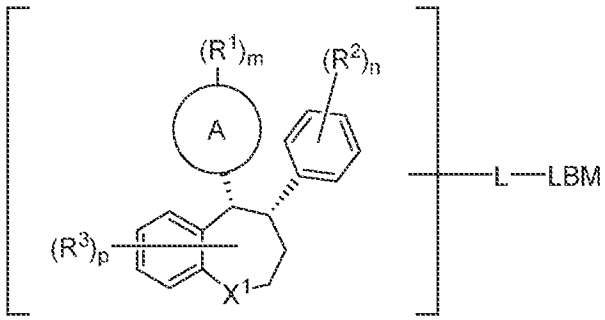
22. The compound of claim 1, wherein the compound is a compound of one of formulas **II-m**, **II-n**, **II-o**, **II-p**, **II-q**, **II-r**, **II-s**, **II-t**, **II-u**, **II-v**, **II-w**, **II-x**, **II-y**, **II-z**, or **II-aa**:



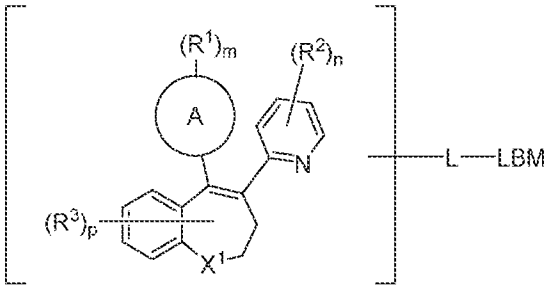
II-m



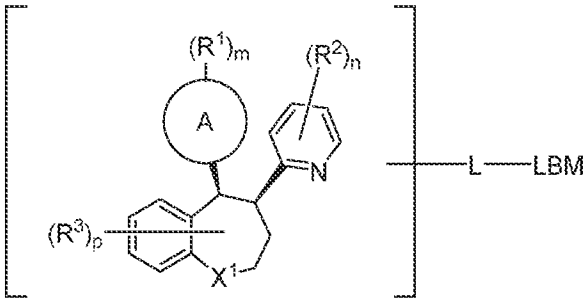
II-n



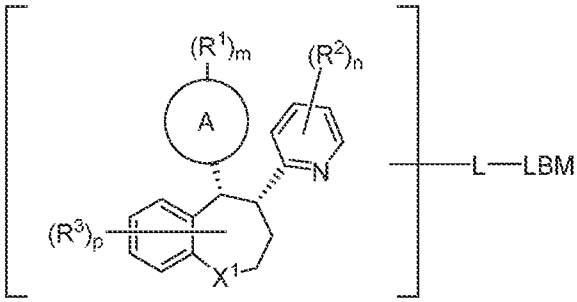
II-o



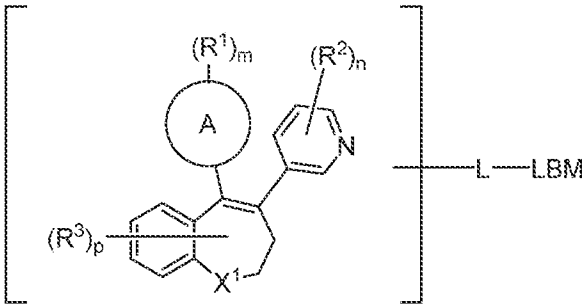
II-p



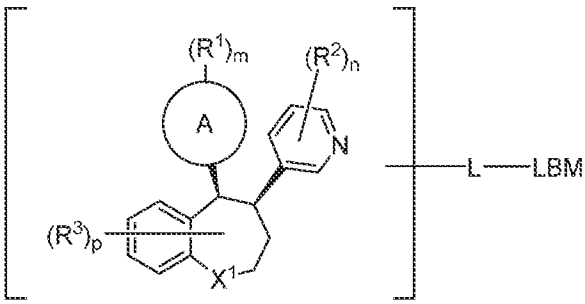
II-q



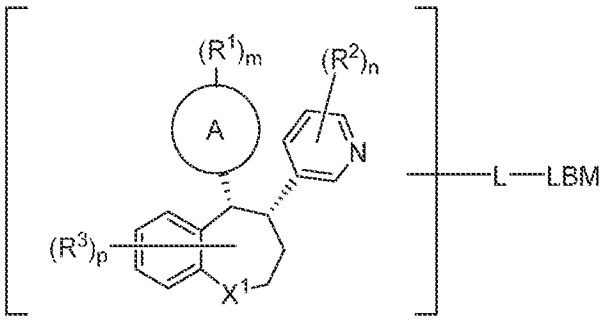
II-r



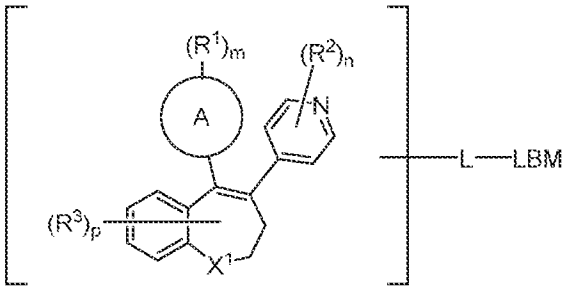
II-s



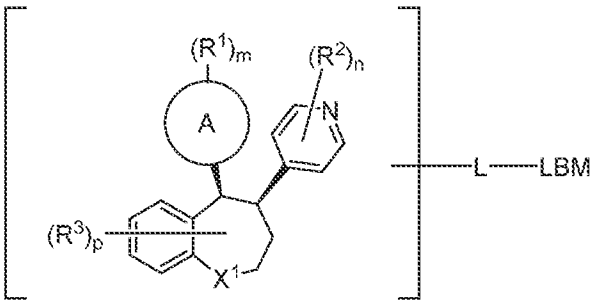
II-t



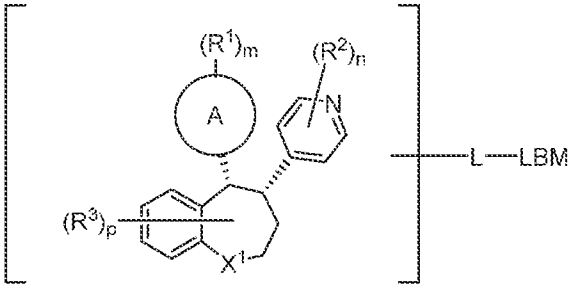
II-u



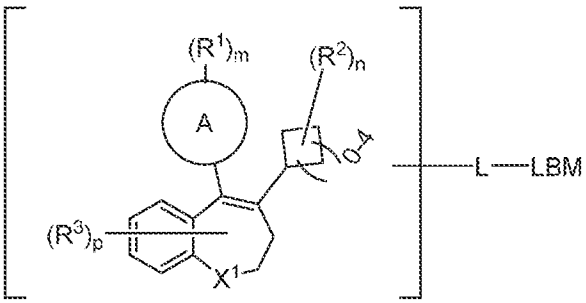
II-v



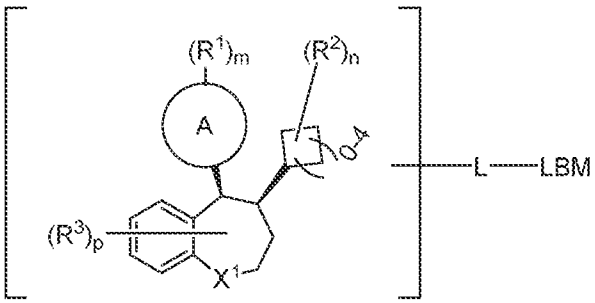
II-w



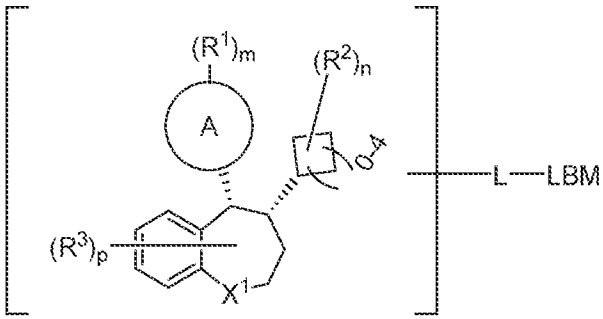
II-x



II-y



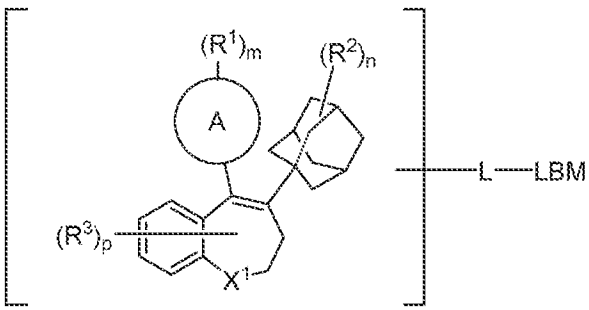
II-z



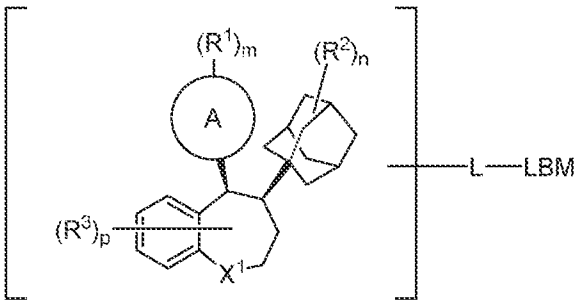
II-aa

or a pharmaceutically acceptable salt thereof.

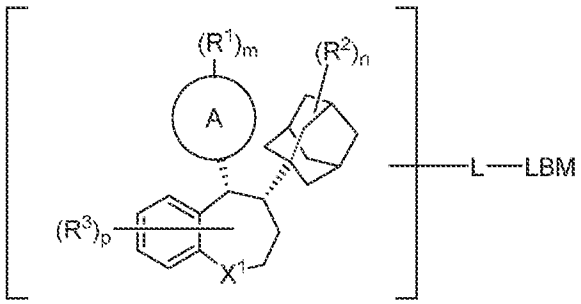
23. The compound of claim 1, wherein the compound is a compound of one of formulas **II-bb**, **II-cc**, **II-dd**, **II-ee**, **II-ff**, or **II-gg**:



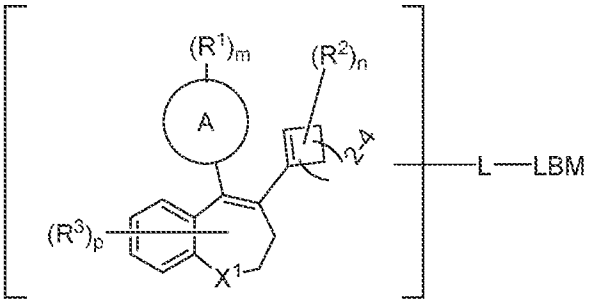
II-bb



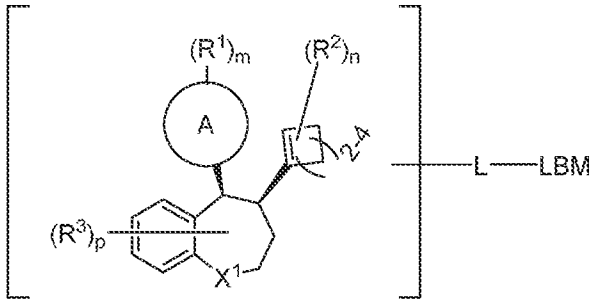
II-cc



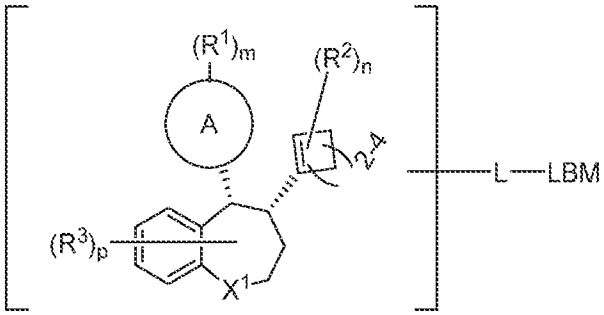
II-dd



II-ee



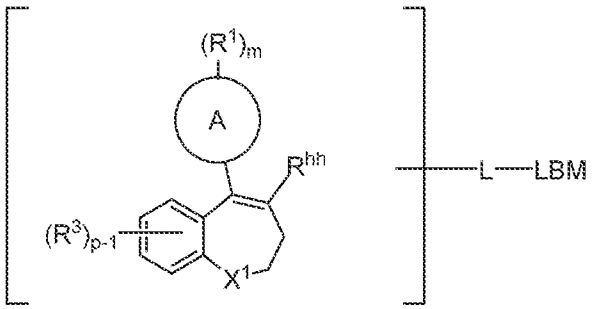
II-ff



II-gg

or a pharmaceutically acceptable salt thereof.

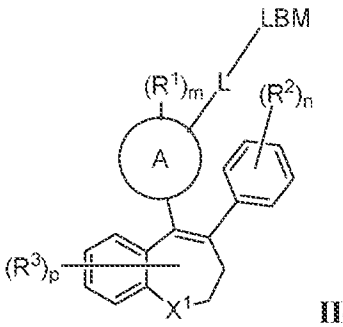
24. The compound of claim 1, wherein the compound is a compound of formula **II-hh**:



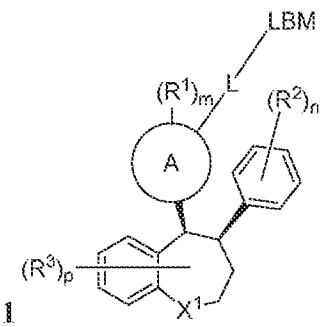
II-hh

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

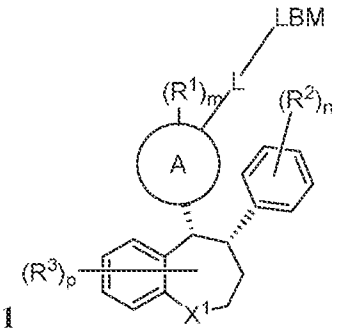
25. The compound of claim 1, wherein the compound is a compound of one of formulas **II-m-1**, **II-n-1**, **II-o-1**, **II-p-1**, **II-q-1**, **II-r-1**, **II-s-1**, **II-t-1**, **II-u-1**, **II-v-1**, **II-w-1**, **II-x-1**, **II-y-1**, **II-z-1**, or **II-aa-1**:



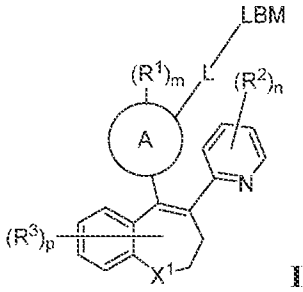
II-m-1



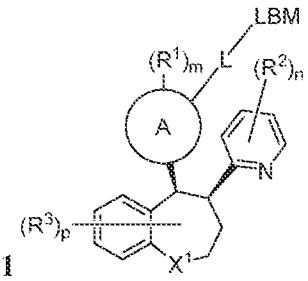
II-n-1



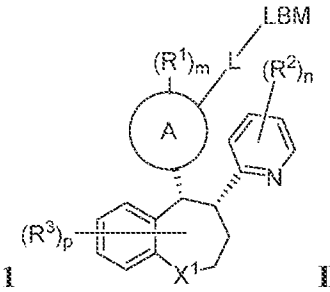
II-o-1



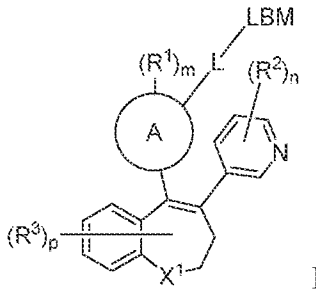
II-p-1



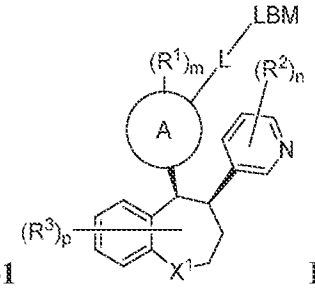
II-q-1



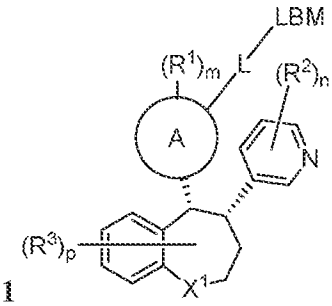
II-r-1



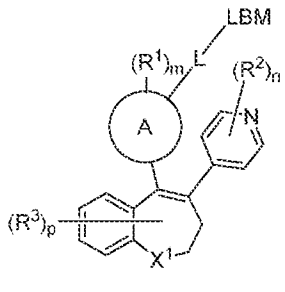
II-s-1



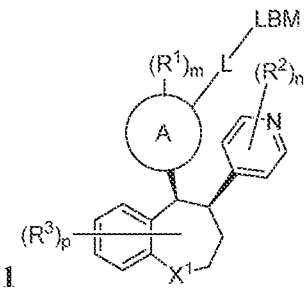
II-t-1



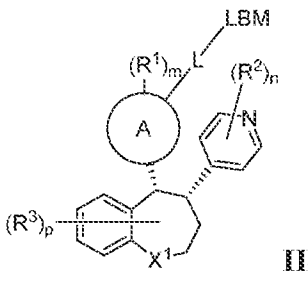
II-u-1



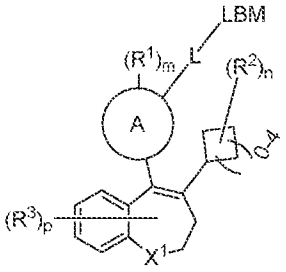
II-v-1



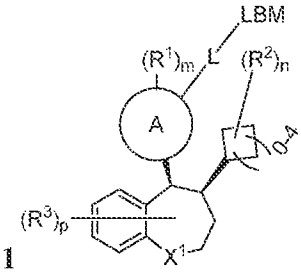
II-w-1



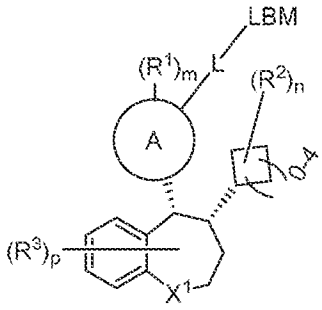
II-x-1



II-y-1



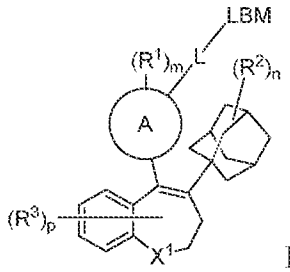
II-z-1



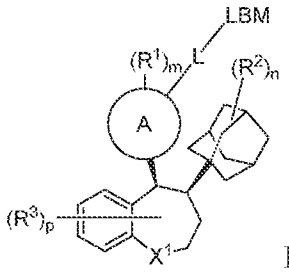
II-aa-1

or a pharmaceutically acceptable salt thereof.

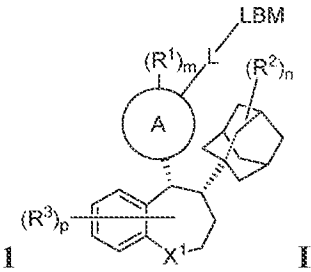
26. The compound of claim 1, wherein the compound is a compound of one of formulas **II-bb-1**, **II-cc-1**, **II-dd-1**, **II-ee-1**, **II-ff-1** or **II-gg-1**:



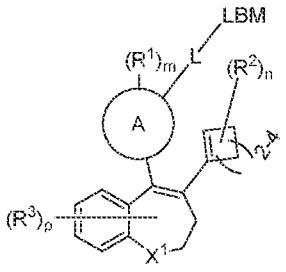
II-bb-1



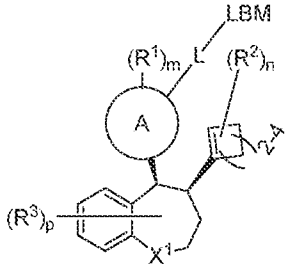
II-cc-1



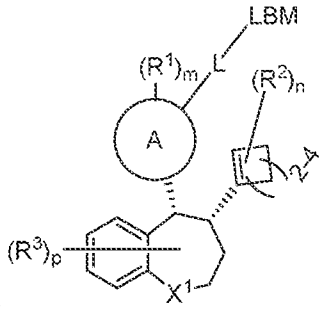
II-dd-1



II-ee-1



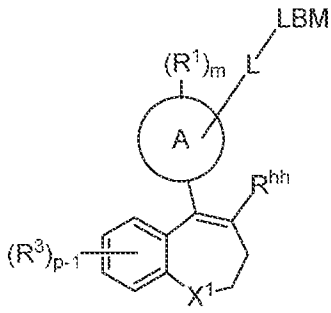
II-ff-1



II-gg-1

or a pharmaceutically acceptable salt thereof.

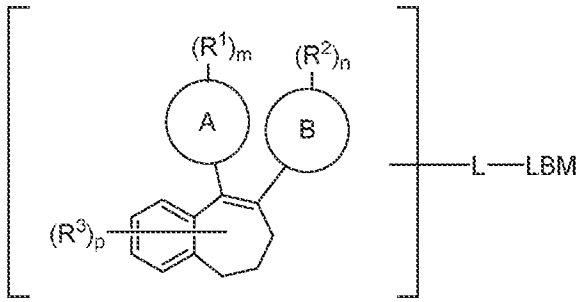
27. The compound of claim 1, wherein the compound is a compound of formula **II-hh-1**:



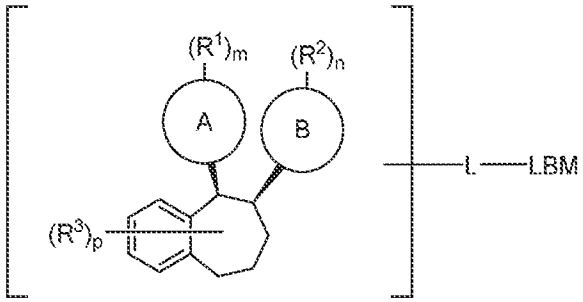
II-hh-1

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $–C_1–C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $–OCH_2CHF_2$, $–OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

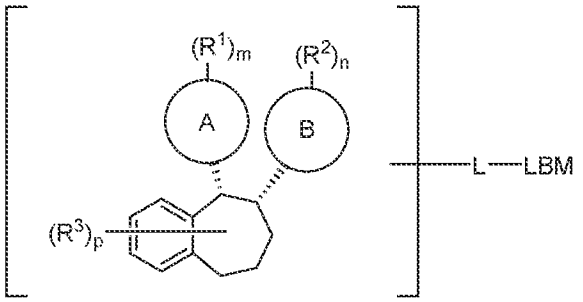
28. The compound of claim 1, wherein the compound is a compound of one of formulas **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, or **III-f**:



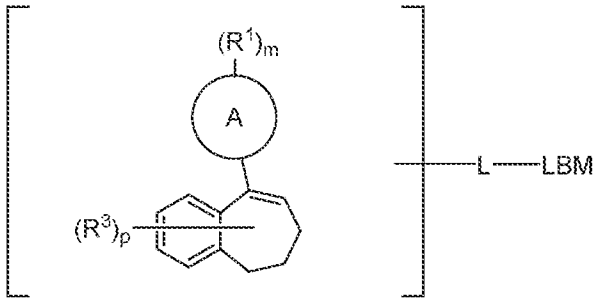
III-a



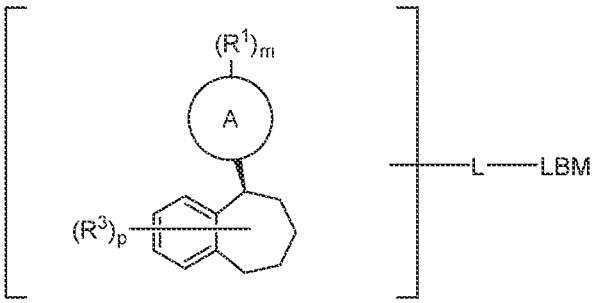
III-b



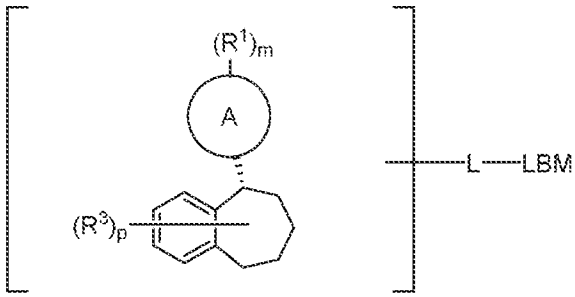
III-c



III-d



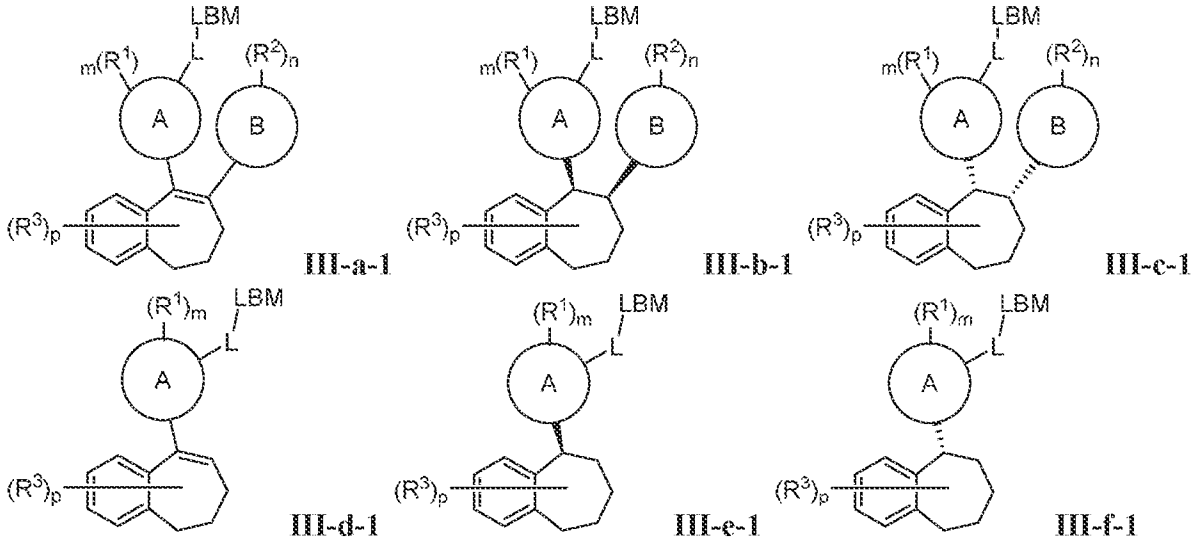
III-e



III-f

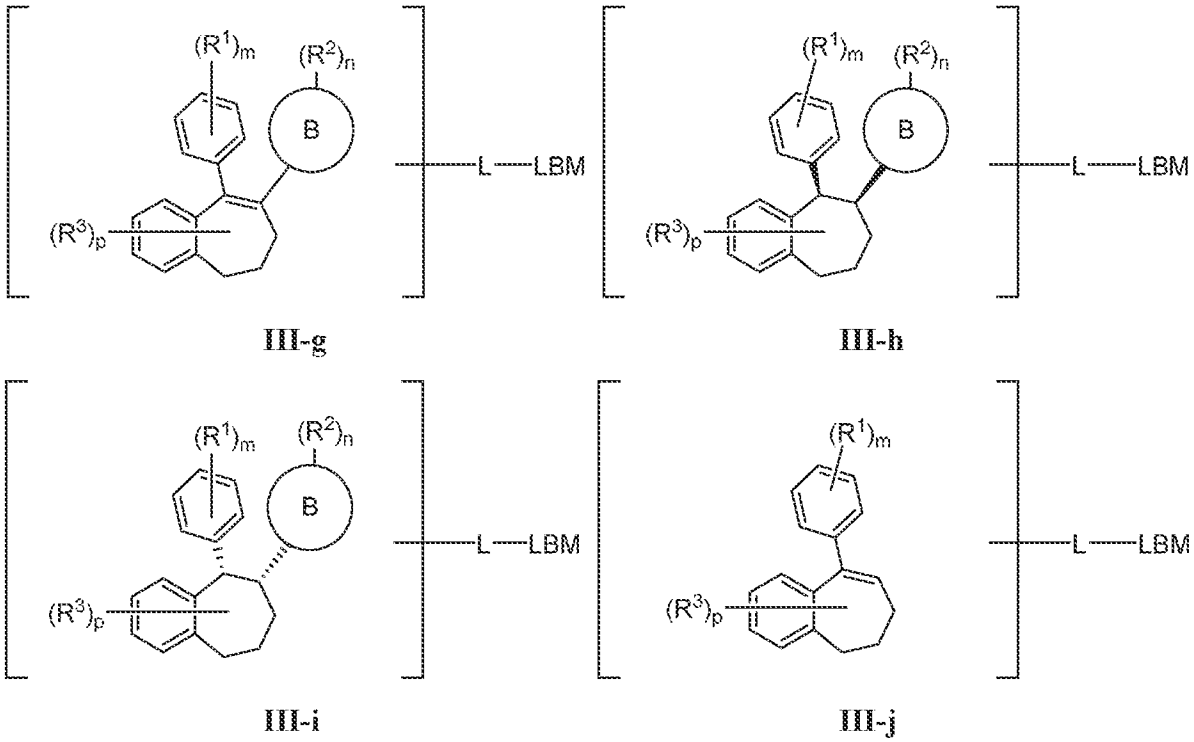
or a pharmaceutically acceptable salt thereof.

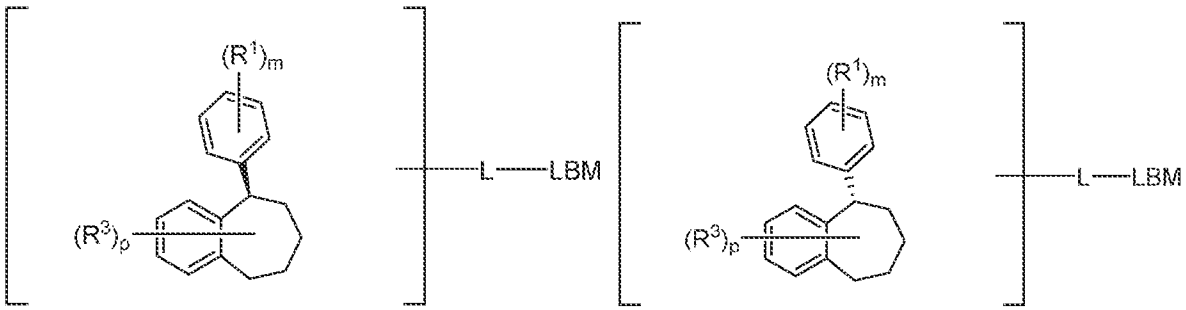
29. The compound of claim 1, wherein the compound is a compound of one of formulas **III-a-1**, **III-b-1**, **III-c-1**, **III-d-1**, **III-e-1**, or **III-f-1**:



or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1, wherein the compound is a compound of one of formulas **III-g**, **III-h**, **III-i**, **III-j**, **III-k**, or **III-l**:

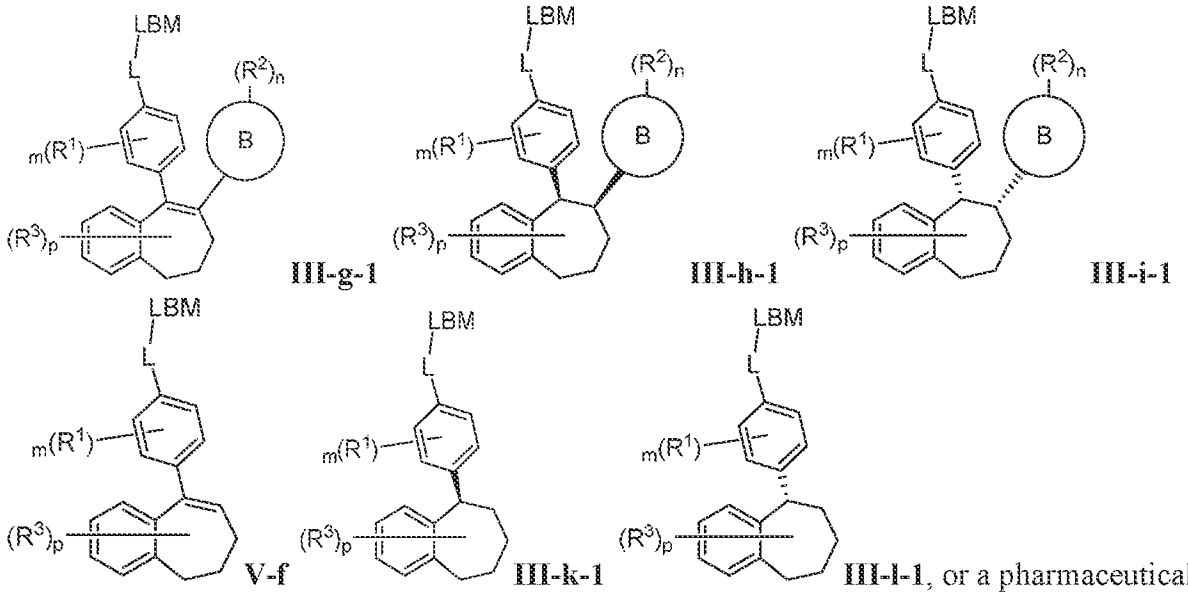




III-k **III-l**

or a pharmaceutically acceptable salt thereof.

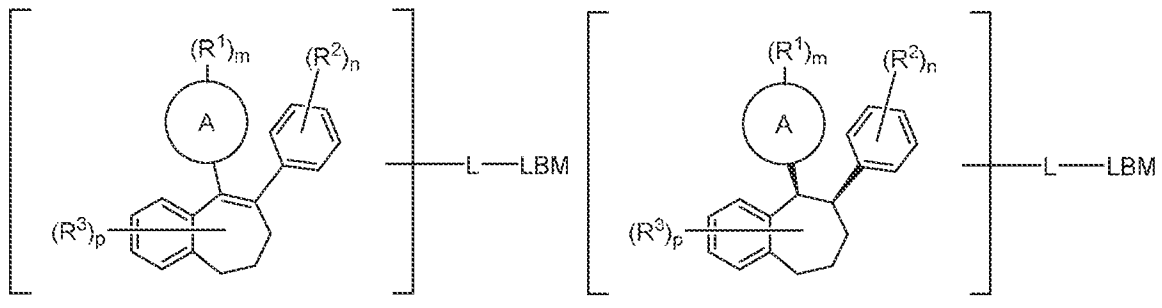
31. The compound of claim 1, wherein the compound is a compound of one of formulas **III-g-1**, **III-h-1**, **III-i-1**, **V-f**, **III-k-1**, or **III-l-1**:



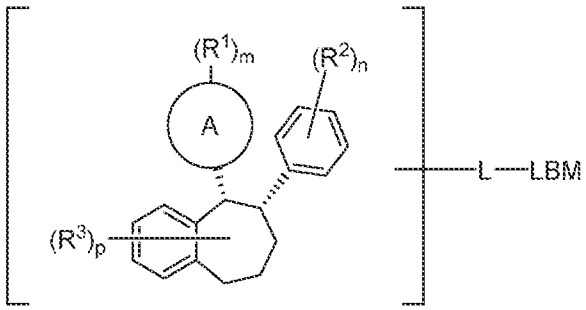
III-g-1 **III-h-1** **III-i-1**

V-f **III-k-1** **III-l-1**, or a pharmaceutically acceptable salt thereof.

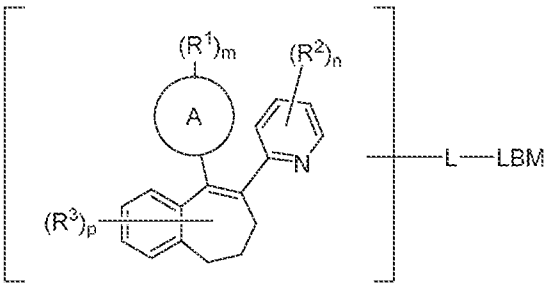
32. The compound of claim 1, wherein the compound is a compound of one of formulas **III-m**, **III-n**, **III-o**, **III-p**, **III-q**, **III-r**, **III-s**, **III-t**, **III-u**, **III-v**, **III-w**, **III-x**, **III-y**, **III-z**, or **III-aa**:



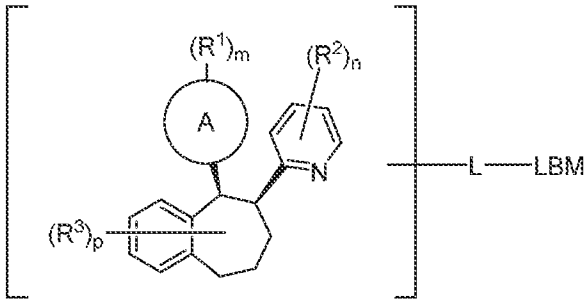
III-m **III-n**



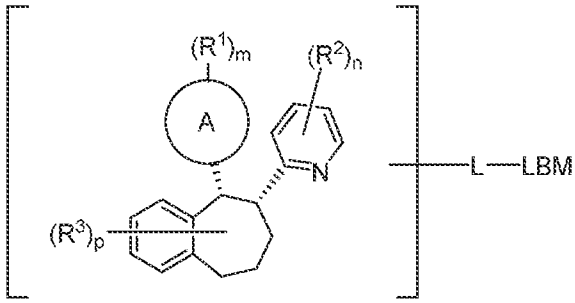
III-o



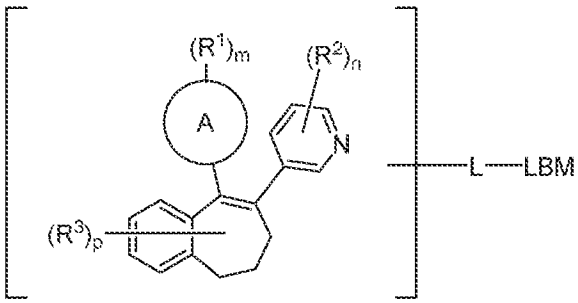
III-p



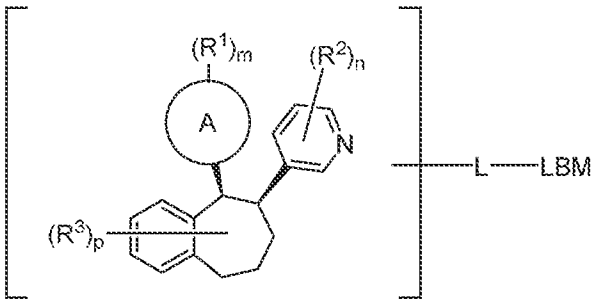
III-q



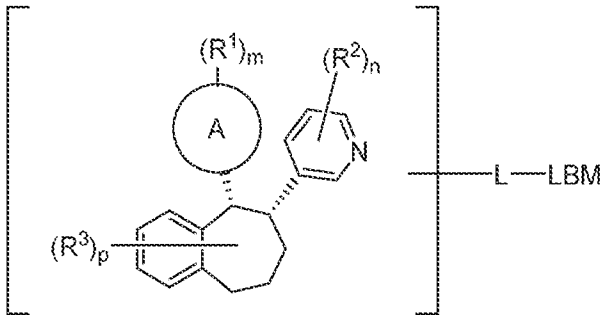
III-r



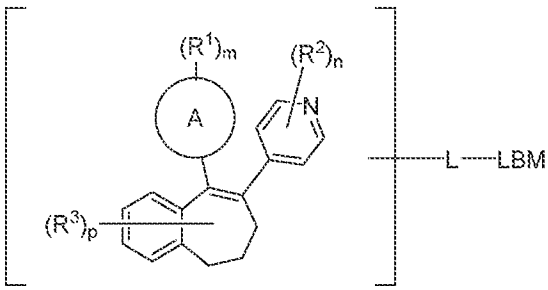
III-s



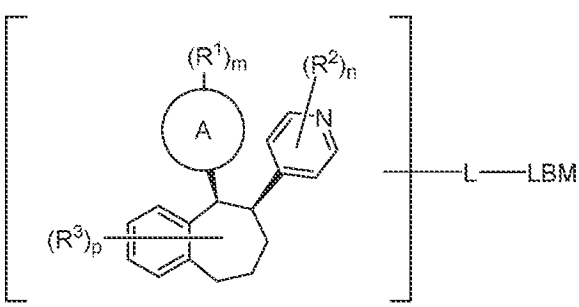
III-t



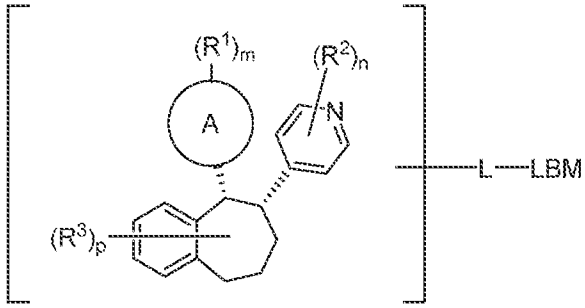
III-u



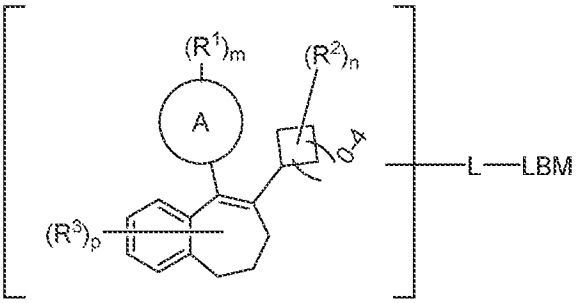
III-v



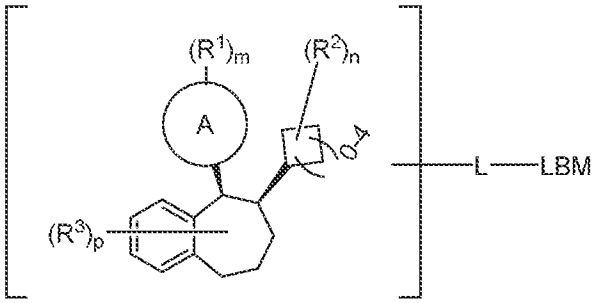
III-w



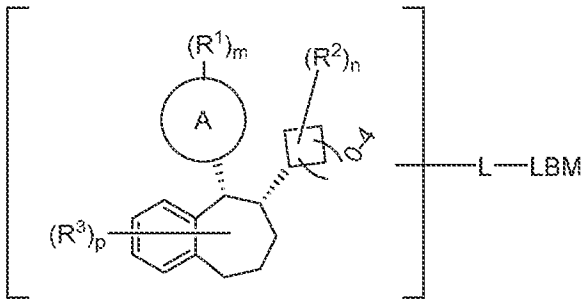
III-x



III-y



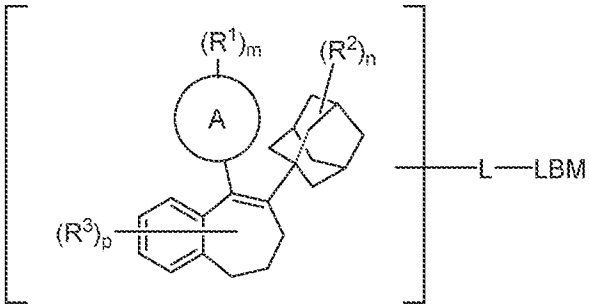
III-z



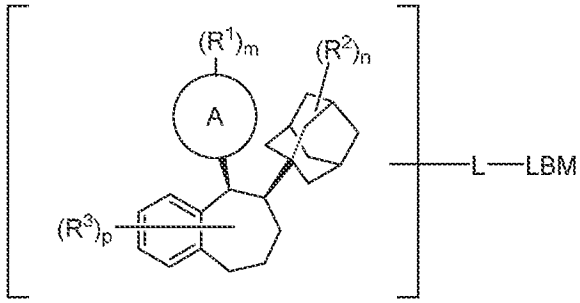
III-aa

or a pharmaceutically acceptable salt thereof.

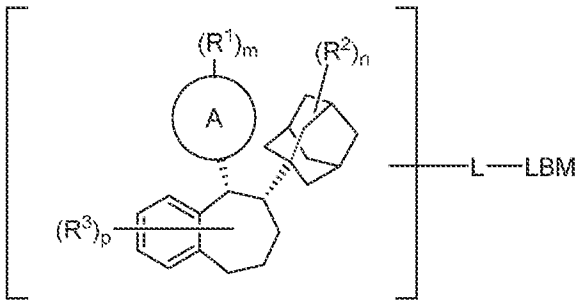
33. The compound of claim 1, wherein the compound is a compound of one of formulas **III-bb**, **III-cc**, **III-dd**, **III-ee**, **III-ff**, or **III-gg**:



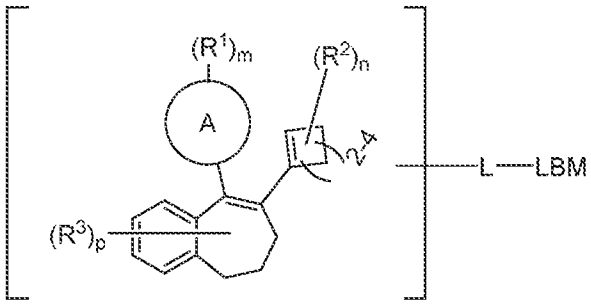
III-bb



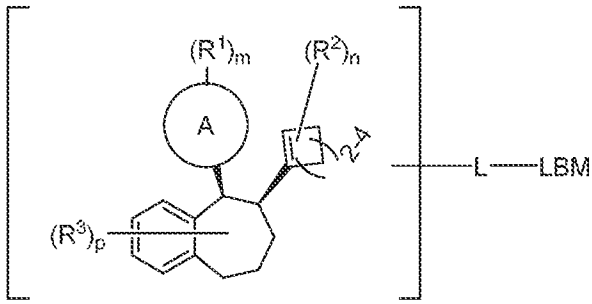
III-cc



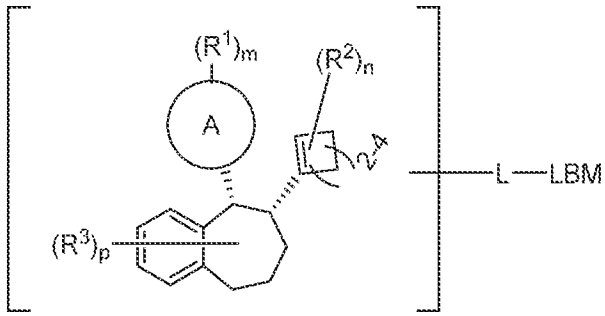
III-dd



III-ee



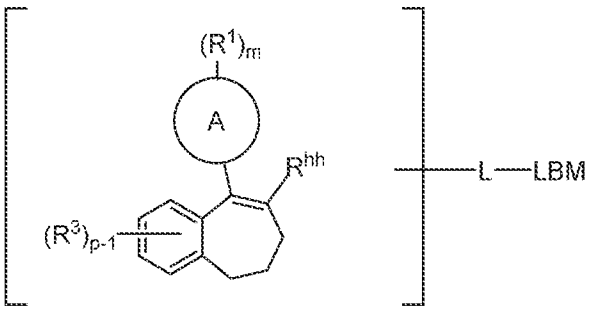
III-ff



III-gg

or a pharmaceutically acceptable salt thereof.

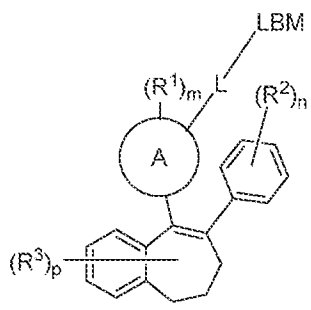
34. The compound of claim 1, wherein the compound is a compound of formula **III-hh**:



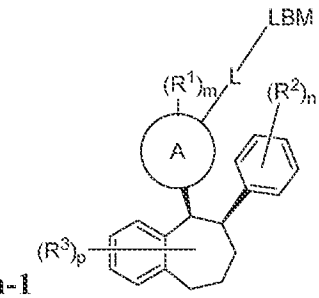
III-hh

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

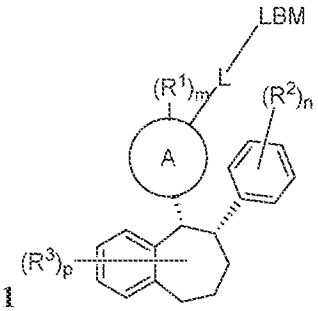
35. The compound of claim 1, wherein the compound is a compound of one of formulas **III-m-1**, **III-n-1**, **III-o-1**, **III-p-1**, **III-q-1**, **III-r-1**, **III-s-1**, **III-t-1**, **III-u-1**, **III-v-1**, **III-w-1**, **III-x-1**, **III-y-1**, **III-z-1**, or **III-aa-1**:



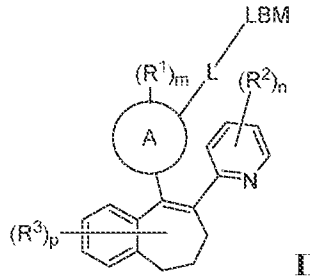
III-m-1



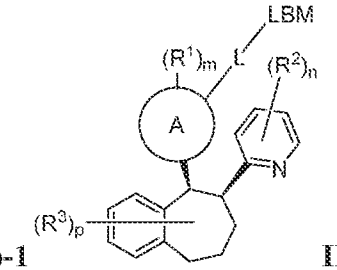
III-n-1



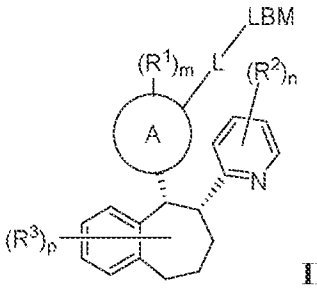
III-o-1



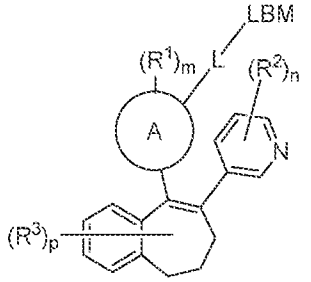
III-p-1



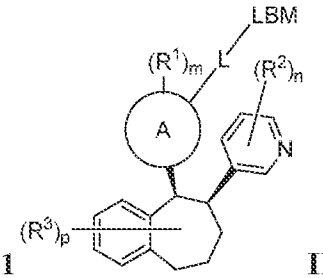
III-q-1



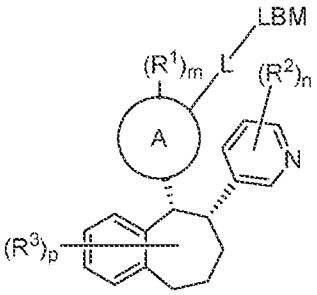
III-r-1



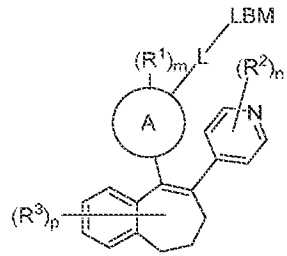
III-s-1



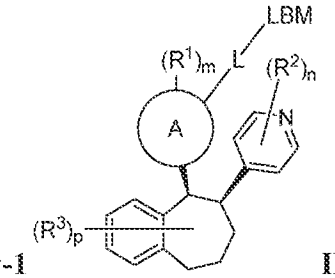
III-t-1



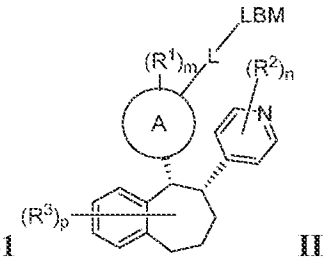
III-u-1



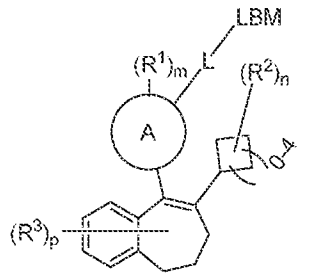
III-v-1



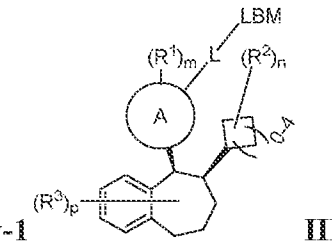
III-w-1



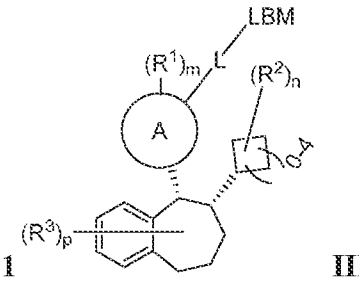
III-x-1



III-y-1



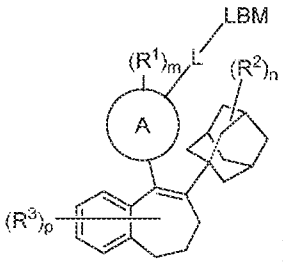
III-z-1



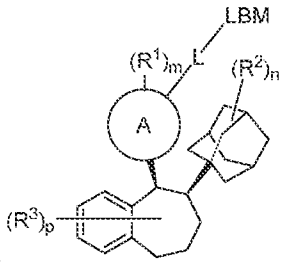
III-aa-1

or a pharmaceutically acceptable salt thereof.

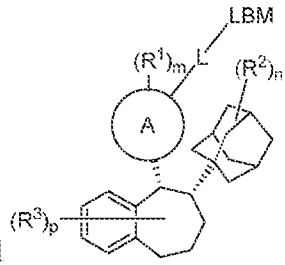
36. The compound of claim 1, wherein the compound is a compound of one of formulas **III-bb-1**, **III-cc-1**, **III-dd-1**, **III-ee-1**, **III-ff-1** or **III-gg-1**:



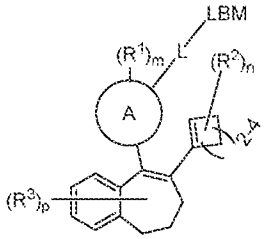
III-bb-1



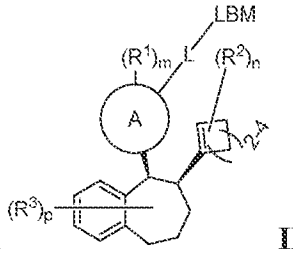
III-cc-1



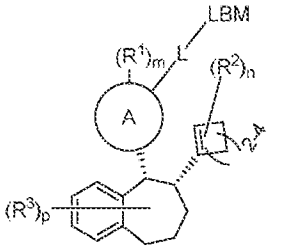
III-dd-1



III-ee-1



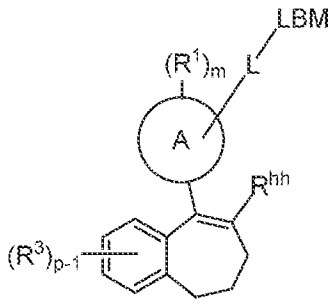
III-ff-1



III-gg-1

or a pharmaceutically acceptable salt thereof.

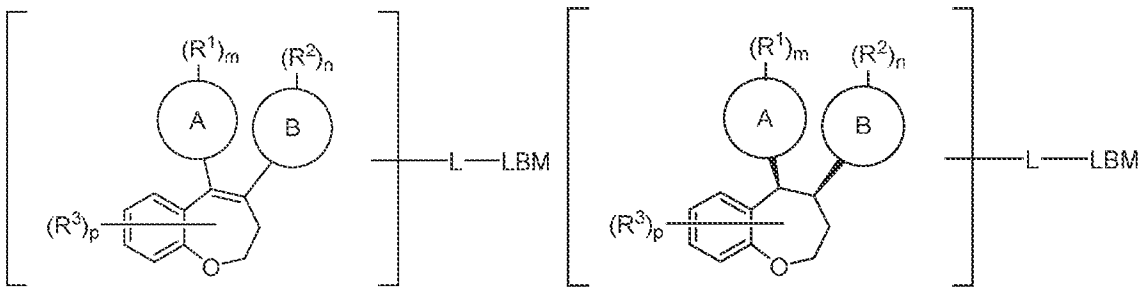
37. The compound of claim 1, wherein the compound is a compound of formula **III-hh-1**:



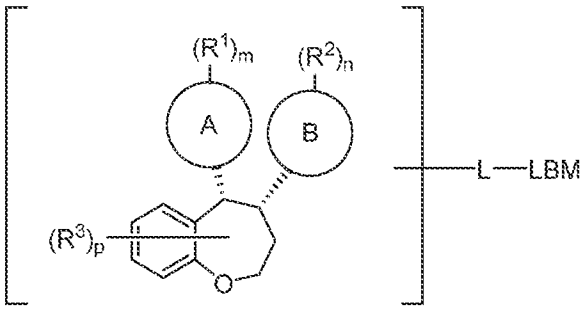
II-hh-1

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1$–C_6 alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

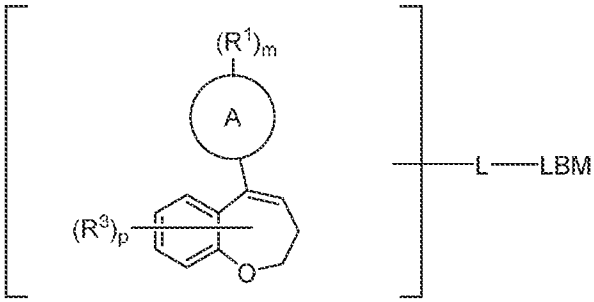
38. The compound of claim 1, wherein the compound is a compound of one of formulas **IV-a**, **IV-b**, **IV-c**, **IV-d**, **IV-e**, or **IV-f**:



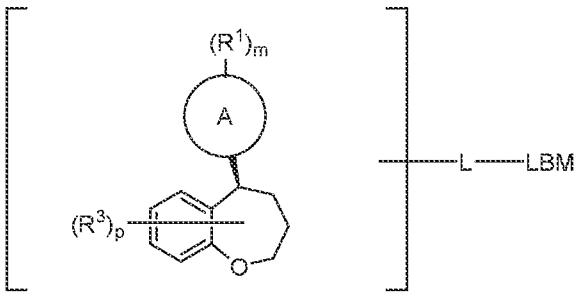
IV-a



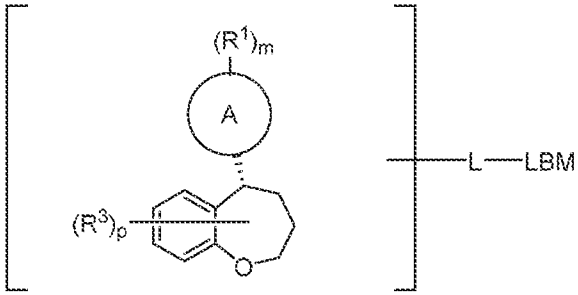
IV-b



IV-c



IV-d

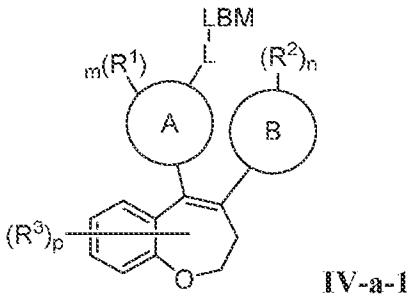


IV-e

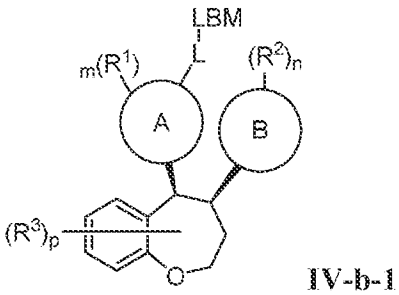
IV-f

or a pharmaceutically acceptable salt thereof.

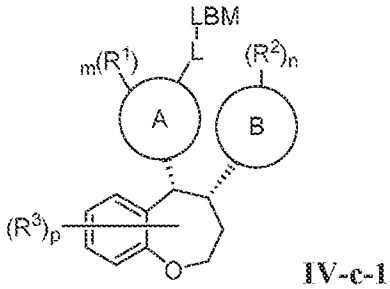
39. The compound of of claim 1, wherein the compound is a compound of one of formulas **IV-a-1**, **IV-b-1**, **IV-c-1**, **IV-d-1**, **IV-e-1**, or **IV-f-1**:



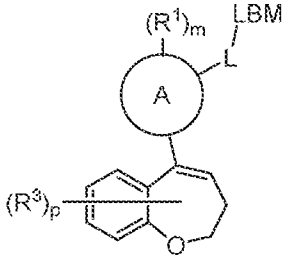
IV-a-1



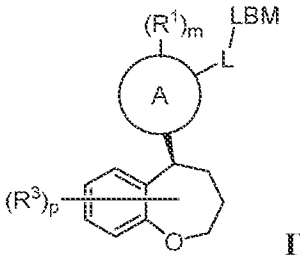
IV-b-1



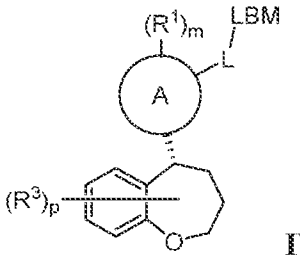
IV-c-1



IV-d-1



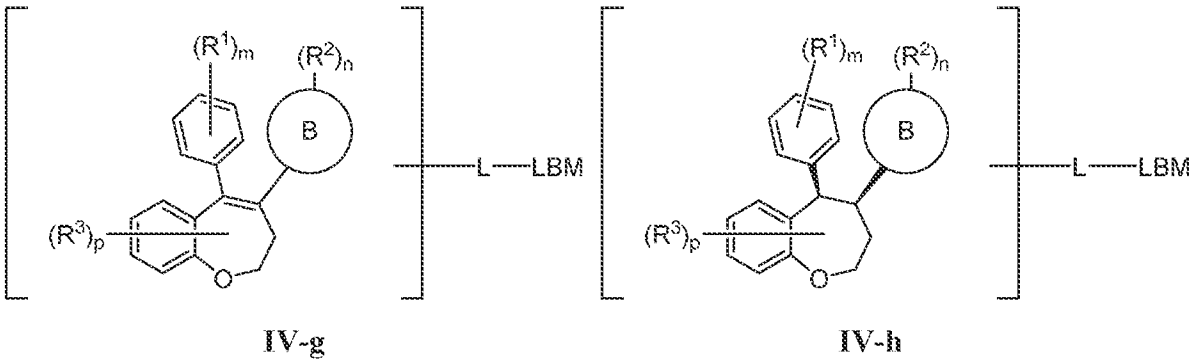
IV-e-1



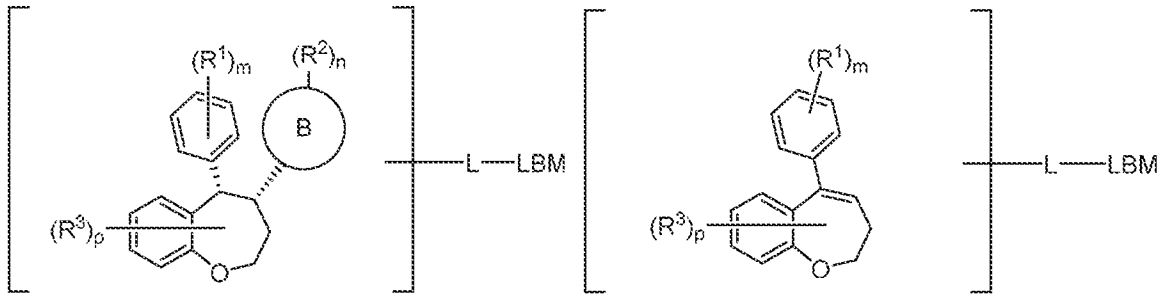
IV-f-1

or a pharmaceutically acceptable salt thereof.

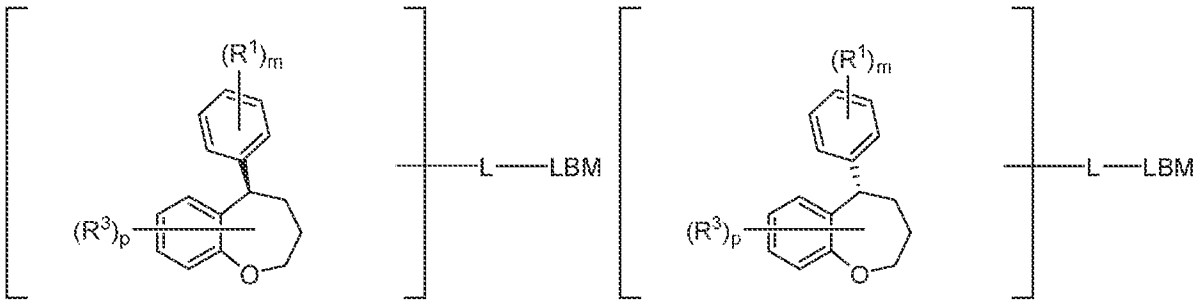
40. The compound of of claim 1, wherein the compound is a compound of one of formulas **IV-g**, **IV-h**, **IV-i**, **IV-j**, **IV-k**, or **IV-l**:



IV-g **IV-h**



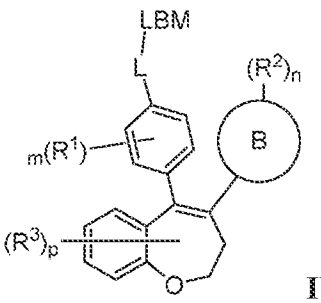
IV-i **IV-j**



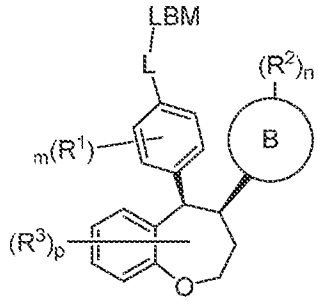
IV-k **IV-l**

or a pharmaceutically acceptable salt thereof.

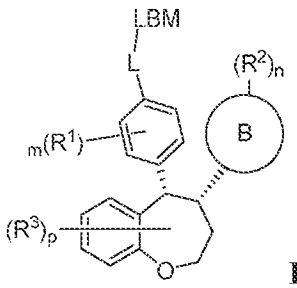
41. The compound of of claim 1, wherein the compound is a compound of one of formulas **IV-g-1**, **IV-h-1**, **IV-i-1**, **V-e**, **IV-k-1** or **IV-l-1**:



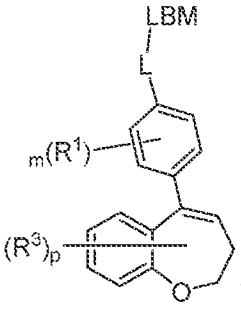
IV-g-1



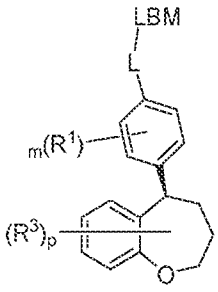
IV-h-1



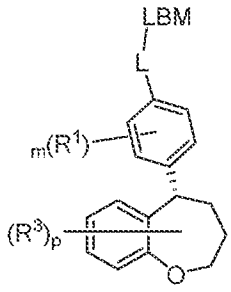
IV-i-1



V-e

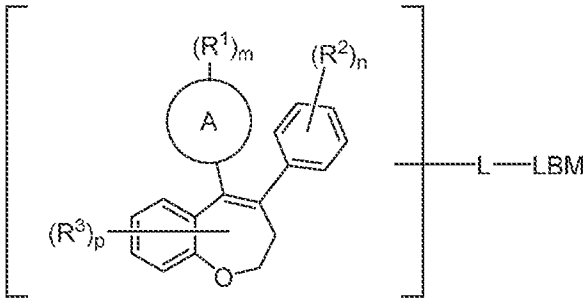


IV-k-1

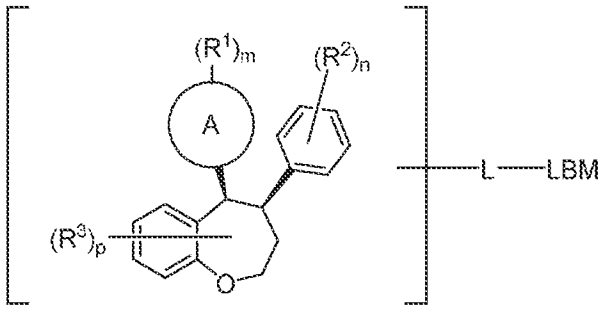


IV-l-1, or a pharmaceutically acceptable salt thereof.

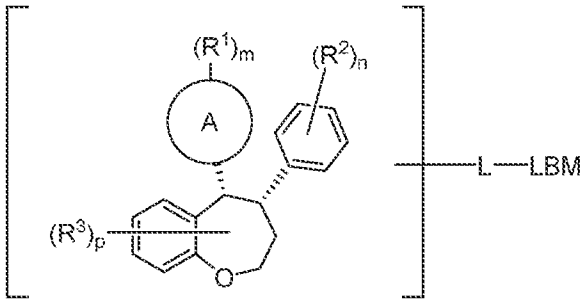
42. The compound of claim 1, wherein the compound is a compound of one of formulas **IV-m**, **IV-n**, **IV-o**, **IV-p**, **IV-q**, **IV-r**, **IV-s**, **IV-t**, **IV-u**, **IV-v**, **IV-w**, **IV-x**, **IV-y**, **IV-z**, or **IV-aa**:



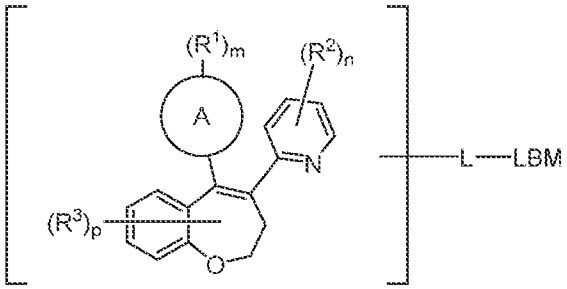
IV-m



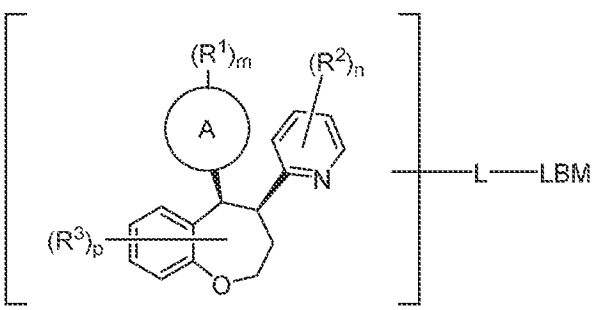
IV-n



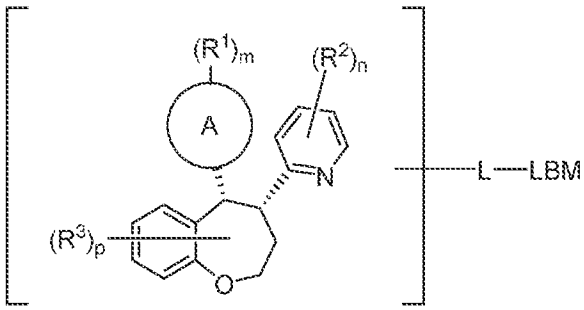
IV-o



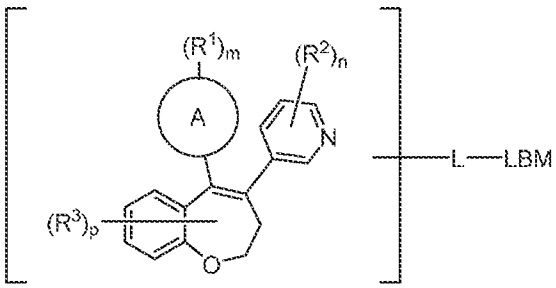
IV-p



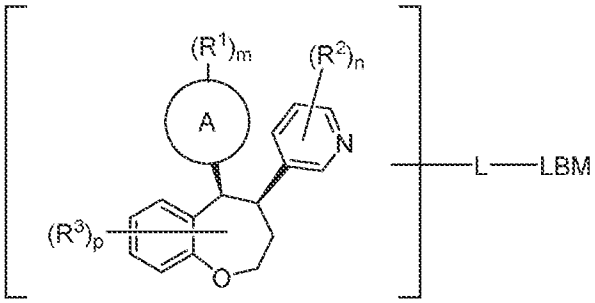
IV-q



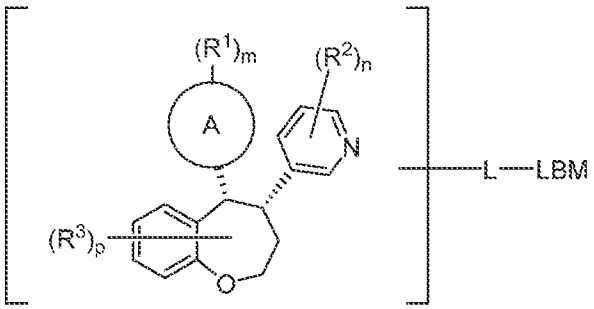
IV-r



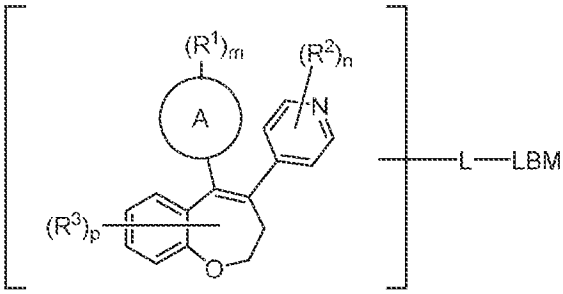
IV-s



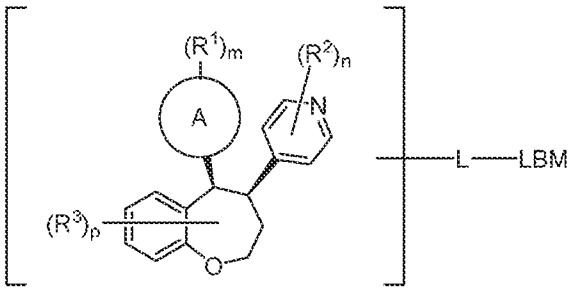
IV-t



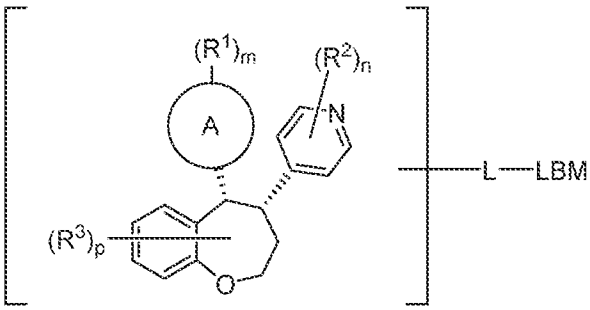
IV-u



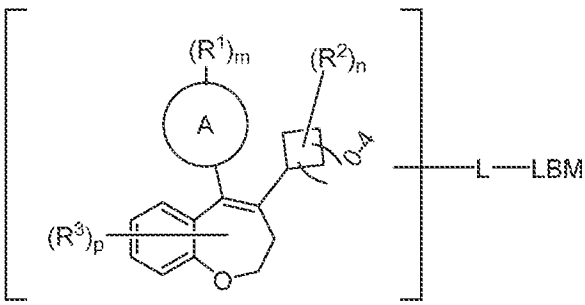
IV-v

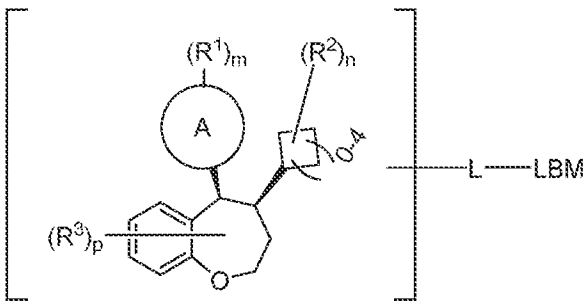


IV-w

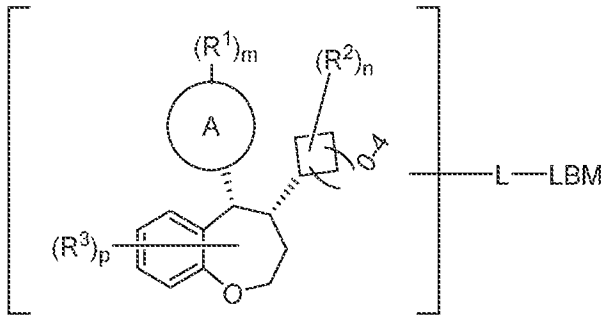


IV-x





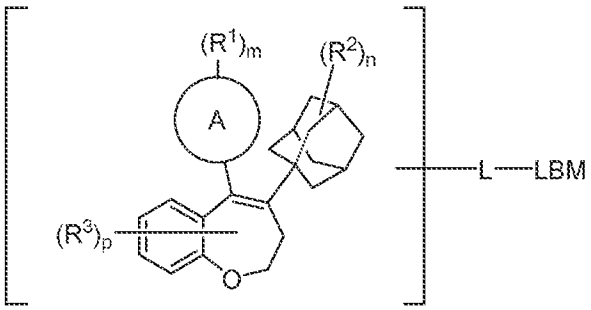
IV-y **IV-z**



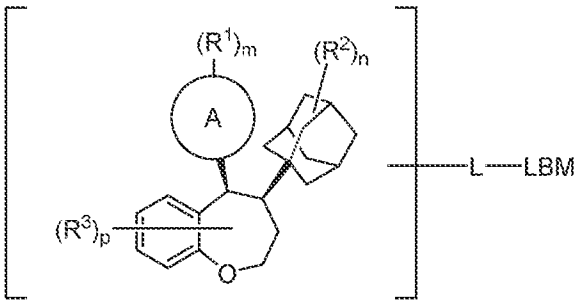
IV-aa

or a pharmaceutically acceptable salt thereof.

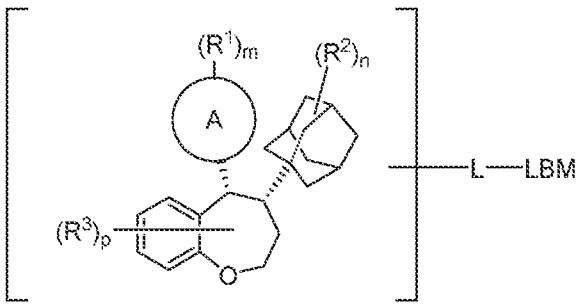
43. The compound of claim 1, wherein the compound is a compound of one of formulas **IV-bb**, **IV-cc**, **IV-dd**, **IV-ee**, **IV-ff**, or **IV-gg**:



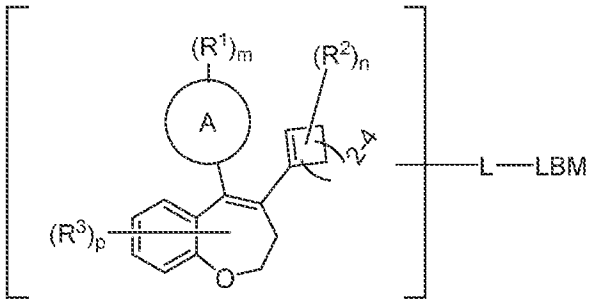
IV-bb



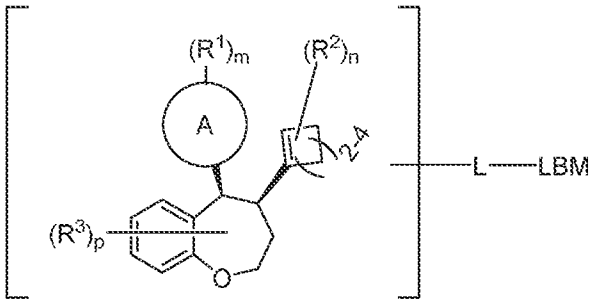
IV-cc



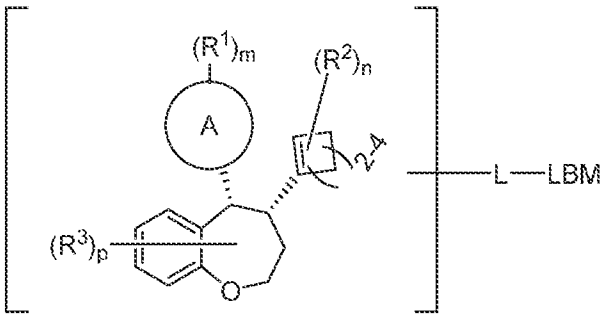
IV-dd



IV-ee



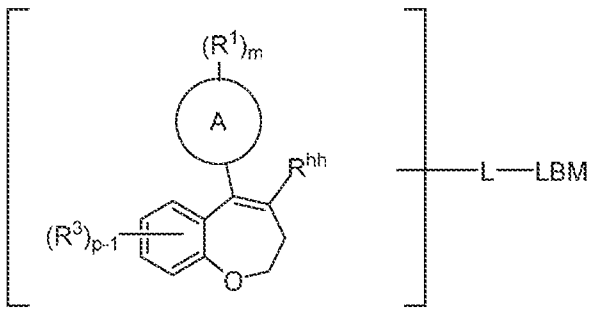
IV-ff



IV-gg

or a pharmaceutically acceptable salt thereof.

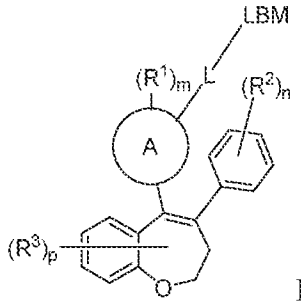
44. The compound of claim 1, wherein the compound is a compound of formula **IV-hh**:



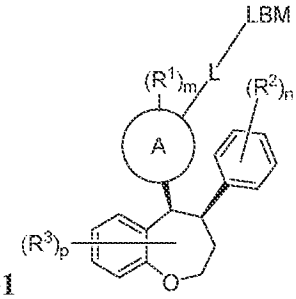
IV-hh

or a pharmaceutically acceptable salt thereof, wherein wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 instances of –F, –OMe, –OEt, $-OCH_2CHF_2$, $-OCH_2CF_3$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

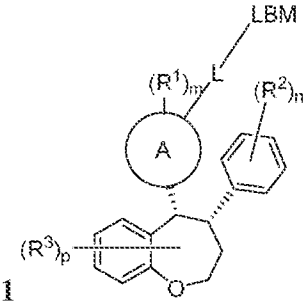
45. The compound of claim 1, wherein the compound is a compound of one of formulas **IV-m-1**, **IV-n-1**, **IV-o-1**, **IV-p-1**, **IV-q-1**, **IV-r-1**, **IV-s-1**, **IV-t-1**, **IV-u-1**, **IV-v-1**, **IV-w-1**, **IV-x-1**, **IV-y-1**, **IV-z-1**, or **IV-aa-1**:



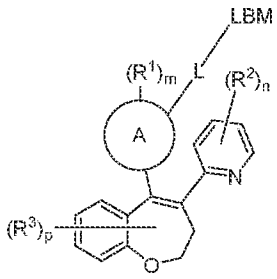
IV-m-1



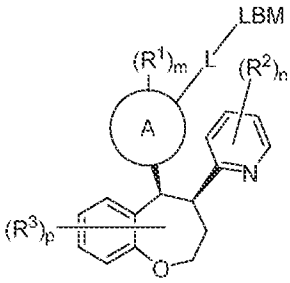
IV-n-1



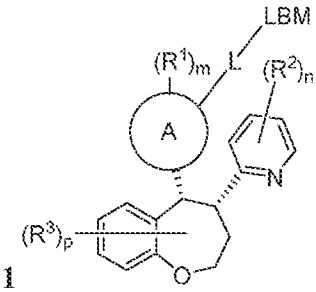
IV-o-1



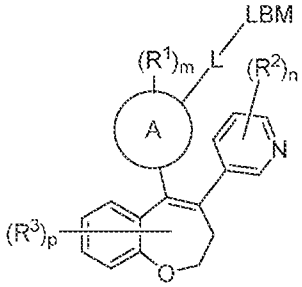
IV-p-1



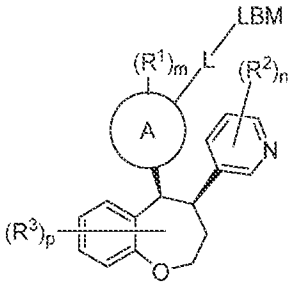
IV-q-1



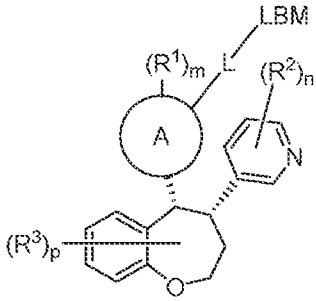
IV-r-1



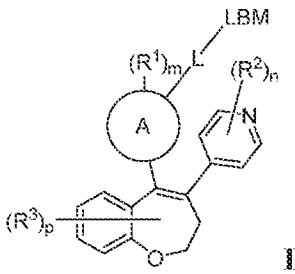
IV-s-1



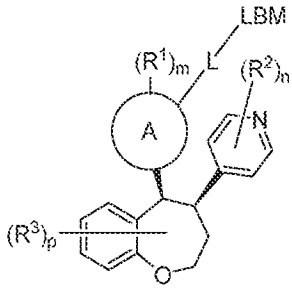
IV-t-1



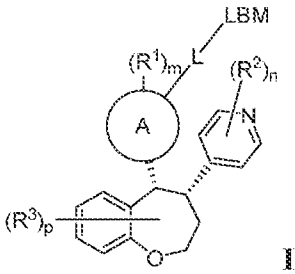
IV-u-1



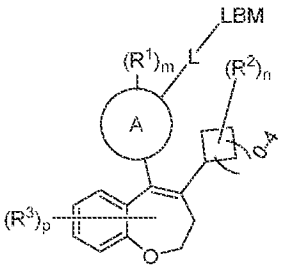
IV-v-1



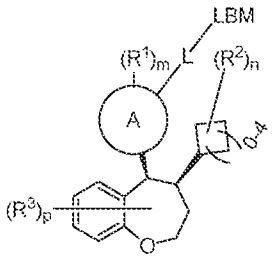
IV-w-1



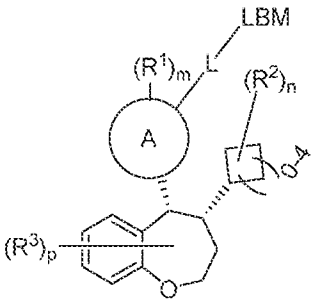
IV-x-1



IV-y-1



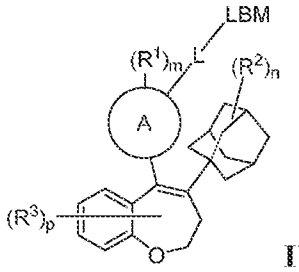
IV-z-1



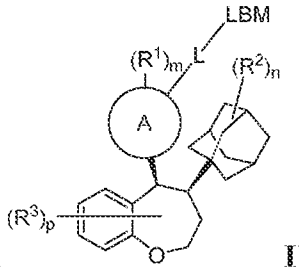
IV-aa-1

or a pharmaceutically acceptable salt thereof.

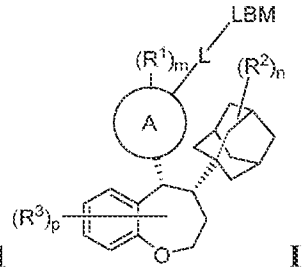
46. The compound of claim 1, wherein the compound is a compound of one of formulas **IV-bb-1**, **IV-cc-1**, **IV-dd-1**, **IV-ee-1**, **IV-ff-1** or **IV-gg-1**:



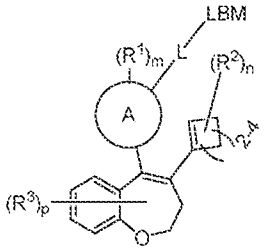
IV-bb-1



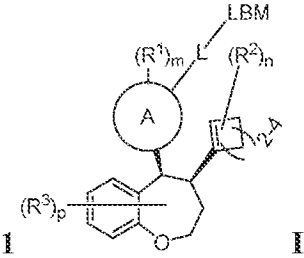
IV-cc-1



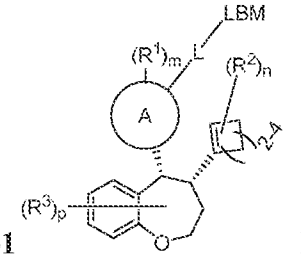
IV-dd-1



IV-ee-1



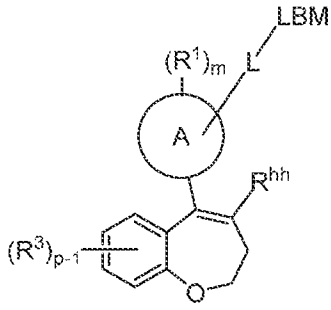
IV-ff-1



IV-gg-1

or a pharmaceutically acceptable salt thereof.

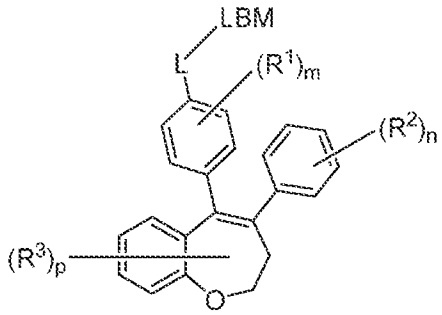
47. The compound of claim 1, wherein the compound is a compound of formula **IV-hh-1**:



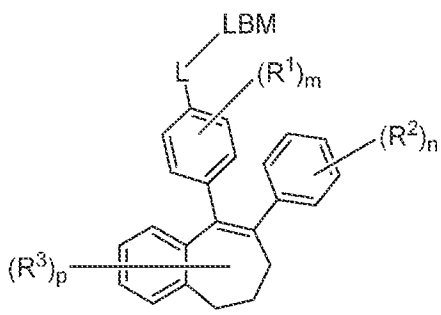
IV-hh-1

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1$–C_6 alkyl substituted with 0, 1, 2, or 3 instances of –F.

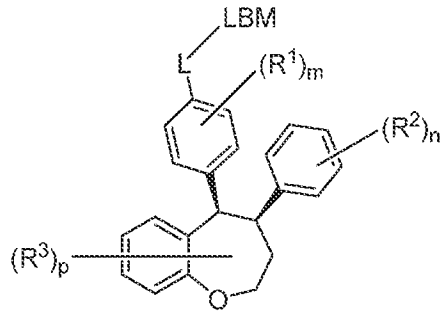
48. The compound of claim 1, wherein the compound is a compound of one of formulas **V-a**, **V-b**, **V-c**, **V-d**, **V-e**, or **V-f**:



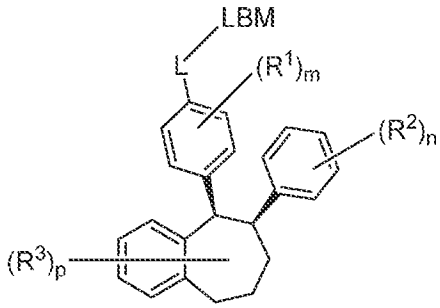
V-a



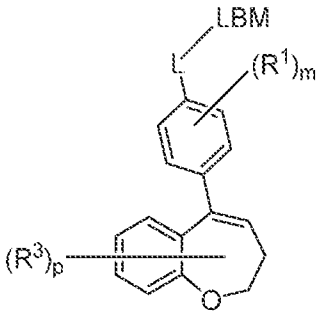
V-b



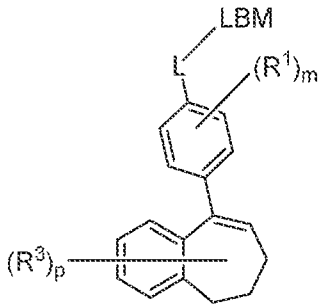
V-c



V-d



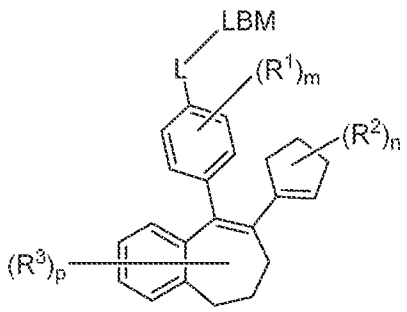
V-e



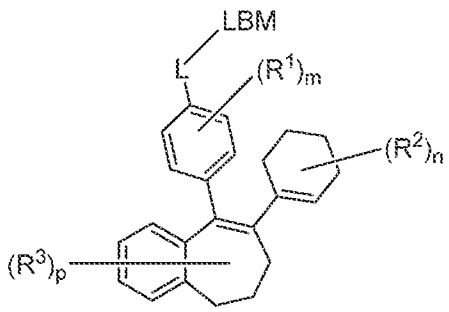
V-f

or a pharmaceutically acceptable salt thereof.

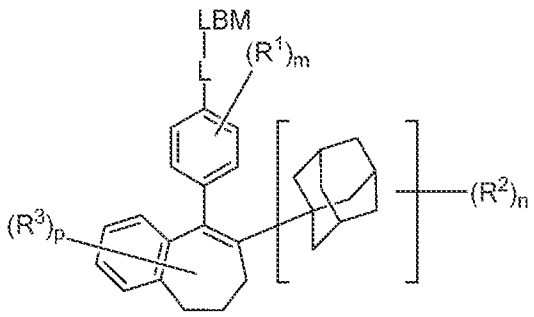
49. The compound of claim 1, wherein the compound is a compound of one of formulas **V-g**, **V-h**, **V-i**, **V-j**, **V-k**, **V-l**, or **V-m**:



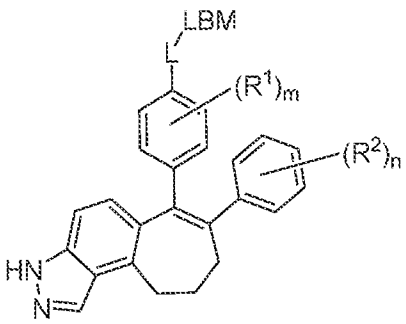
V-g



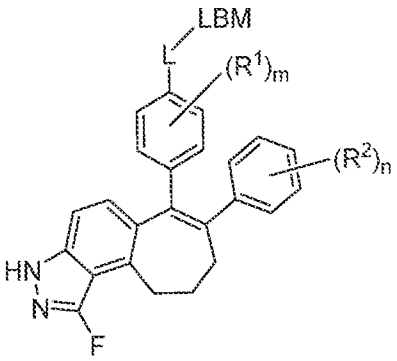
V-h



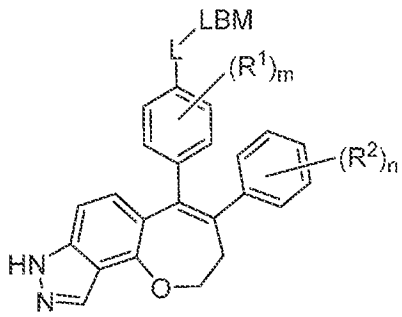
V-i



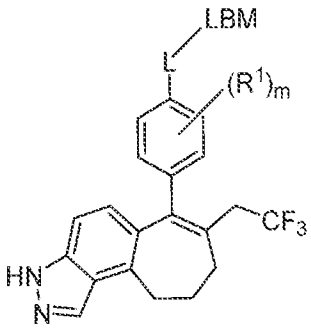
V-j



V-k



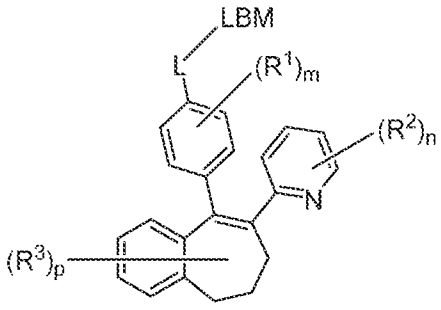
V-l



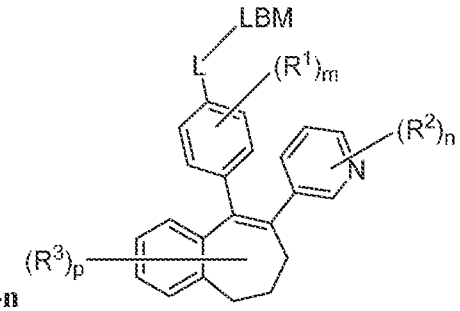
V-m

or a pharmaceutically acceptable salt thereof.

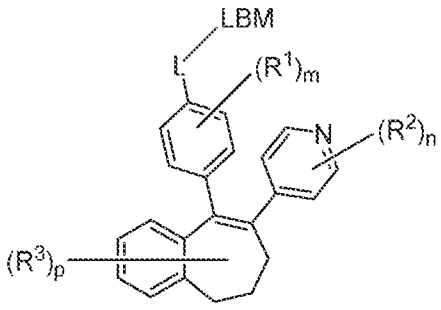
50. The compound of claim 1, wherein the compound is a compound of one of formulas **V-n**, **V-o**, **V-p**, **V-q** or **V-r**:



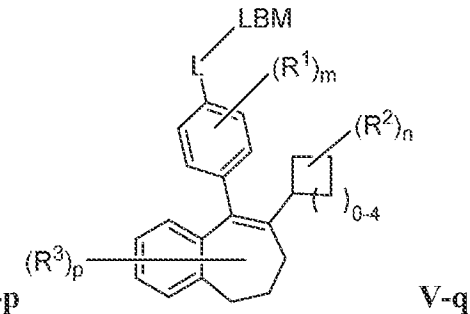
V-n



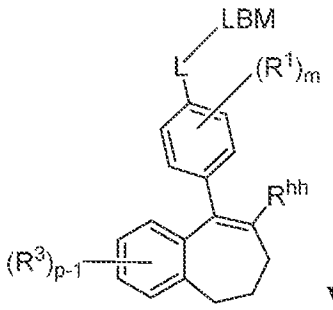
V-o



V-p



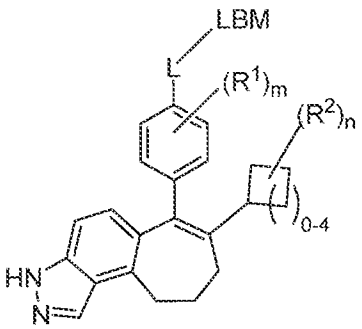
V-q



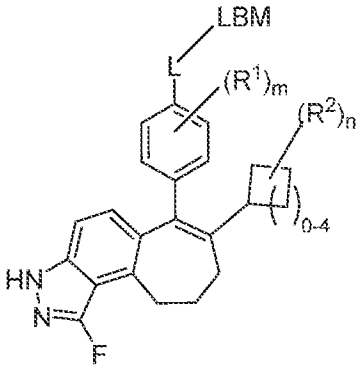
V-r

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is $-C_1-C_6$ alkyl substituted with 0, 1, 2, or 3 instances of –F.

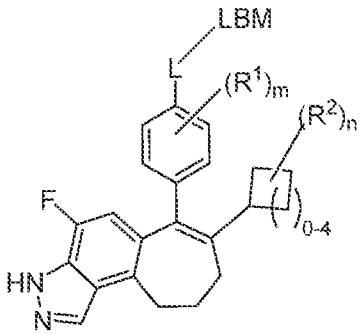
51. The compound of claim 1, wherein the compound is a compound of one of formulas **V-s**, **V-t**, **V-u**, **V-v**, **V-w**, **V-x** or **V-y**:



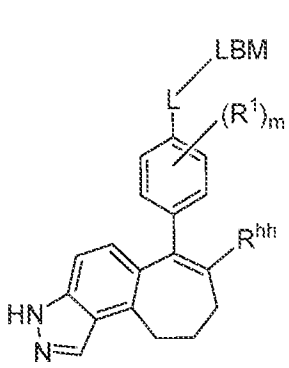
V-s



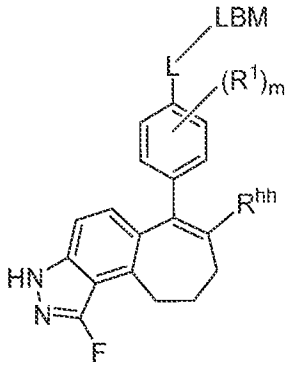
V-t



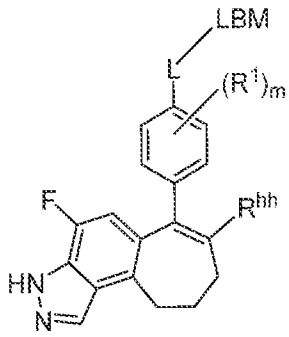
V-u



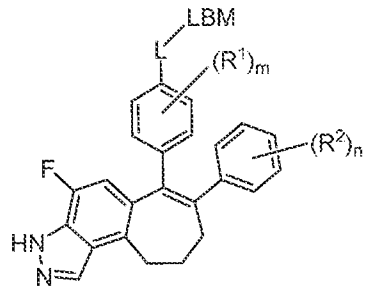
V-v



V-w



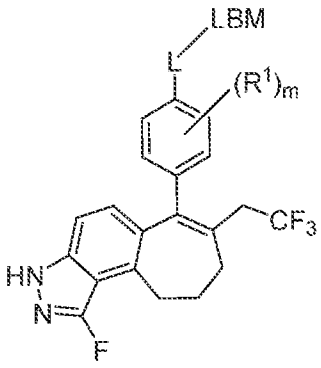
V-x



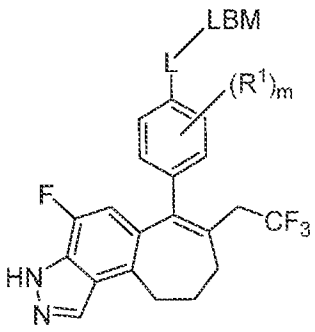
V-y

or a pharmaceutically acceptable salt thereof, wherein R^{hh} is –C_1–C_6 alkyl substituted with 0, 1, 2, or 3 instances of –F.

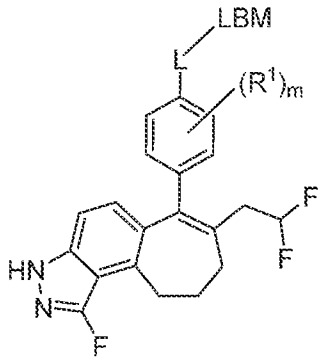
52. The compound of claim 1, wherein the compound is a compound of one of formulas **V-z**, **V-aa**, **V-bb**, **V-cc**, **V-dd**, **V-ee**, **V-ff**, **V-gg** or **V-hh**:



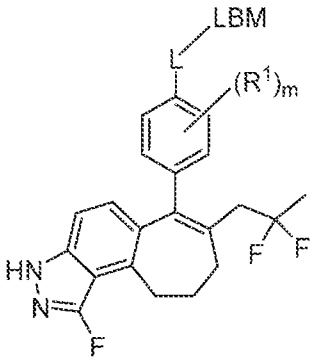
V-z



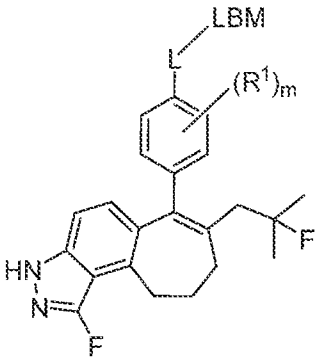
V-aa



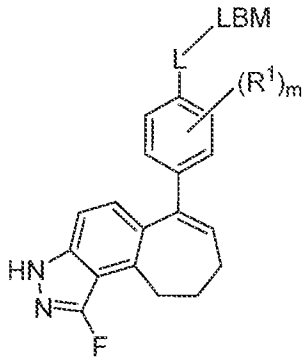
V-bb



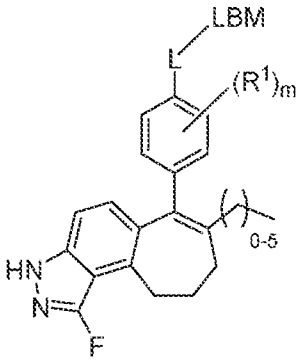
V-cc



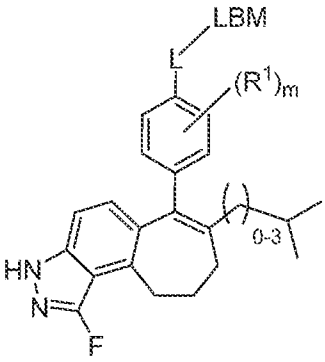
V-dd



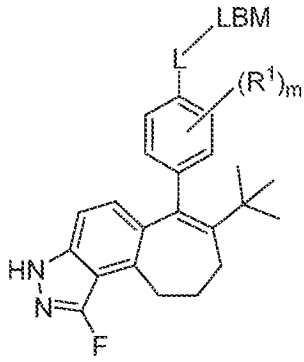
V-ee



V-ff



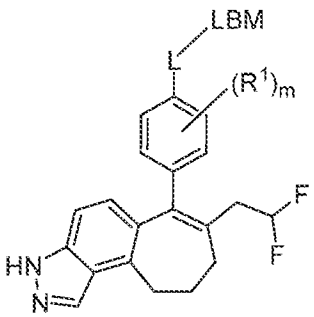
V-gg



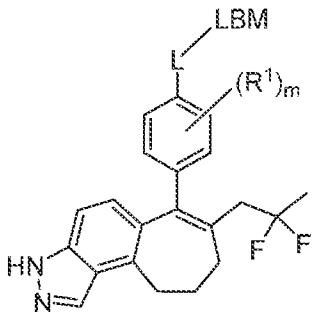
V-hh

or a pharmaceutically acceptable salt thereof.

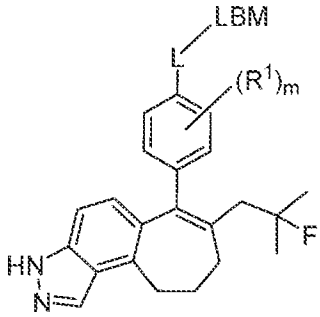
53. The compound of claim 1, wherein the compound is a compound of one of formulas **V-ii**, **V-jj**, **V-kk**, **V-ll**, **V-mm**, **V-nn**, **V-oo**, **V-pp**, **V-qq**, **V-rr**, **V-ss**, **V-tt**, **V-uu**, or **V-vv**:



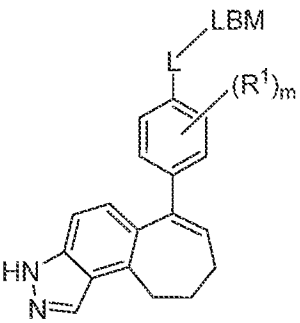
V-ii

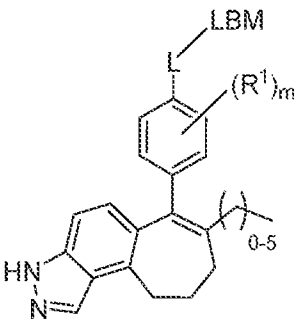


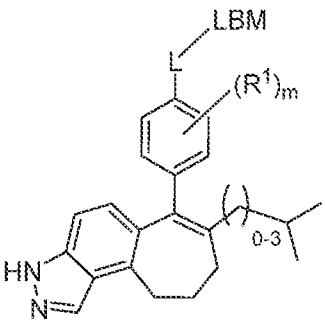
V-jj



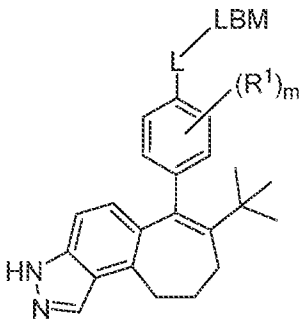
V-kk



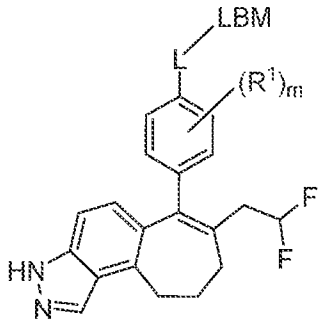




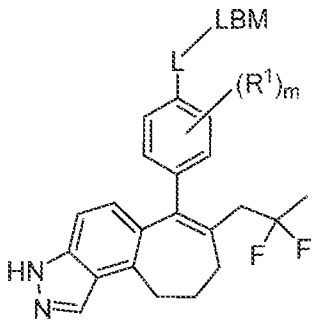
V-ll



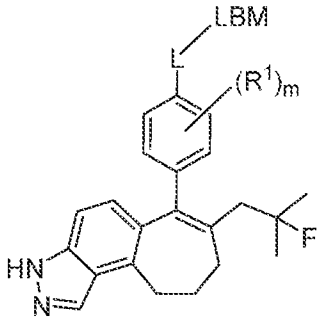
V-mm



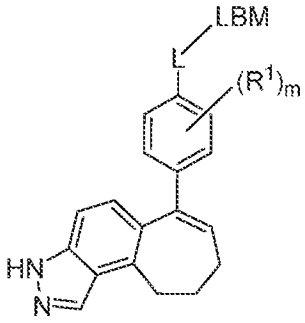
V-nn



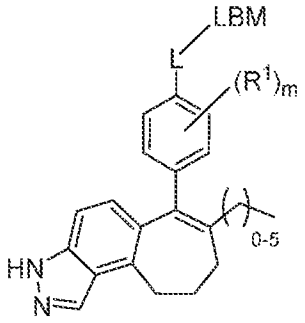
V-oo



V-pp



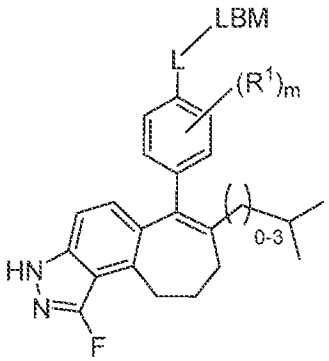
V-qq

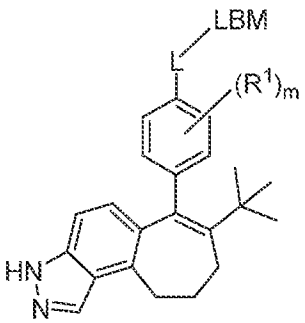


V-rr

V-ss

V-tt



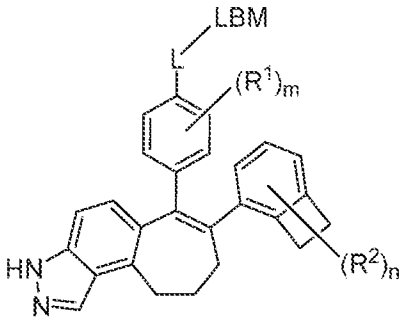


V-uu

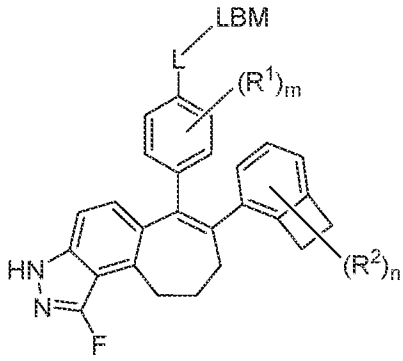
V-vv

or a pharmaceutically acceptable salt thereof.

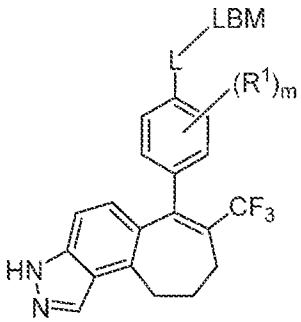
54. The compound of claim 1, wherein the compound is a compound of one of formulas **V-ww**, **V-xx**, **V-yy**, **V-zz**, **V-aa-1**, **V-bb-1**, **V-cc-1**, **V-dd-1**, **V-ee-1**, **V-ff-1**, **V-gg-1**, **V-hh-1**, **V-ii-1**, **V-jj-1**, **V-kk-1**, or **V-ll-1**:



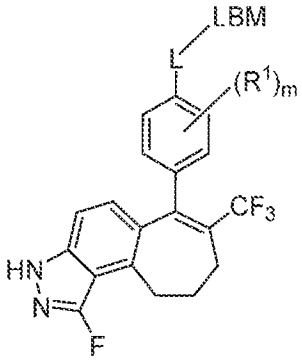
V-ww



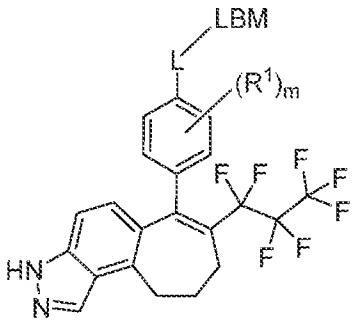
V-xx



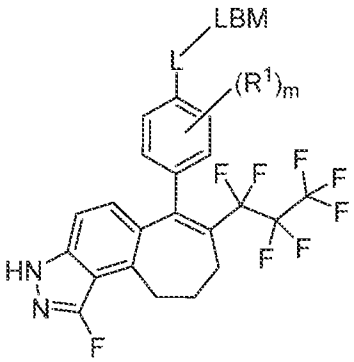
V-yy



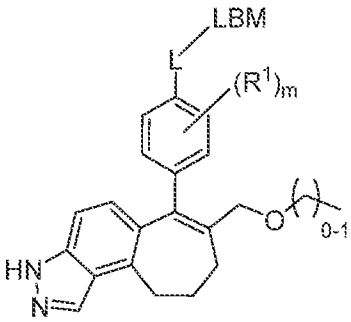
V-zz



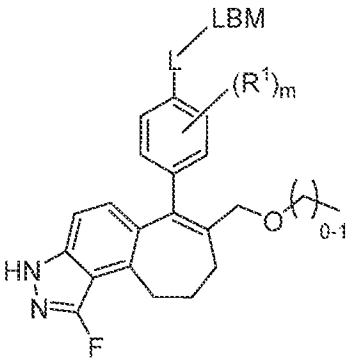
V-aa-1



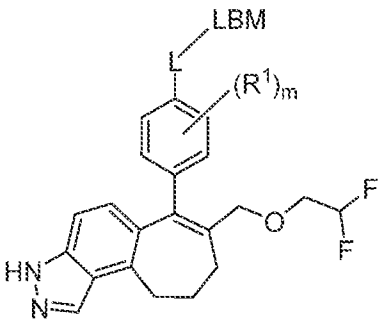
V-bb-1



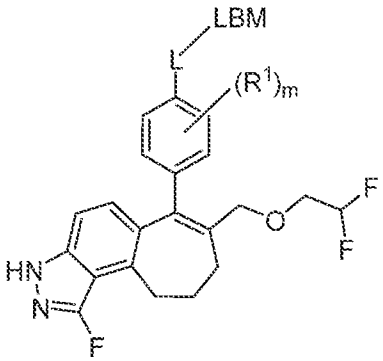
V-cc-1



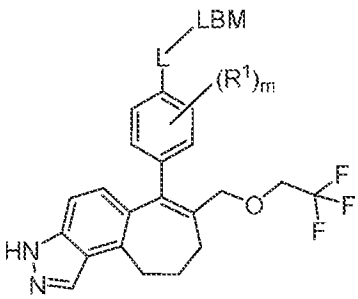
V-dd-1



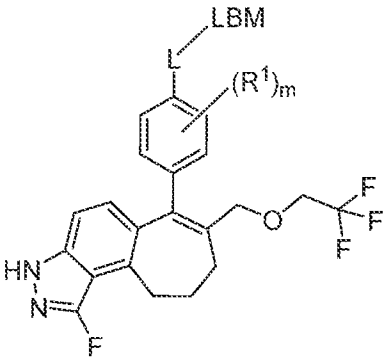
V-ee-1



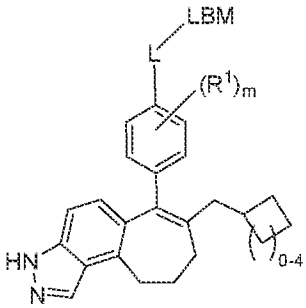
V-ff-1



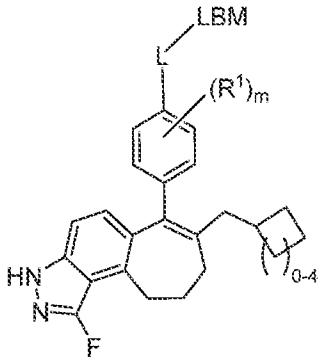
V-gg-1



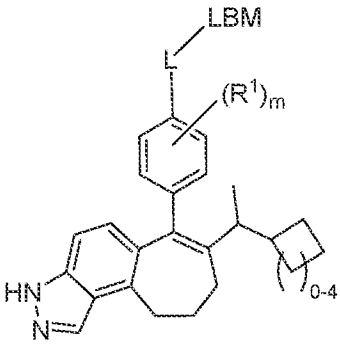
V-hh-1



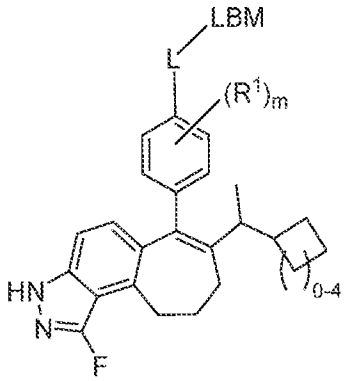
V-ii-1



V-jj-1



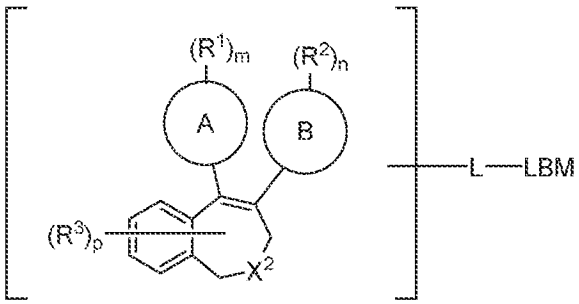
V-kk-1



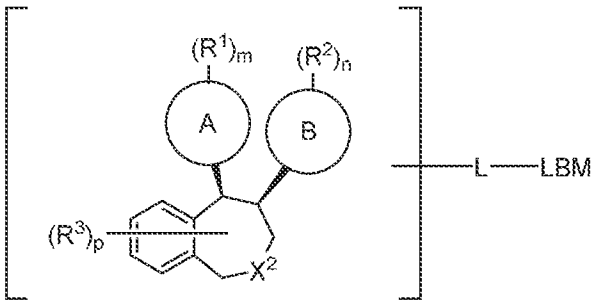
V-ll-1

or a pharmaceutically acceptable salt thereof.

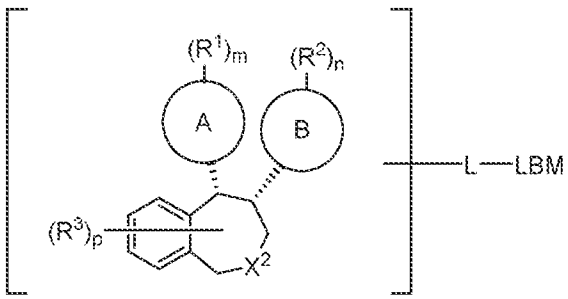
55. The compound of claim 1, wherein the compound is a compound of one of formulas **VI-a**, **VI-b**, **VI-c**, **VI-d**, **VI-e**, or **VI-f**:

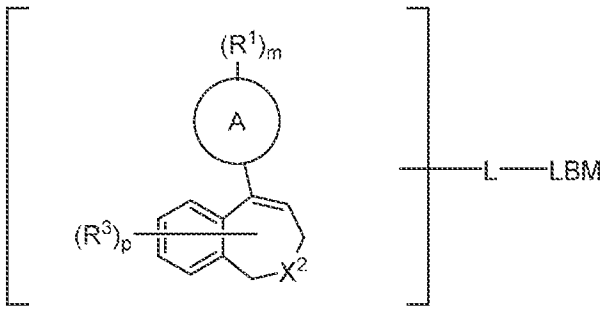


VI-a

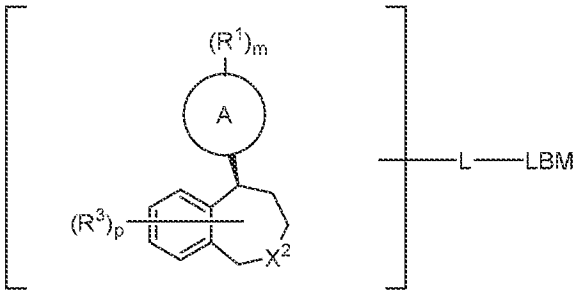


VI-b

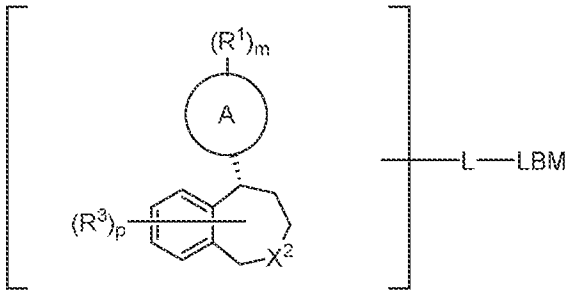




VI-c



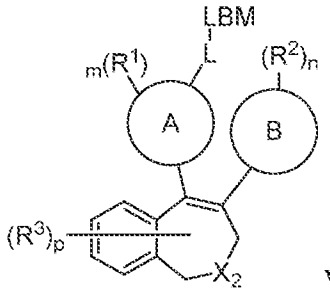
VI-d



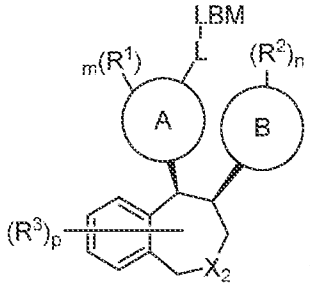
VI-e VI-f

or a pharmaceutically acceptable salt thereof.

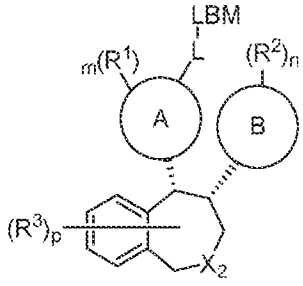
56. The compound of claim 1, wherein the compound is a compound of one of formulas **VI-a-1**, **VI-b-1**, **VI-c-1**, **VI-d-1**, **VI-e-1**, or **VI-f-1**:



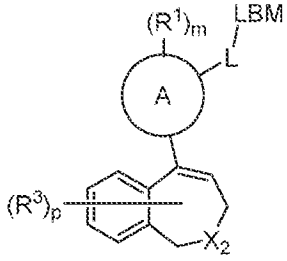
VI-a-1



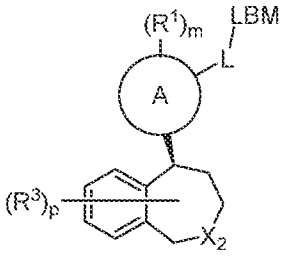
VI-b-1



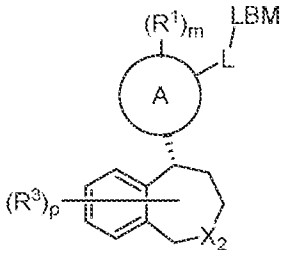
VI-c-1



VI-d-1



VI-e-1



VI-f-1

or a pharmaceutically acceptable salt thereof.

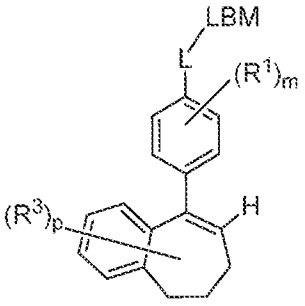
57. The compound of claim 55 or 56, wherein X^2 is selected from –CH(R^{A1})–, –C(R^{A1})$_2$–, –O–, –S–, –S(O)$_2$–, and –N(R^{A2})–.

58. The compound of claim 57, wherein X^2 is selected from –CH(R^{A1})–, –C(R^{A1})$_2$– and –O–.

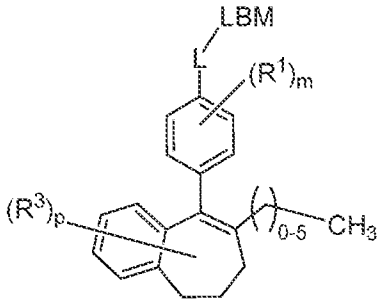
59. The compound of claim 58, wherein X^2 is –CH(R^{A1})– or –C(R^{A1})$_2$–.

60. The compound of claim 57, wherein X^2 is –O–.

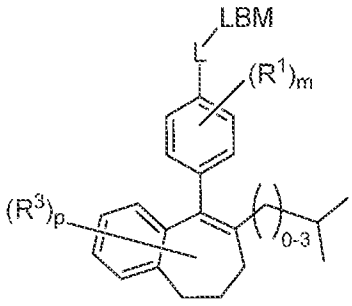
61. The compound of claim 1, wherein the compound is a compound of one of formulas **VII-a**, **VII-b**, **VII-c**, **VII-d**, **VII-e**, **VII-f**, **VII-g**, or **VII-h**:



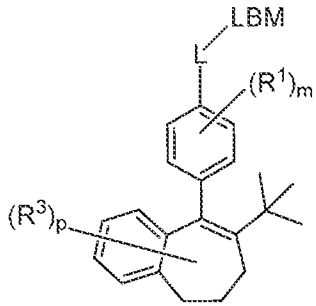
VII-a



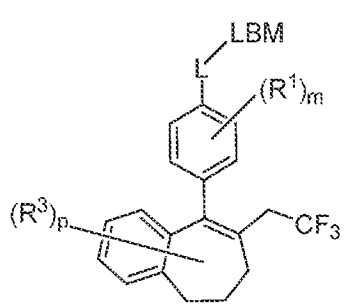
VII-b



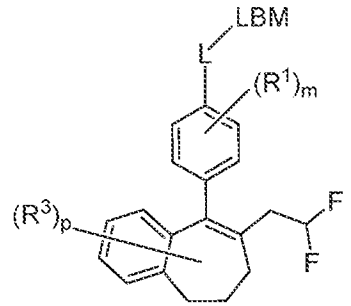
VII-c



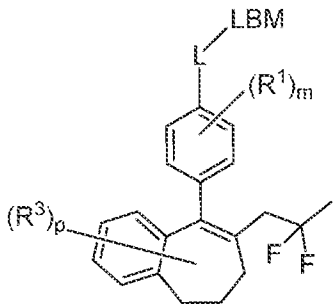
VII-d



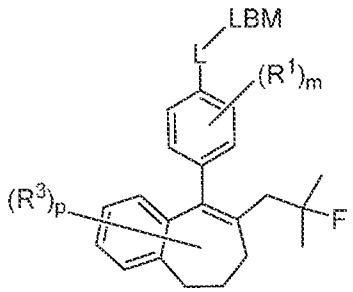
VII-e



VII-f

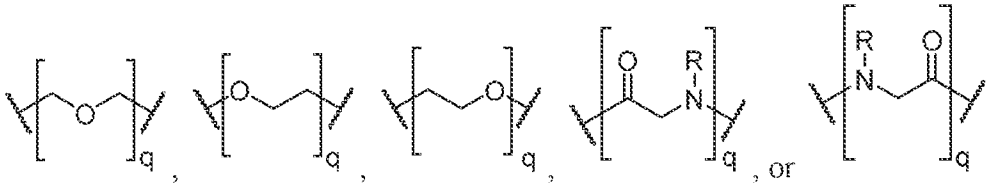


VII-g

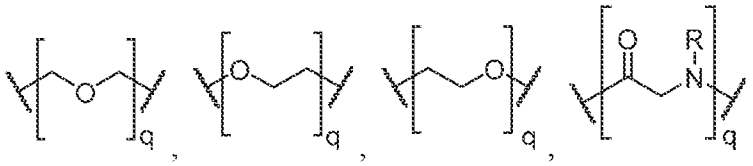
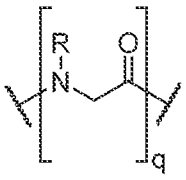


VII-h

or a pharmaceutically acceptable salt thereof.

62. The compound of any one of claims 1-61, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy–, –CH(R)–, –$C(R)_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –$S(O)_2$–, –$NRS(O)_2$–, –$S(O)_2NR$–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–, 

, or .

63. The compound of any one of claims 1-61, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 0, 1, 2 or 3 methylene units of L are independently replaced by –Cy–, –CH(R)–, –C(R)$_2$–, –O–, –NR–, –S–, –OC(O)–, –C(O)O–, –C(O)–, –S(O)–, –S(O)$_2$–, –NRS(O)$_2$–, –S(O)$_2$NR–, –NRC(O)–, –C(O)NR–, –OC(O)NR–, –NRC(O)O–,  , or  .

64. The compound of any one of claims 1-61, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 1, 2 or 3 methylene units of L are independently replaced by –Cy–, –CH(R)–, –C(R)$_2$–, –O– or–NR– .

65. The compound of any one of claims 1-61, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{3-5} hydrocarbon chain, wherein 1, 2 or 3 methylene units of L are independently replaced by –Cy– or–NR– .

66. The compound of any one of claims 1-65, wherein each –Cy– is independently an optionally substituted bivalent ring selected from a 4-7 membered saturated or partially unsaturated monocyclic carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated monocyclic heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-11 membered monocyclic saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur and a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl having 1185-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

67. The compound of any one of claims 1-65, wherein each –Cy– is independently an optionally substituted bivalent ring selected from a 4-7 membered saturated or partially

unsaturated monocyclic carbocyclylenyl, a 5-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated monocyclic heterocyclylenyl containing 1-2 nitrogen atoms, a 5-11 membered monocyclic saturated or partially unsaturated spiro heterocyclylenyl containing 1-2 nitrogen atoms, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl containing 1-2 nitrogen atoms, and a 6-10 membered bridged bicyclic saturated or partially unsaturated heterocyclylenyl containing 1-2 nitrogen atoms.

68. The compound of any one of claims 1-65, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from $–C_1–C_4$ alkyl, $–C_1–C_4$ haloalkyl, $–C_3–C_7$ cycloalkyl, $–O–C_1–C_4$ alkyl, halo, cyano, –OH, $–NH_2$, $–N(H)(C_1–C_4$ alkyl) and $–N(C_1–C_4$ alkyl$)_2$.

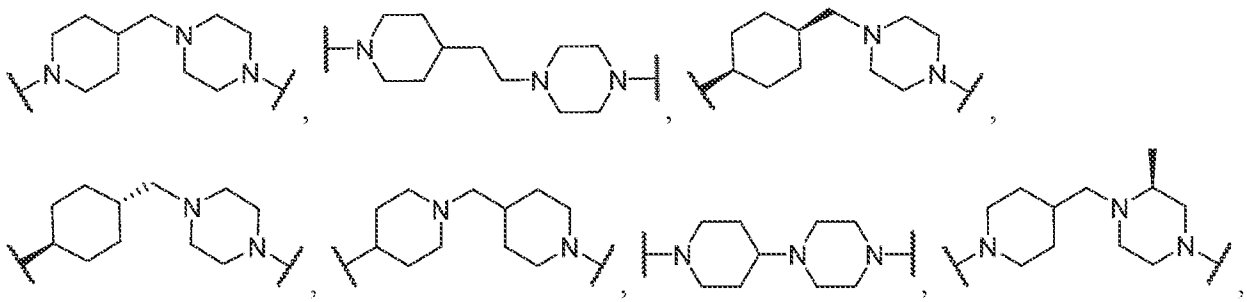
69. The compound of any one of claims 1-65, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from –Me, –Et, –Pr, $–^i$Pr, cyclopropyl, $–CF_3$, –OMe, –F, –Cl, –CN, $–NH_2$, –NHMe and $–NMe_2$.

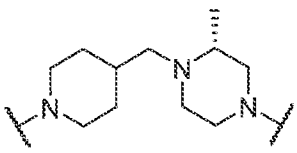
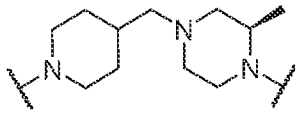
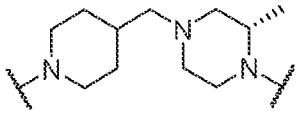
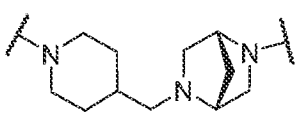
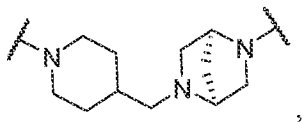
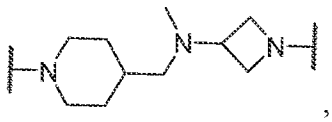
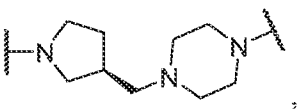
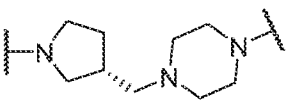
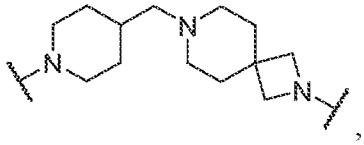
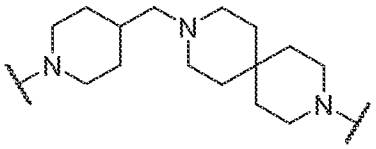
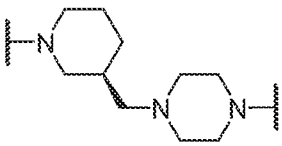
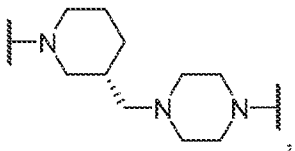
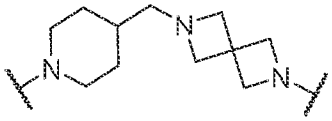
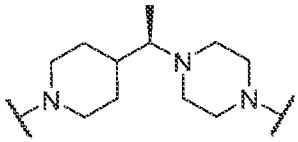
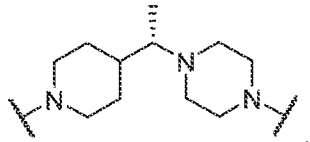
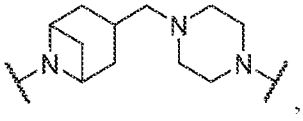
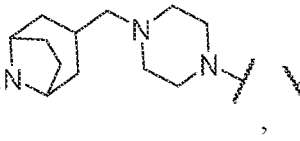
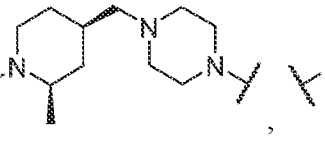
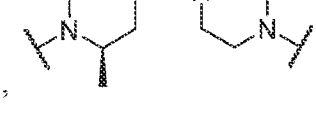
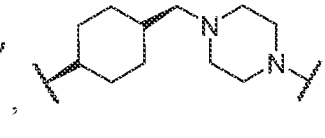
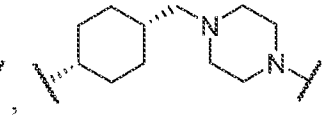
70. The compound of any one of claims 1-65, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 substituents independently selected from Me, –OMe and –F.

71. The compound of any one of claims 1-65, wherein the bivalent ring of each –Cy– is independently substituted with 0, 1 or 2 instances of Me.

72. The compound of any one of claims 1-65, wherein the bivalent ring of each –Cy– is unsubstituted.

73. The compound of any one of claims 1-72, wherein L is selected from



 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
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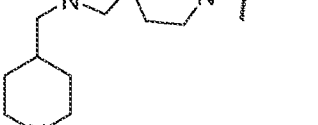 ,
,
, and
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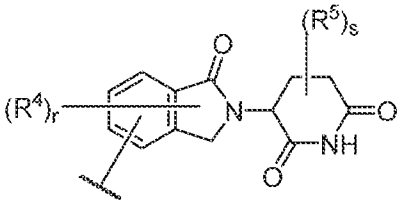
74. The compound of any one of claims 1-73, wherein LBM is selected from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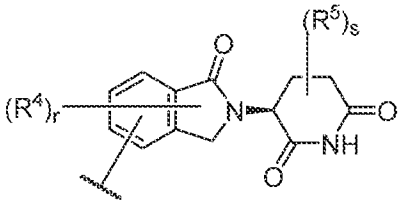
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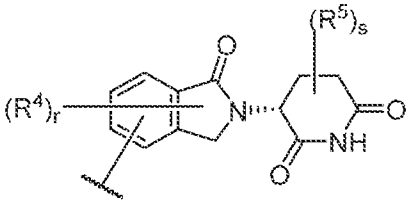
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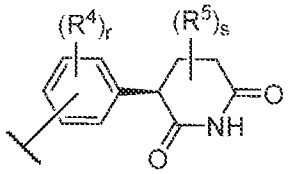
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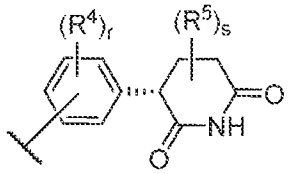
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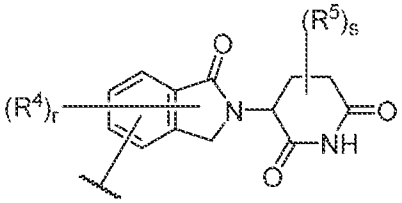
75. The compound of any one of claims 1-73, wherein LBM is selected from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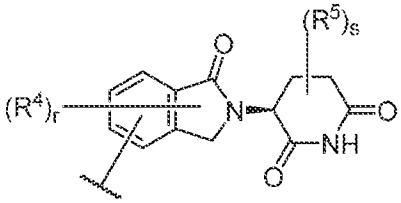
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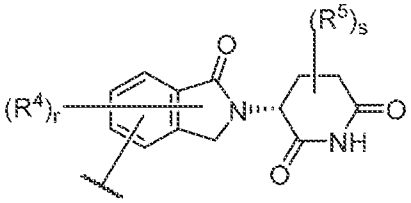

.

76. The compound of any one of claims 1-75, wherein each R^4 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, $–C(O)NR_2$, –C(O)N(R)OR, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$ and $–N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

77. The compound of any one of claims 1-76, wherein each R^4 is independently selected from –Me, –Et, –F, –Cl, $–CF_3$, –CN, –OH, –OMe, $–NH_2$, –NHMe and $–NMe_2$.

78. The compound of any one of claims 1-77, wherein each R^5 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, $–C(O)NR_2$, –C(O)N(R)OR, –

$OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2NR_2$ and $-N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

79. The compound of any one of claims 1-78, wherein each R^5 is independently selected from –Me, –Et, –F, –Cl, $-CF_3$, –CN, –OH, –OMe, $-NH_2$, –NHMe and $-NMe_2$.

80. The compound of any one of claims 1-79, wherein each R^5 is independently selected from –Me and –F.

81. The compound of any one of claims 1-80, wherein r is 0, 1 or 2.

82. The compound of any one of claims 1-81, wherein r is 0.

83. The compound of any one of claims 1-81, wherein r is 1.

84. The compound of any one of claims 1-81, wherein r is 2.

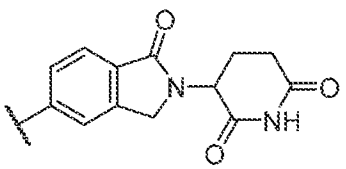
85. The compound of any one of claims 1-84, wherein s is 0, 1 or 2.

86. The compound of any one of claims 1-85, wherein s is 0.

87. The compound of any one of claims 1-85, wherein s is 1.

88. The compound of any one of claims 1-85, wherein s is 2.

89. The compound of any one of claims 1-88, wherein LBM is selected from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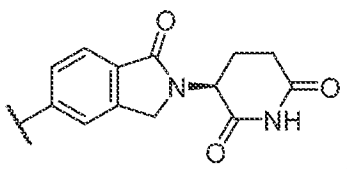
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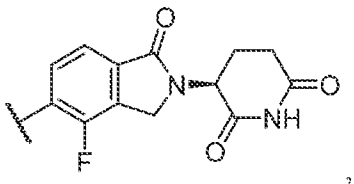
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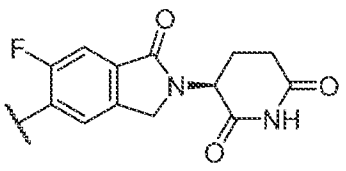
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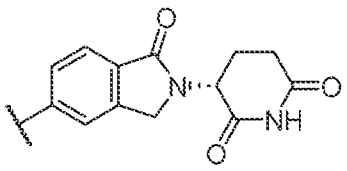
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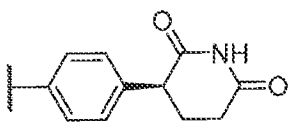
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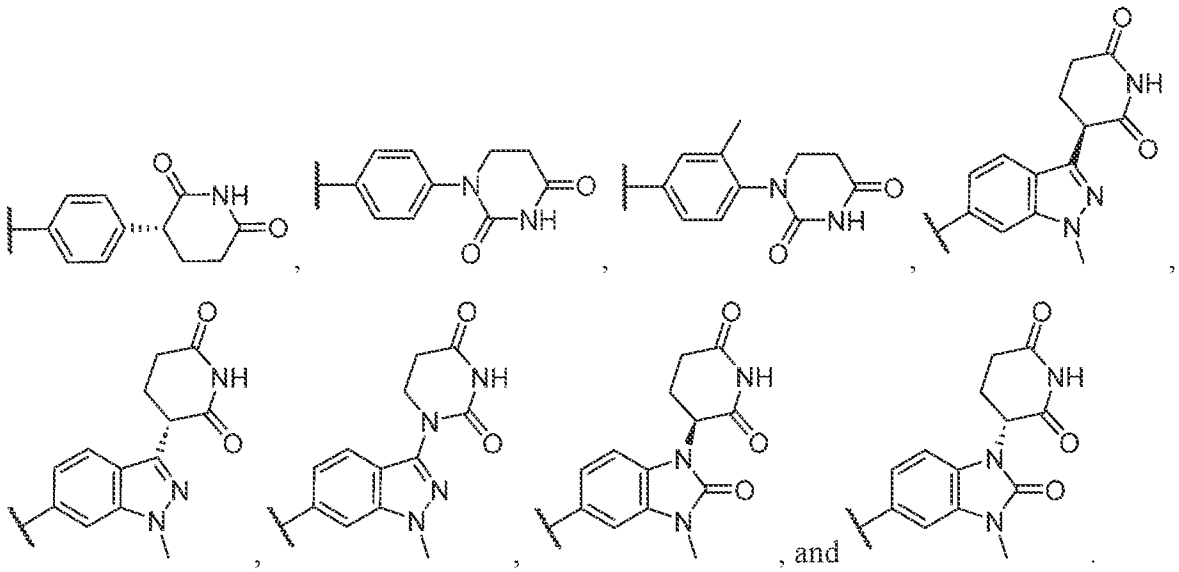
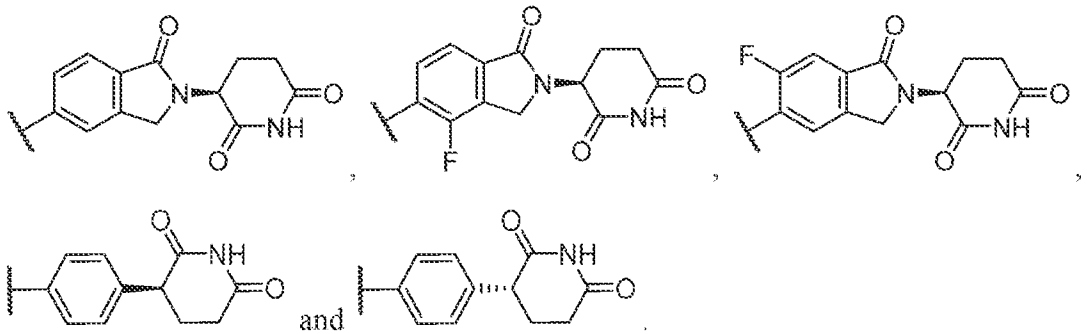
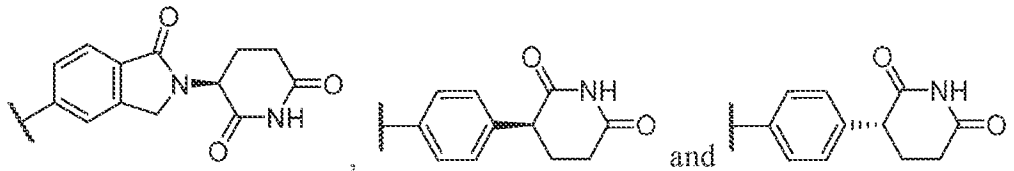


90. The compound of any one of claims 1-88, wherein LBM is selected from



91. The compound of any one of claims 1-88, wherein LBM is selected from



92. The compound of any one of claims 1-91, wherein each R^1 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –SR, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, –C(O)N(R)OR, $–OC(O)NR_2$, –N(R)C(O)OR, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$ and $–N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain substituted with 0-3 instances of halo.

93. The compound of any one of claims 1-92, wherein each R^1 is independently selected from –Me, –Et, –F, –Cl, $–SCF_3$, $–OCF_3$, $–CF_3$, –CN, –OH, –OMe, $–NH_2$, –NHMe and $–NMe_2$.

94. The compound of any one of claims 1-93, wherein R^1 is –F.

95. The compound of any one of claims 1-94, wherein each R^2 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, $–C(O)N(R)OR$, $–OC(O)NR_2$, $–N(R)C(O)OR$, –N(R)C(O)R, $–N(R)C(O)NR_2$, $–N(R)S(O)_2NR_2$ and $–N(R)S(O)_2R$, wherein R is –H or a C_{1-6} aliphatic chain.

96. The compound of any one of claims 1-95, wherein each R^2 is independently selected from –Me, –Et, –F, –Cl, $–CF_3$, $–CHF_2$, –CN, –OH, –OMe, $–OCF_3$, $–NH_2$, –NHMe and $–NMe_2$.

97. The compound of any one of claims 1-96, wherein each R^2 is independently selected from –Me, –Et, –F, –Cl, $–CF_3$, –CN, –OH, –OMe, $–NH_2$, –NHMe and $–NMe_2$.

98. The compound of any one of claims 1-97, wherein each R^2 is independently selected from –F, –Cl, $–CF_3$, $–CHF_2$, –OH, $–OCF_3$ and $–SCF_3$.

99. The compound of any one of claims 1-98, wherein each R^2 is independently selected from –F, –Cl and $–SCF_3$.

100. The compound of any one of claims 1-99, wherein m is 0, 1 or 2.

101. The compound of any one of claims 1-100, wherein m is 0.

102. The compound of any one of claims 1-100, wherein m is 1.

103. The compound of any one of claims 1-100, wherein m is 2.

104. The compound of any one of claims 1-103, wherein n is 0, 1 or 2.

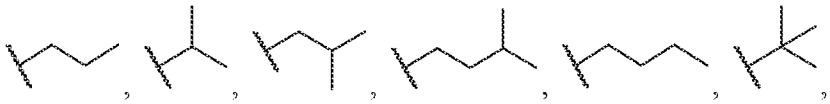
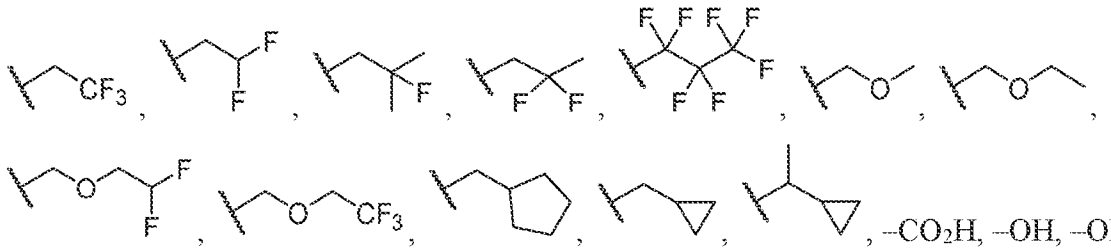
105. The compound of any one of claims 1-104, wherein n is 0.

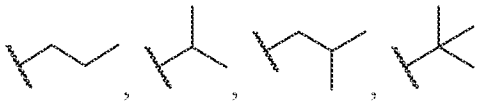
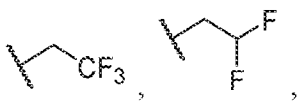
106. The compound of any one of claims 1-104, wherein n is 1.

107. The compound of any one of claims 1-104, wherein n is 2.

108. The compound of any one of claims 1-107, wherein each R^3 is independently selected from deuterium, C_{1-6} aliphatic chain substituted with 0-3 instances of halo, halogen, –CN, –OR, $–NR_2$, $–S(O)_2R$, $–S(O)_2NR_2$, –S(O)R, $–S(O)NR_2$, –S(O)(NR)R, –C(O)OR, $–C(O)NR_2$, –

C(O)N(R)OR, –OC(O)NR$_2$, –N(R)C(O)OR, –N(R)C(O)R, –N(R)C(O)NR$_2$, –N(R)S(O)$_2$NR$_2$, –N(R)S(O)$_2$R and –B(OR)$_2$, wherein R is –H or a C$_{1-6}$ aliphatic chain.

109. The compound of any one of claims 1-108, wherein each R^3 is independently selected from –Me, –Et,  , –F, –CF$_3$,  , –CO$_2$H, –OH, –OMe, and –B(OH)$_2$.

110. The compound of any one of claims 1-109, wherein each R^3 is independently selected from –Me, –Et,  , –F, –Cl, –CF$_3$,  , –CO$_2$H, –CN, –OH, –OMe, –NH$_2$, –NHMe, –NMe$_2$ and –B(OH)$_2$.

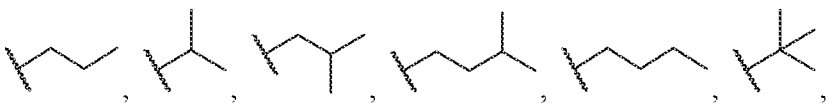
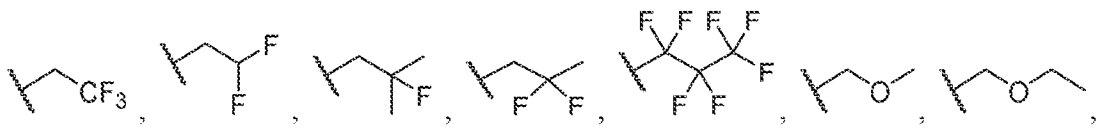
111. The compound of any one of claims 1-110, wherein each R^3 is independently selected from –Me, –Et, –F, –Cl, –CF$_3$,-CO$_2$H, –CN, –OH, –OMe, –NH$_2$, –NHMe and –NMe$_2$.

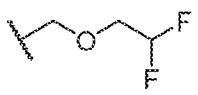
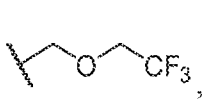
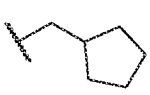
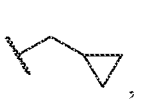
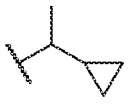
112. The compound of any one of claims 1-111, wherein p is 0, 1 or 2.

113. The compound of any one of claims 1-112, wherein p is 0.

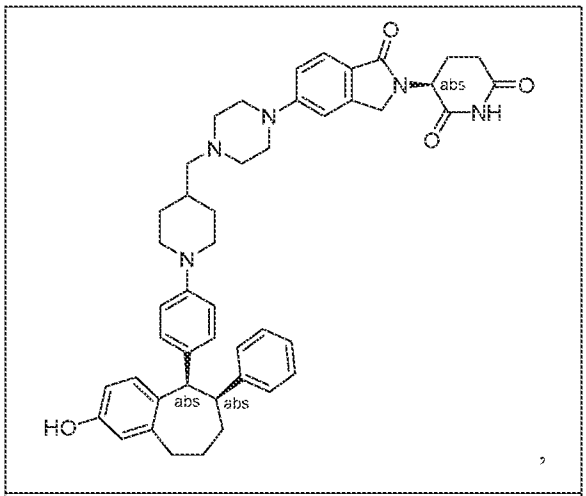
114. The compound of any one of claims 1-112, wherein p is 1.

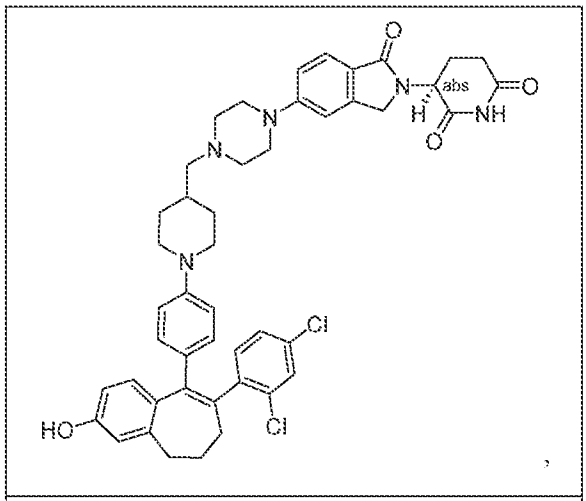
115. The compound of any one of claims 1-112, wherein p is 2.

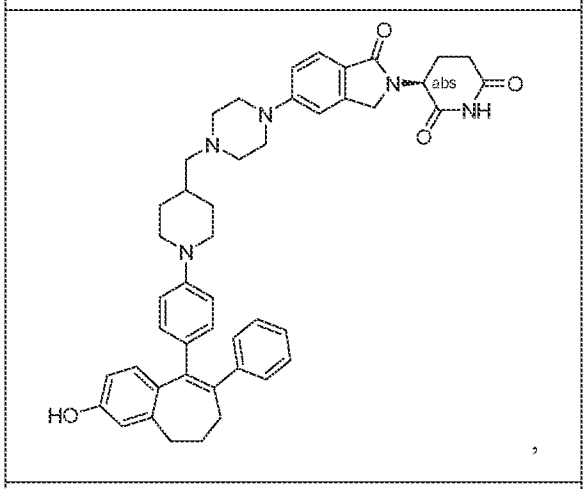
116. The compound of any one of claims 1-115, wherein each R^{hh} is independently selected from–Me, –Et,  , –F, –CF$_3$,  ,

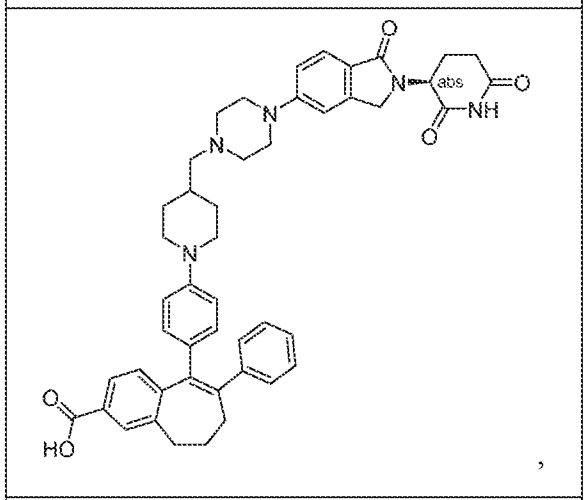
 ,  ,  ,  ,  , –CO_2H, –OH, –OMe, and –$B(OH)_2$.

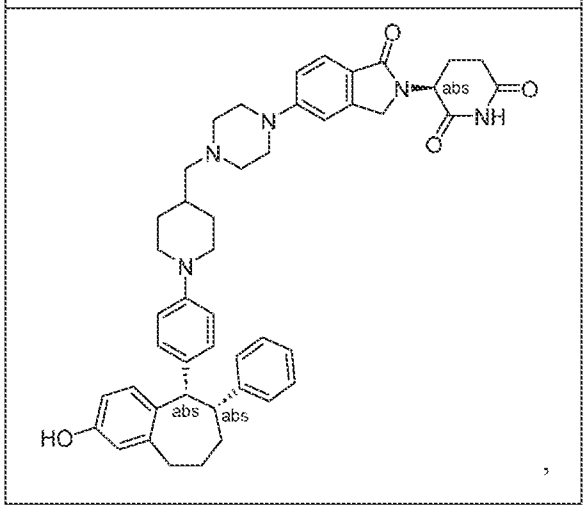
117. A compound selected from:

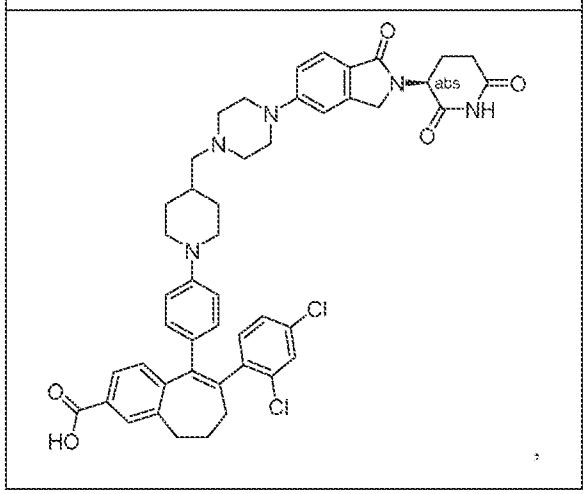
 ,

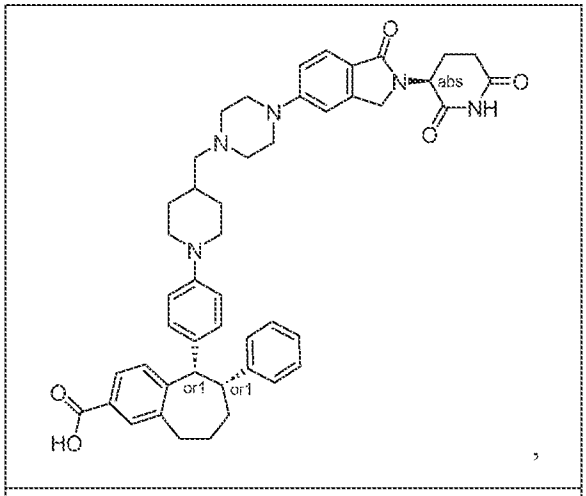
 ,

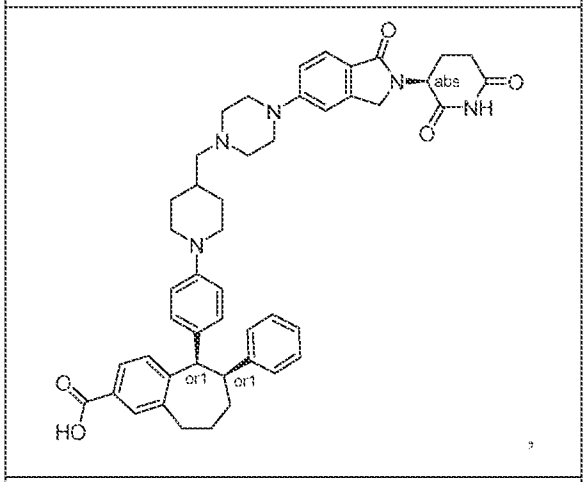
 ,

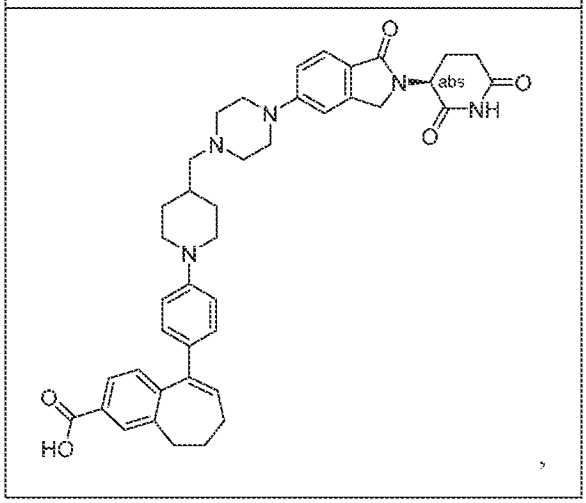
 ,

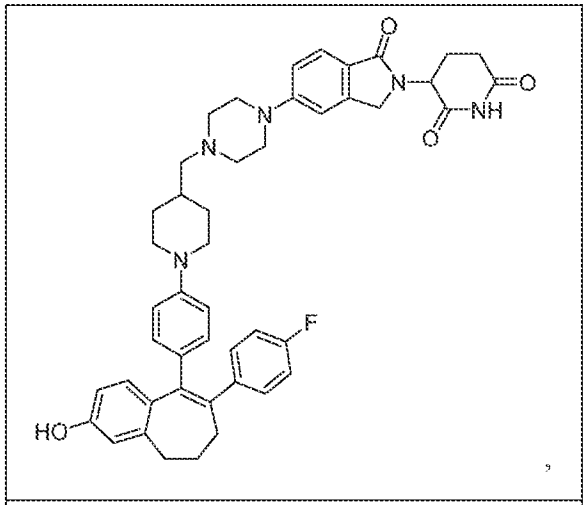
 ,

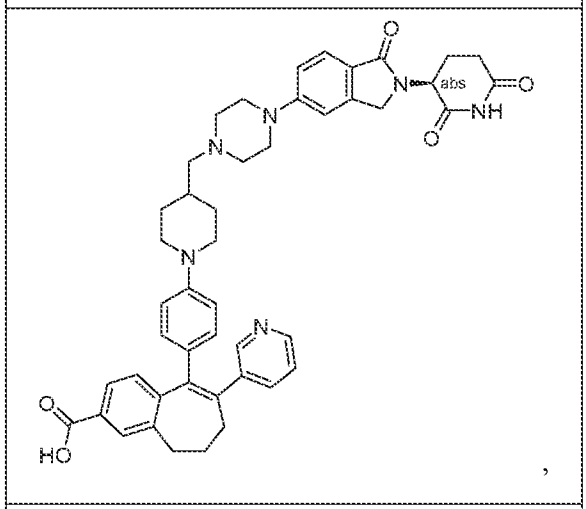
 ,

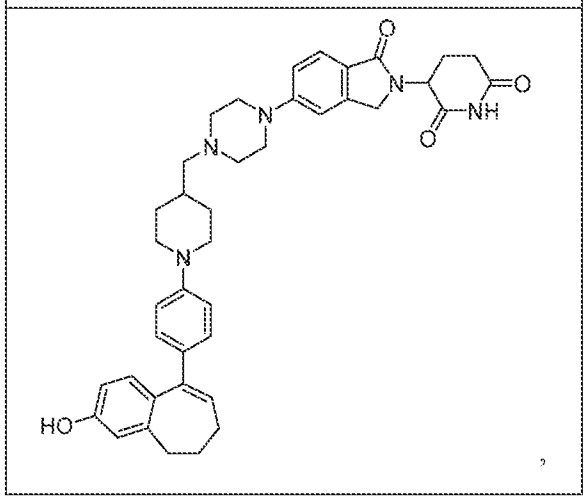


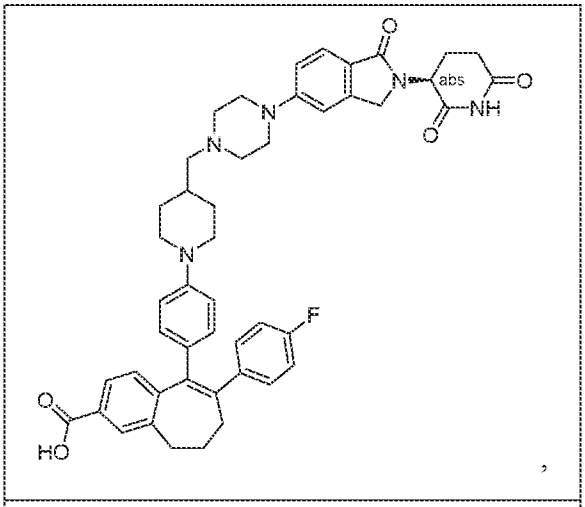


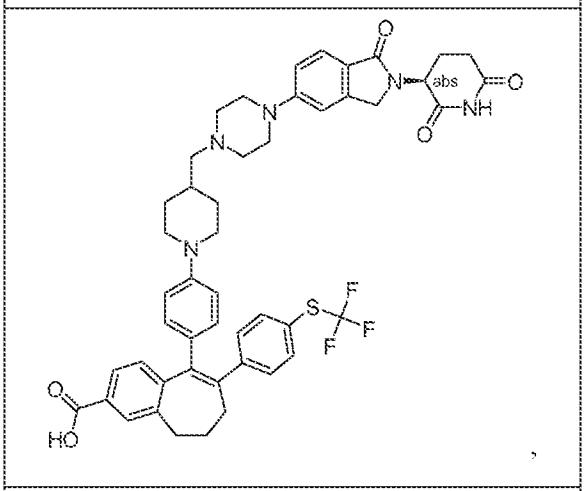


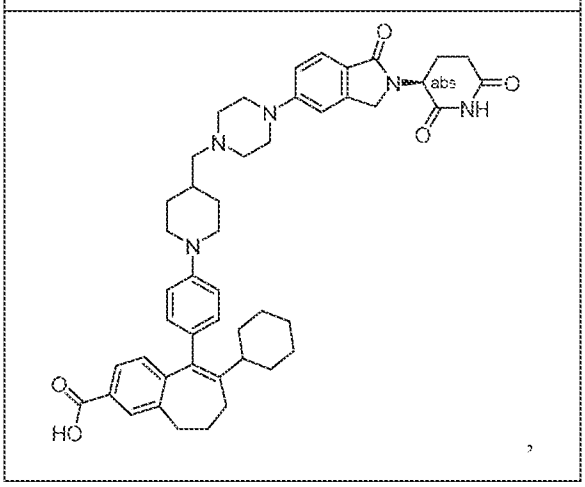


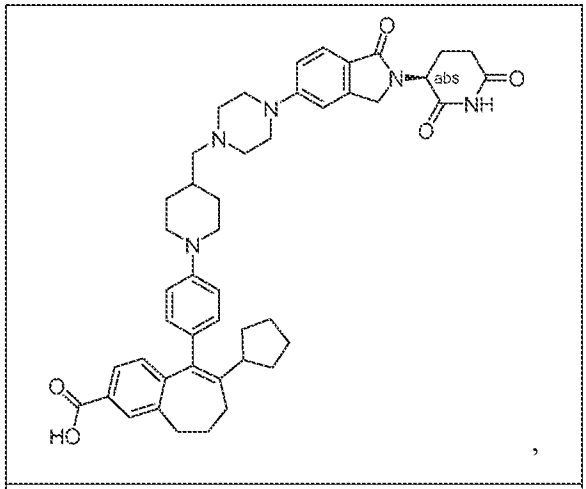


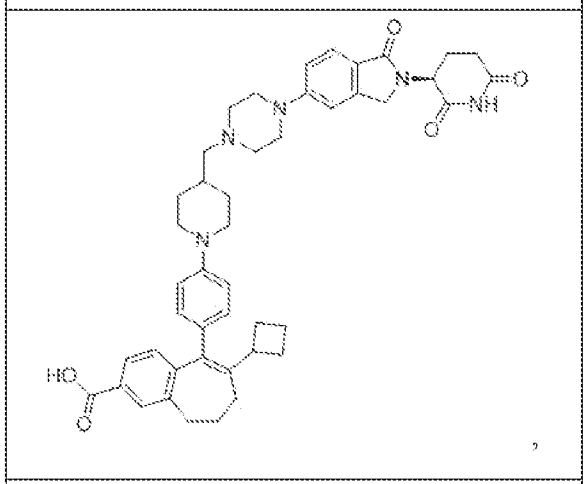


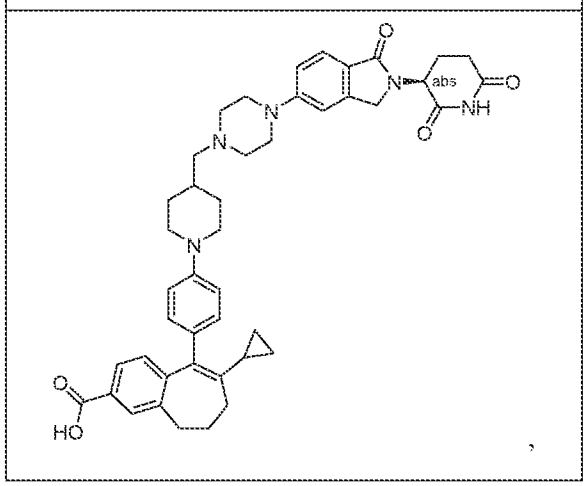


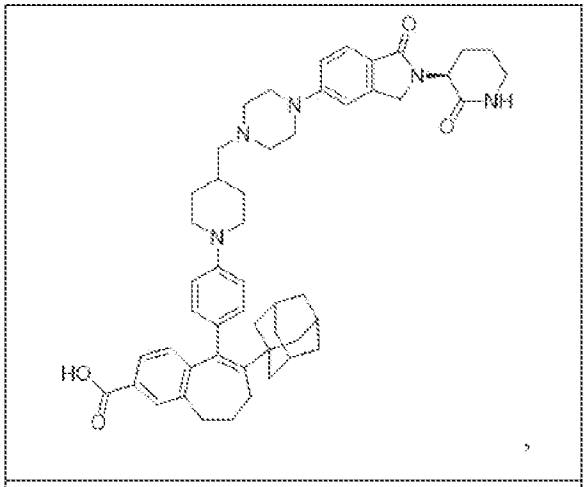


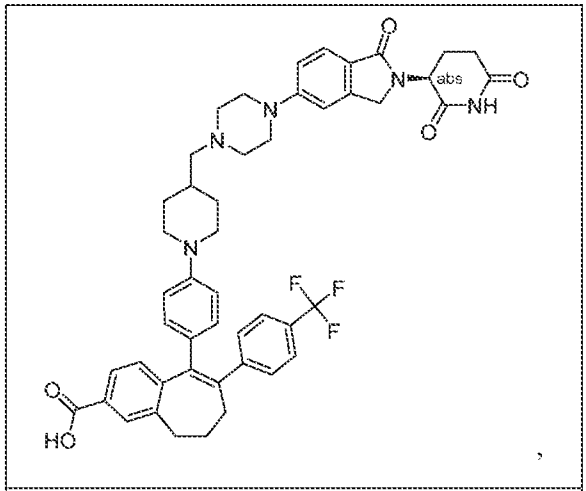


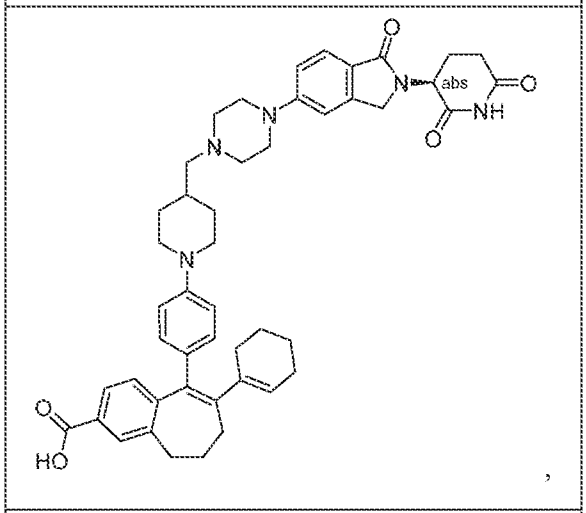


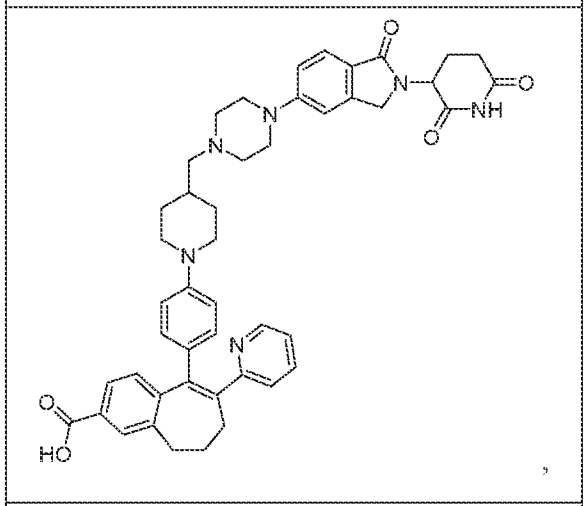


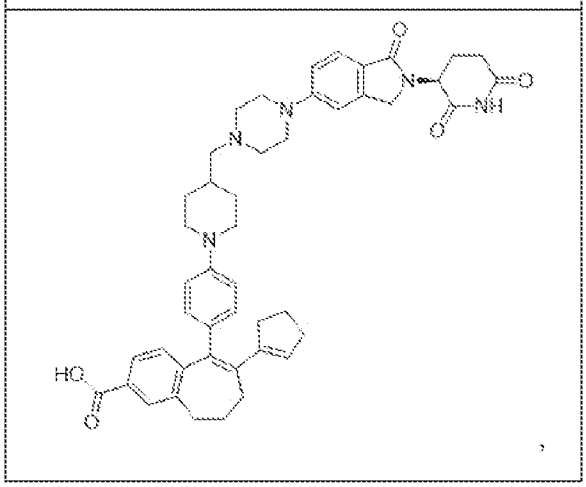


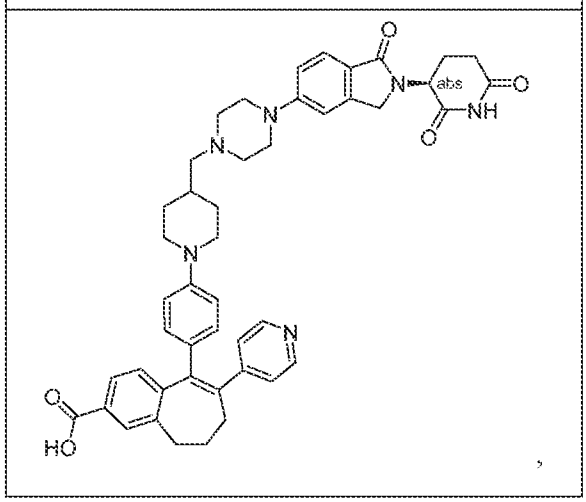


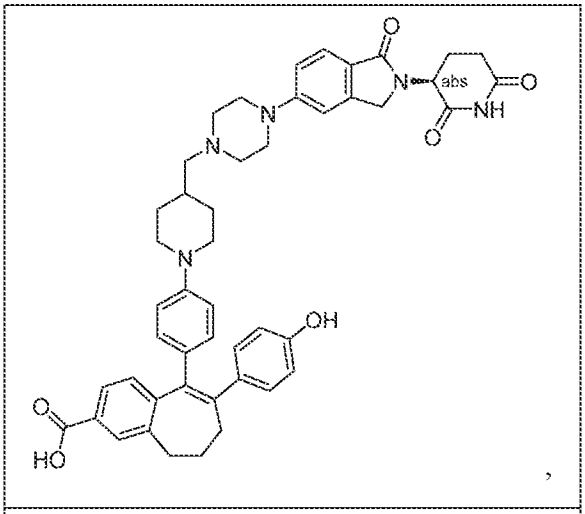


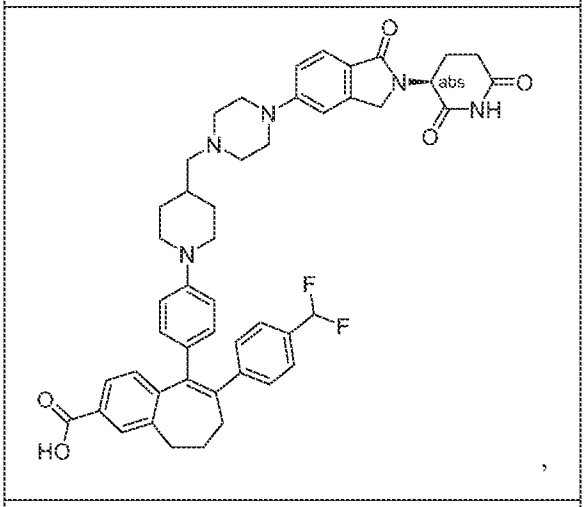


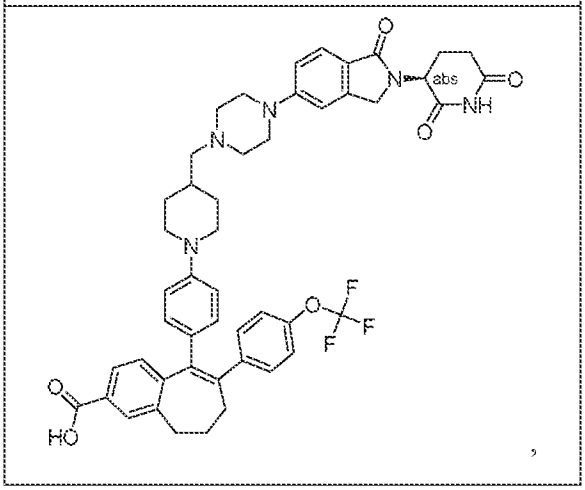


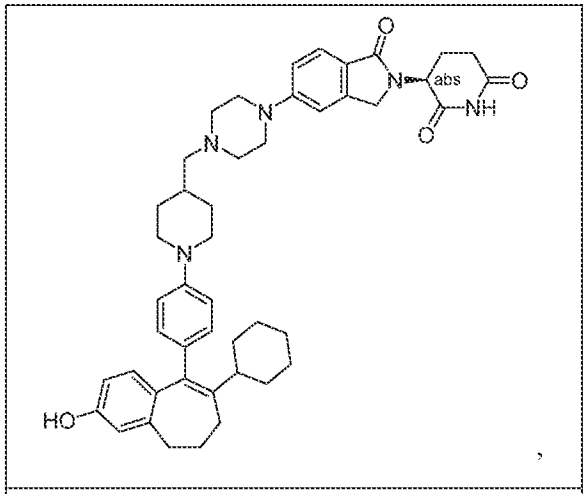


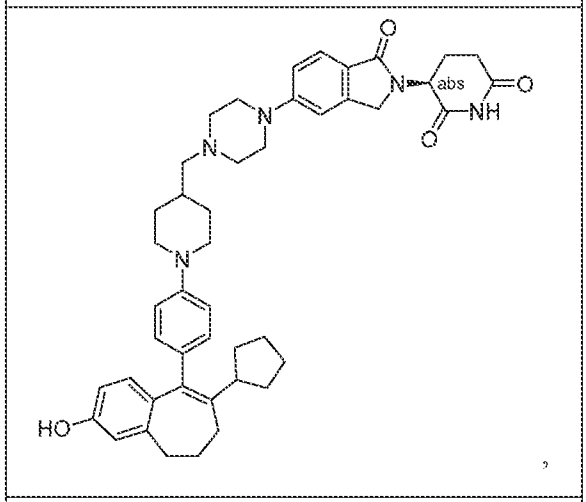


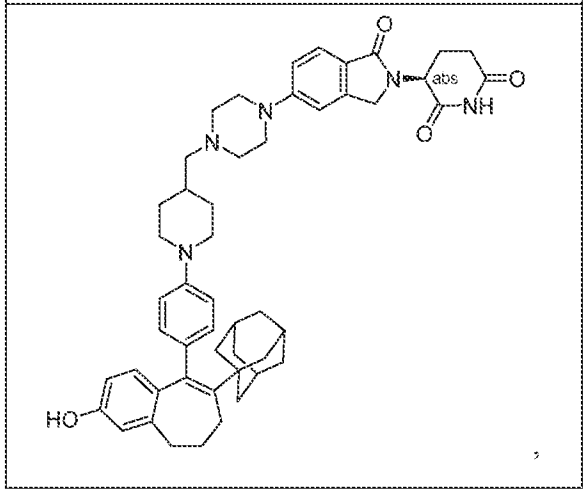


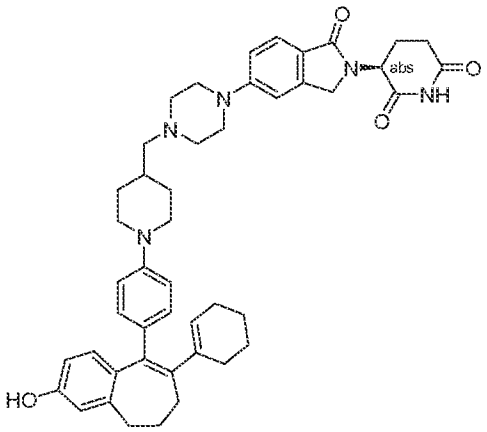












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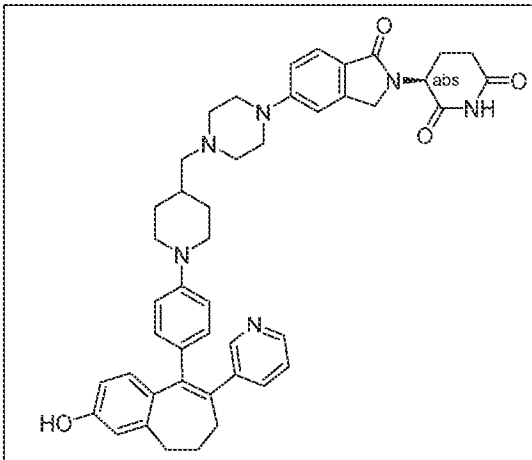

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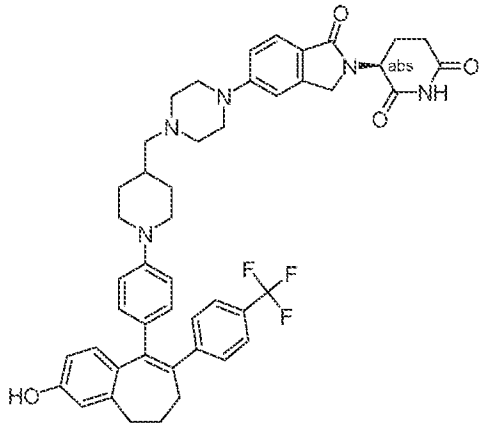

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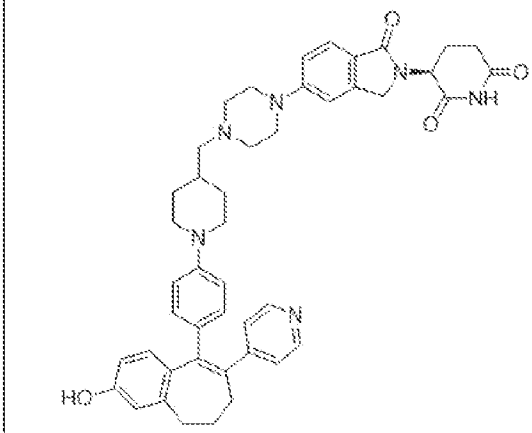

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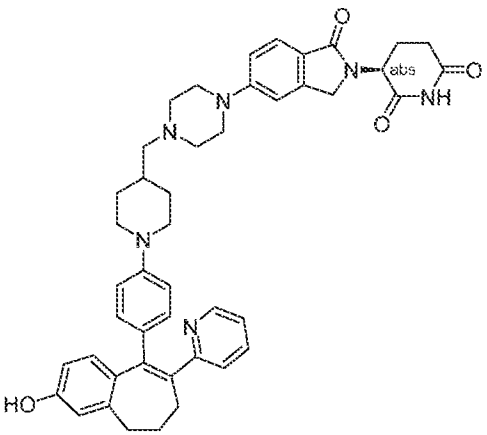

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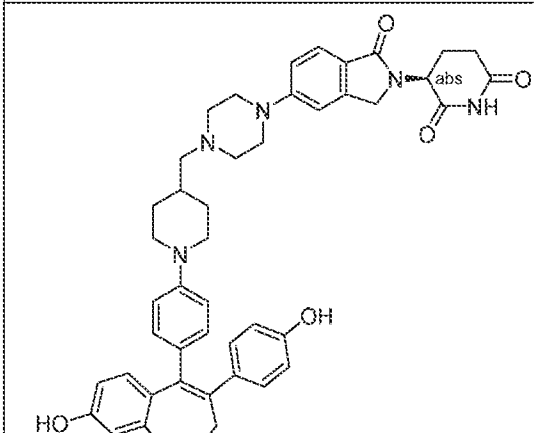

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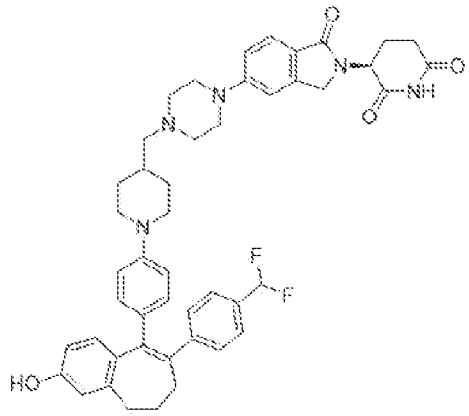

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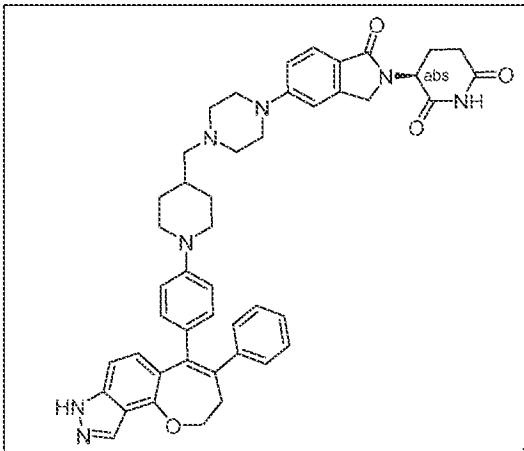

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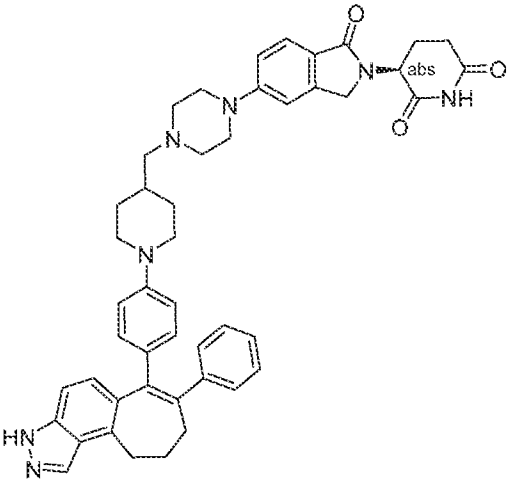

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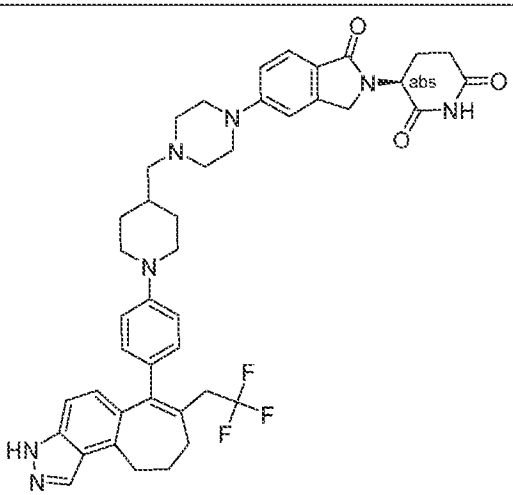

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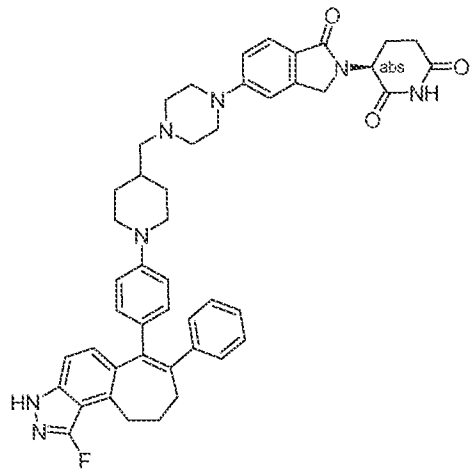

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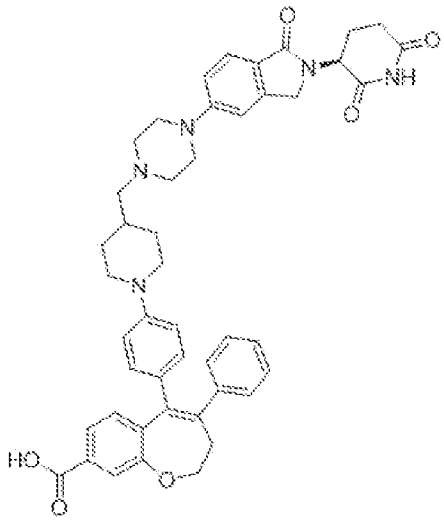

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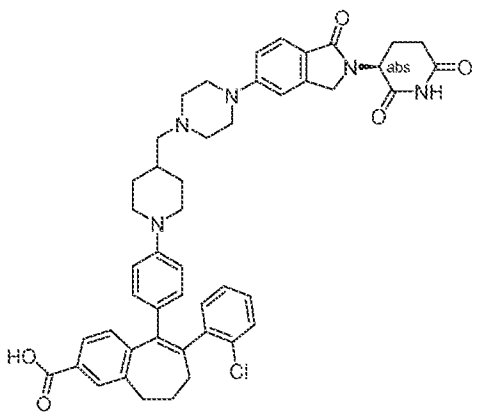

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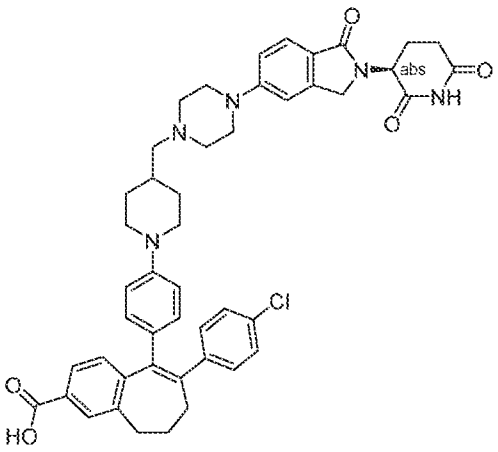

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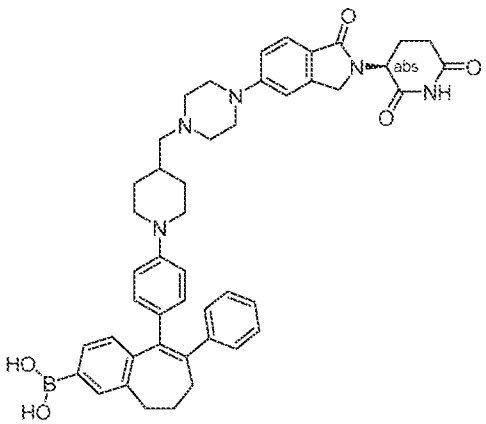

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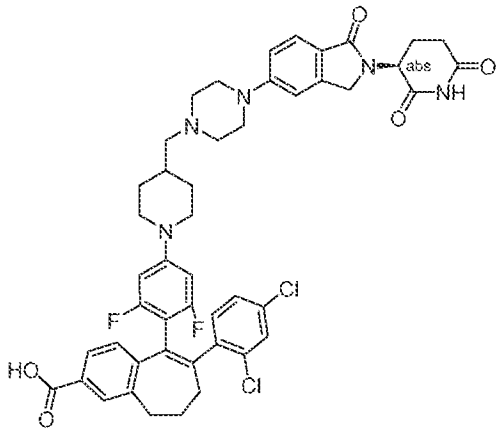

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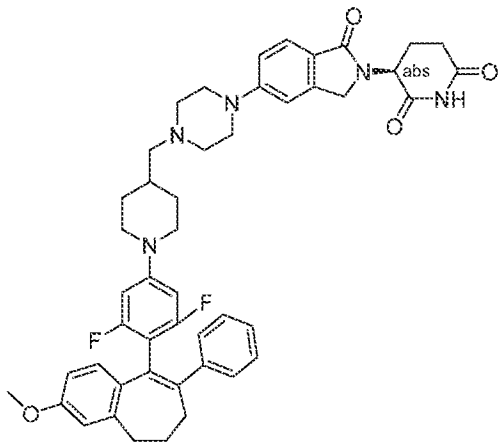

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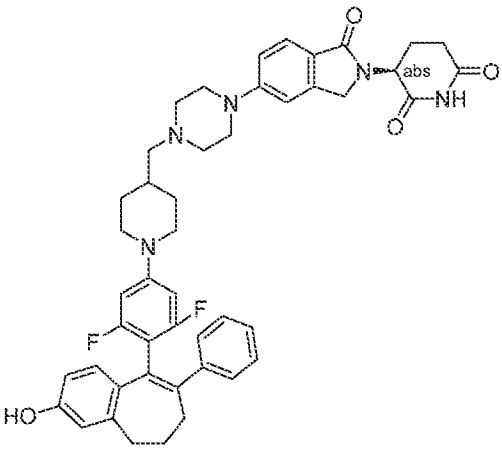

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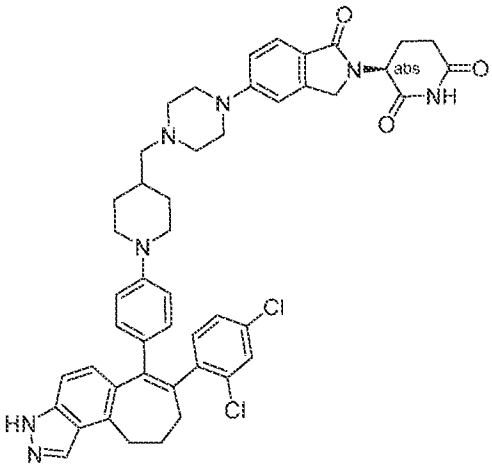

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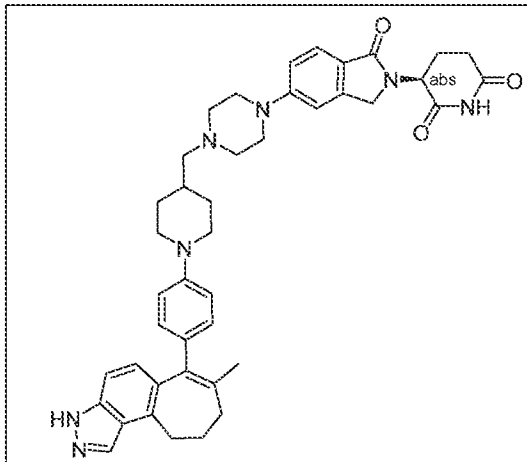

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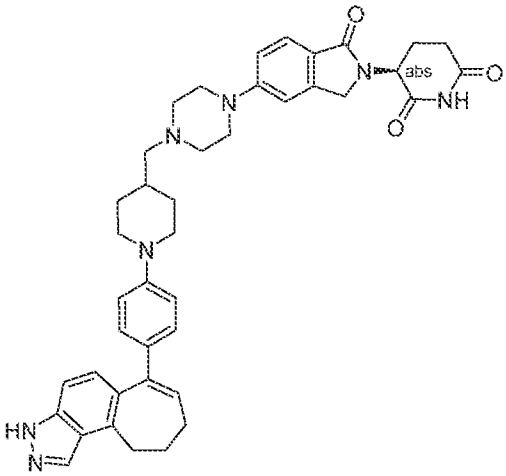

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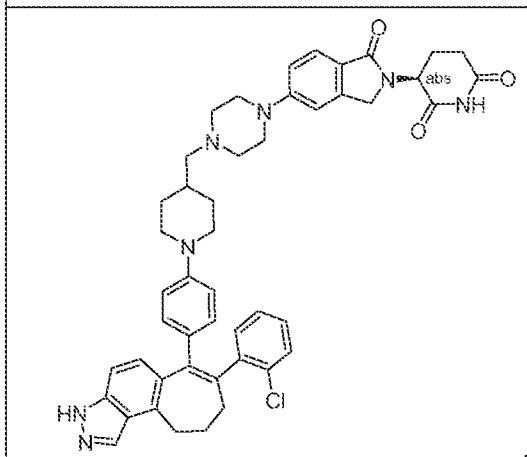

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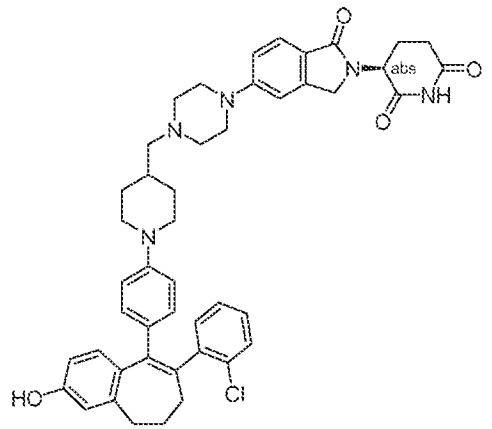

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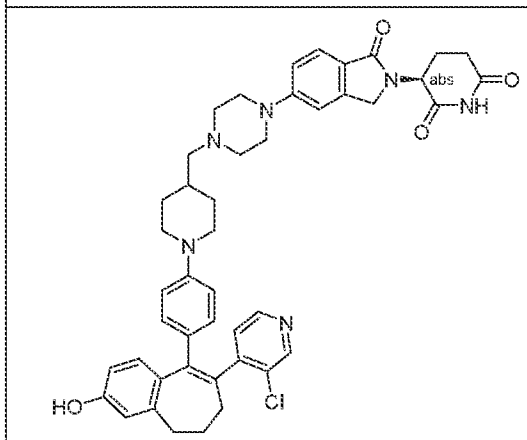

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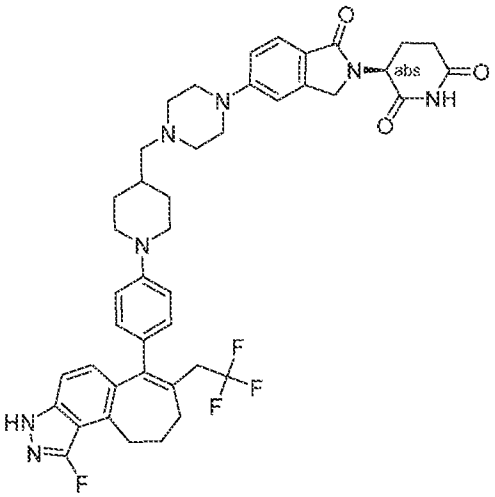

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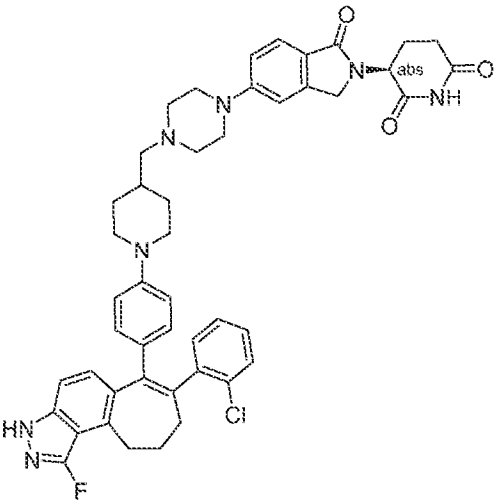

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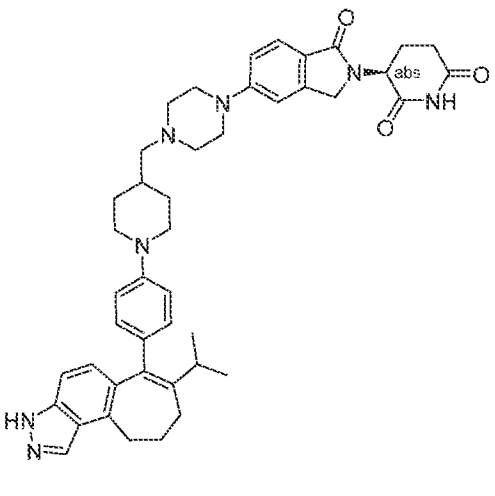

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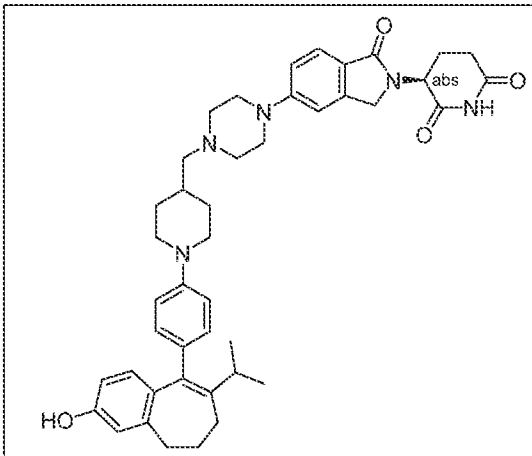

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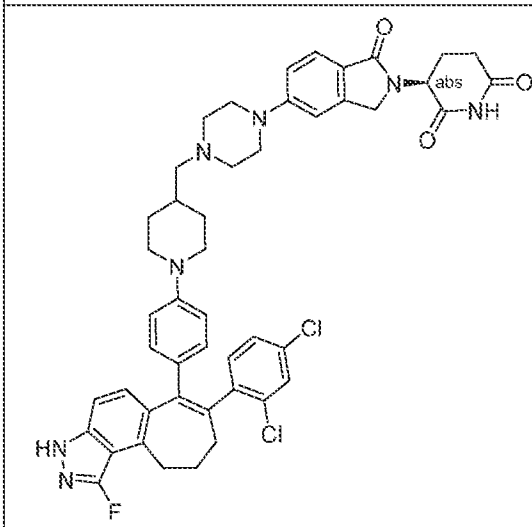

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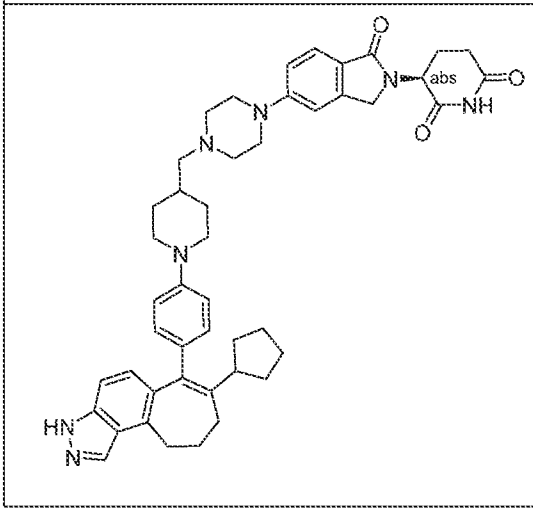

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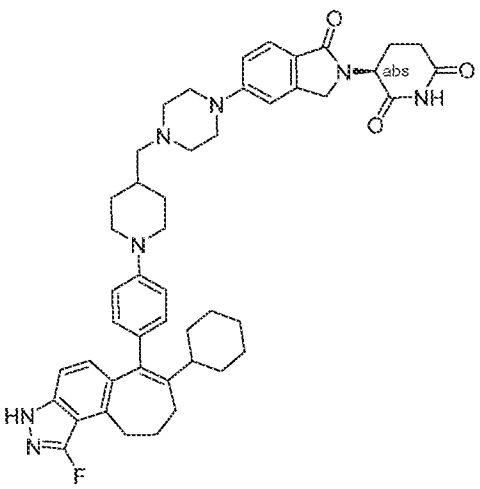

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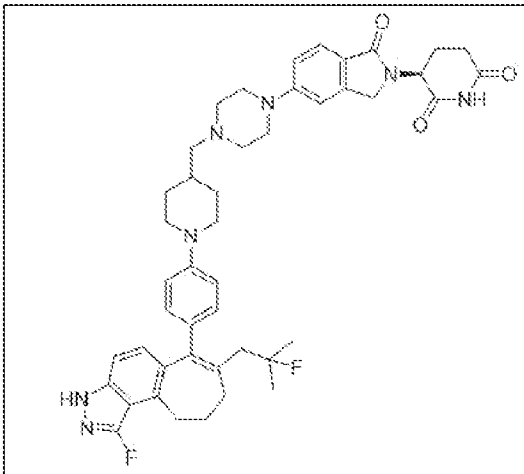

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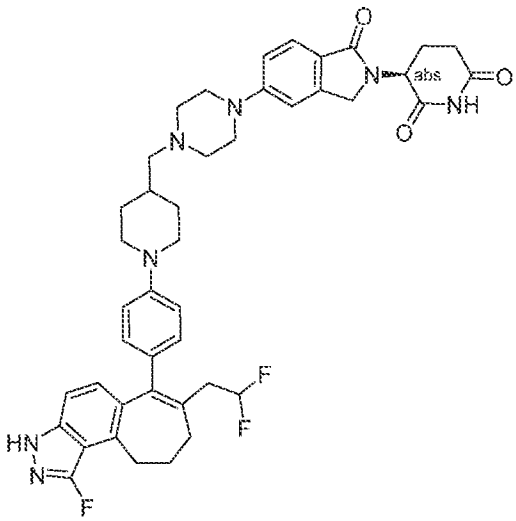

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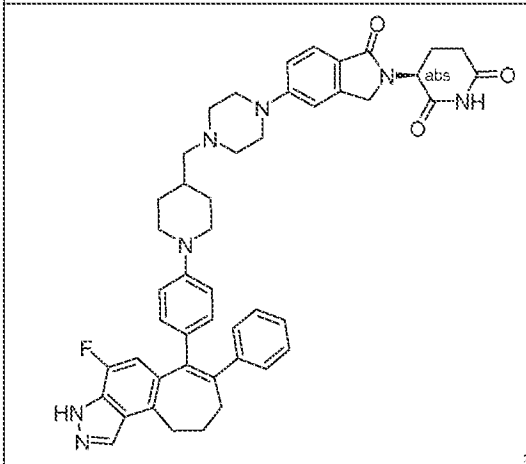

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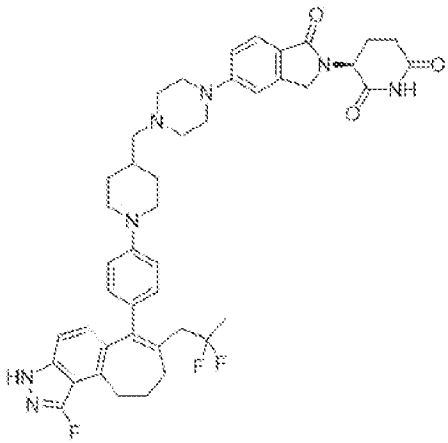

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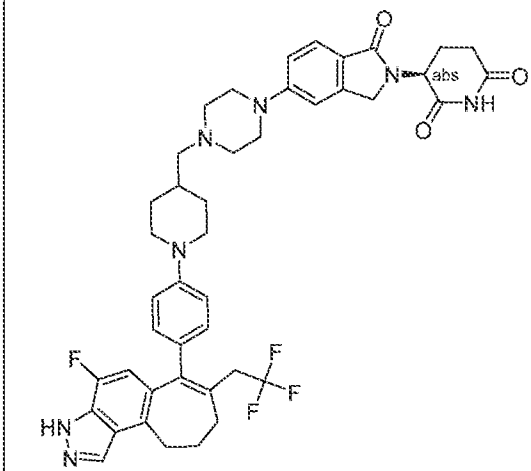

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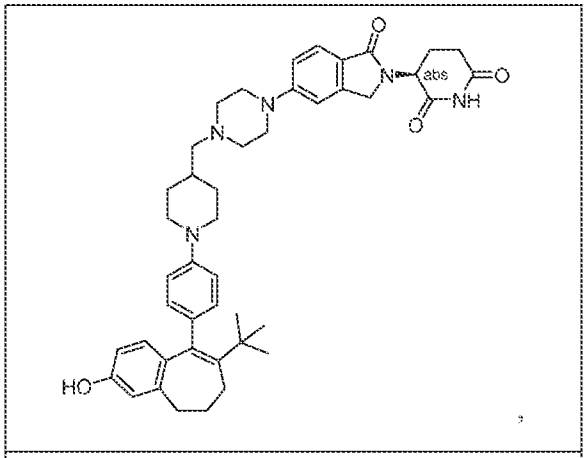

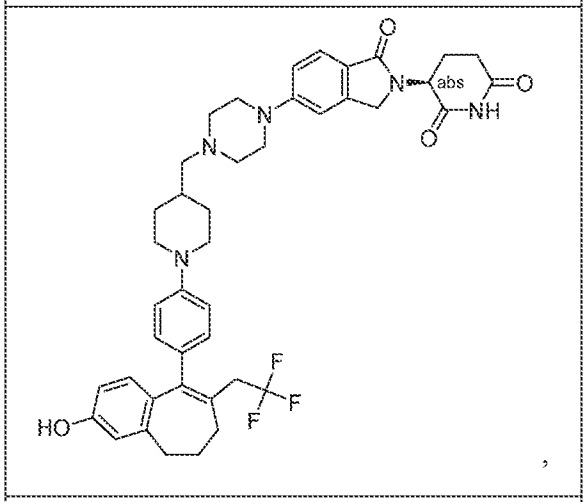

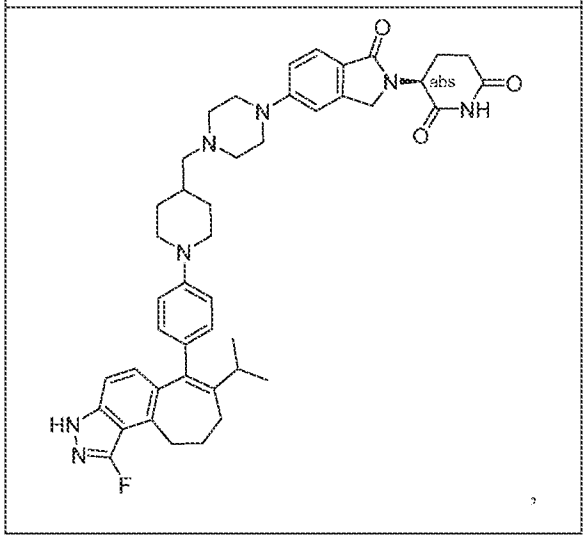

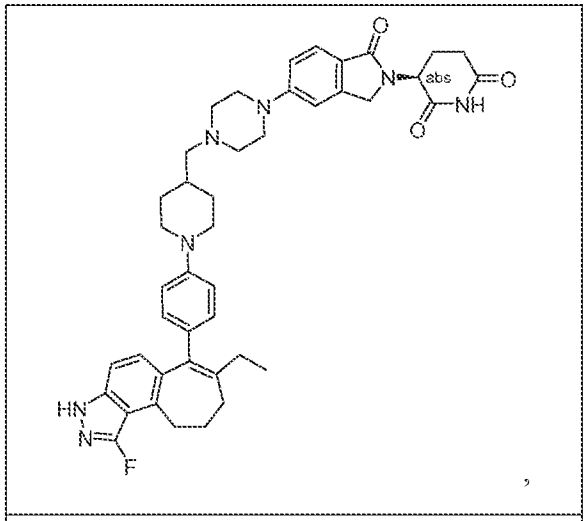

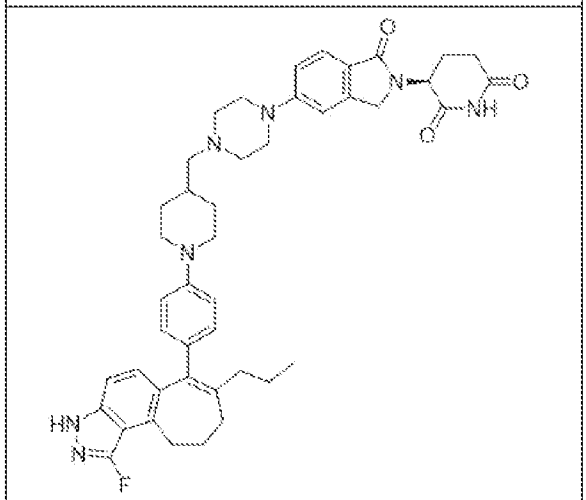

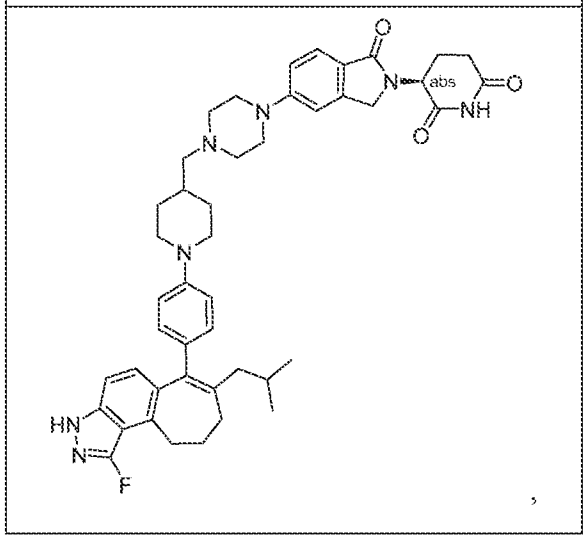

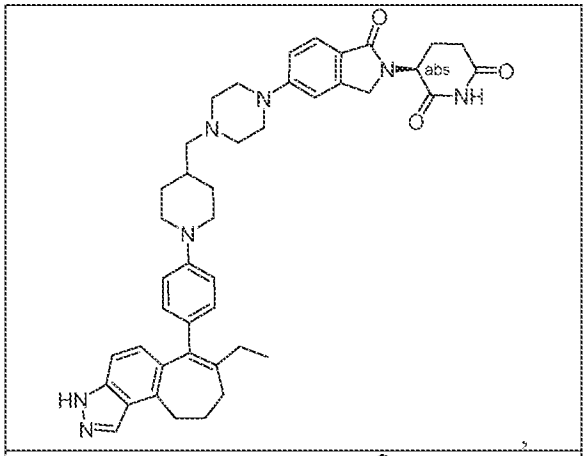

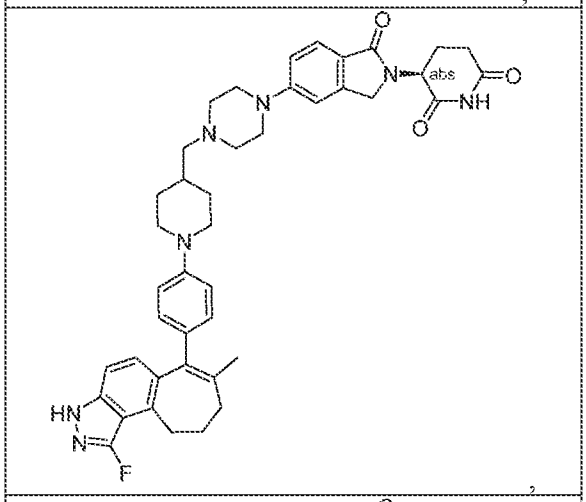

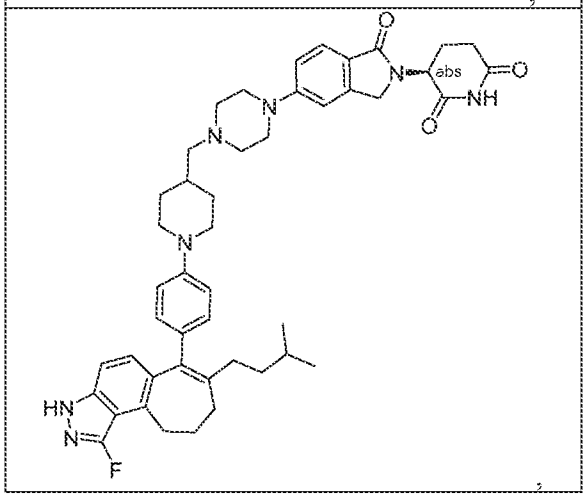

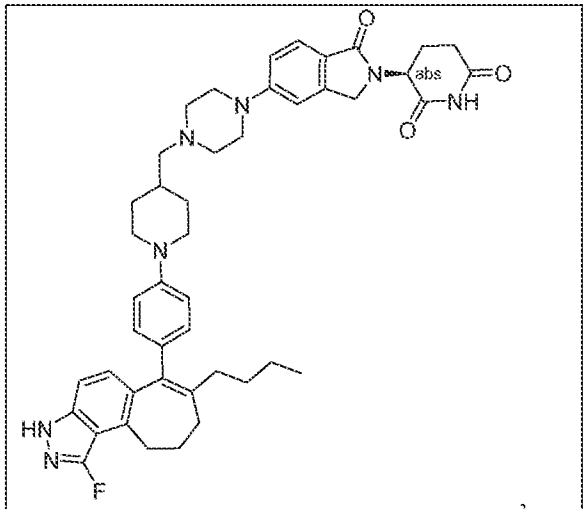

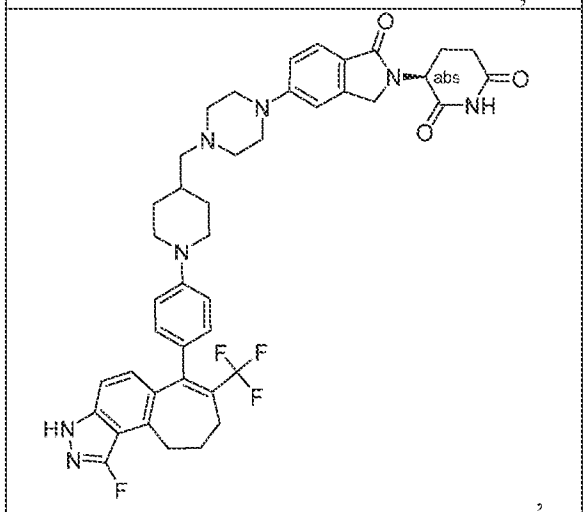

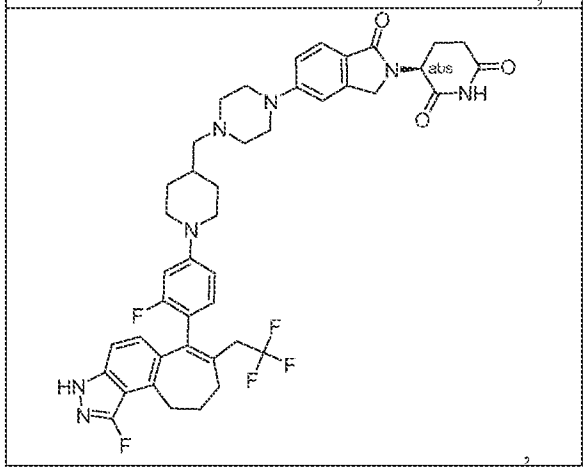

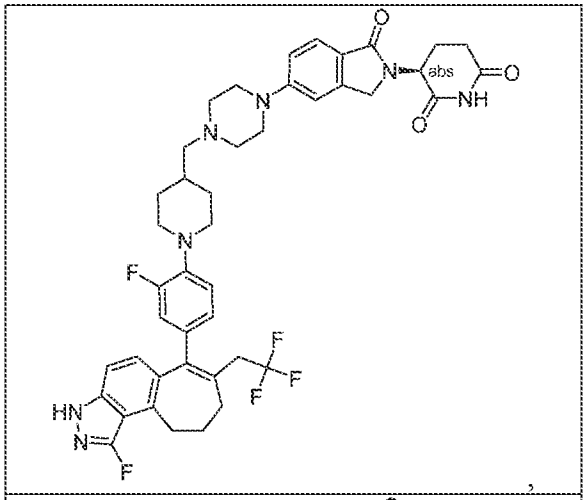

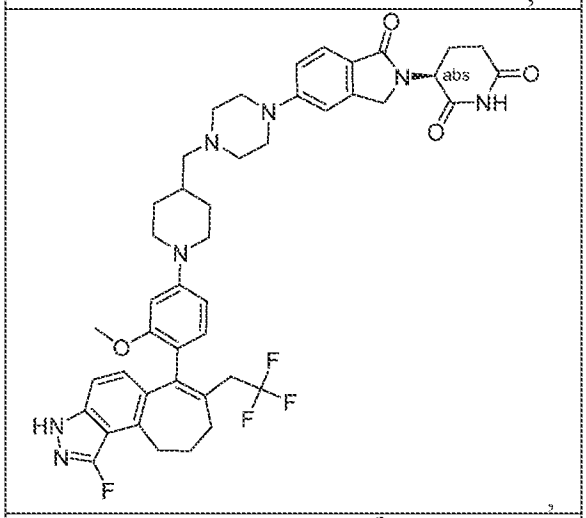

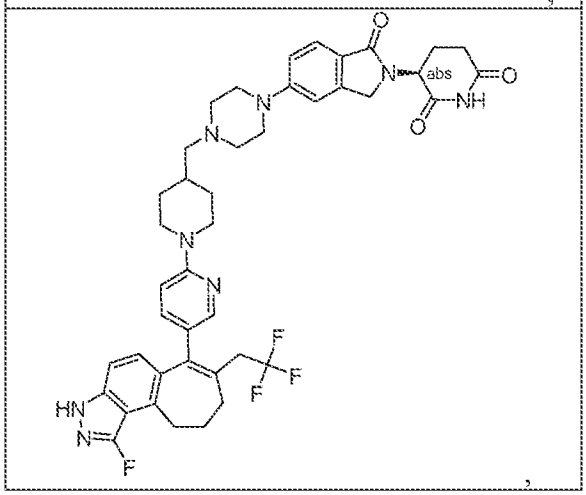

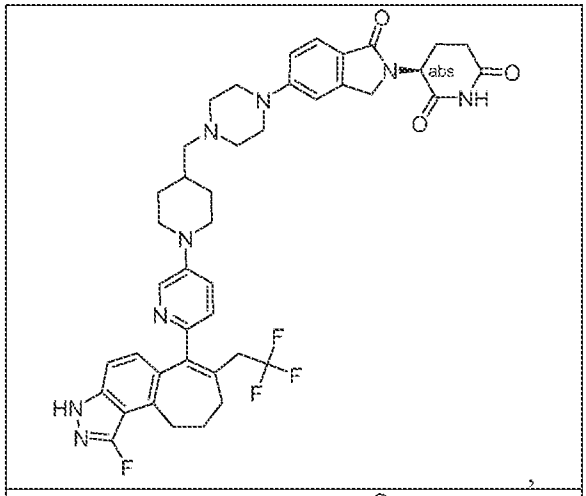

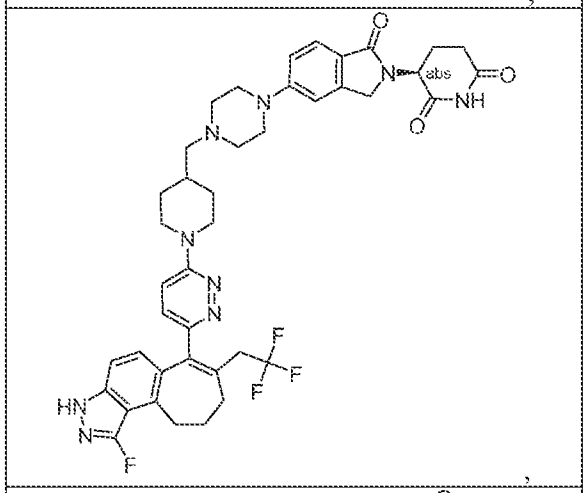

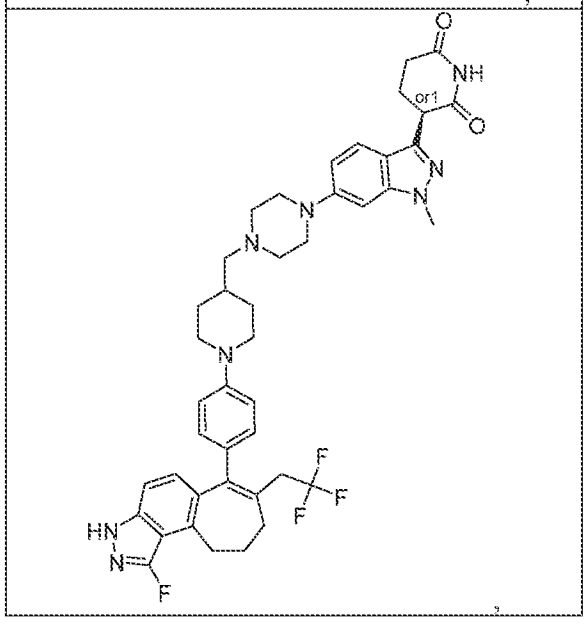

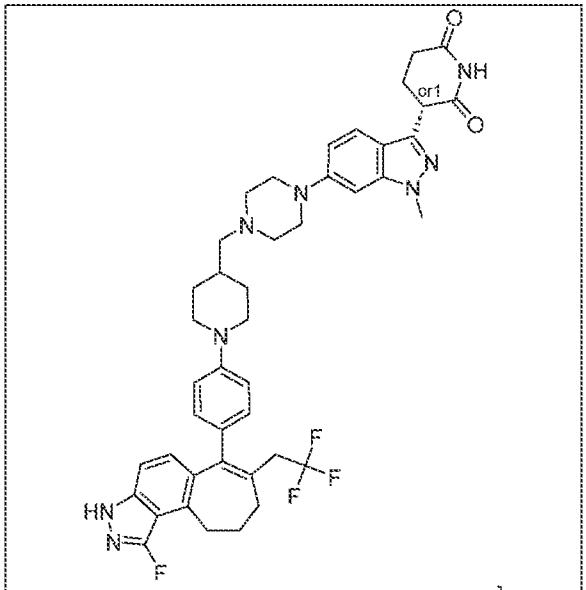

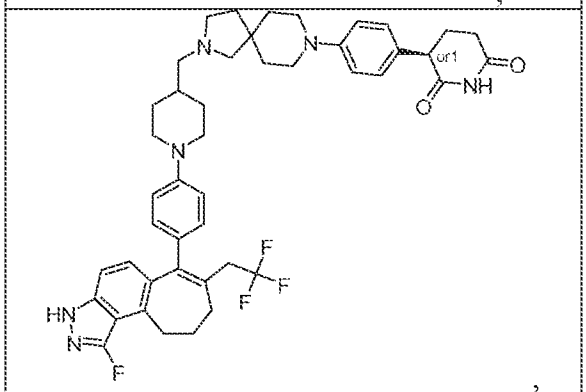

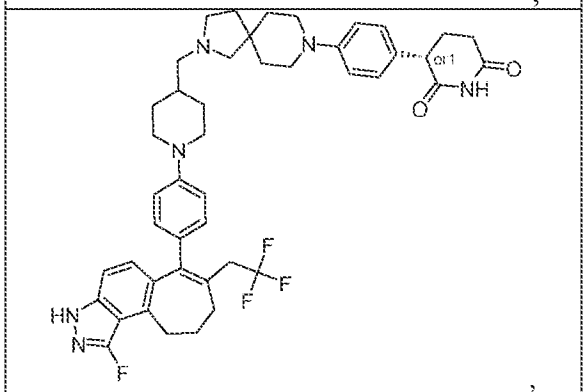

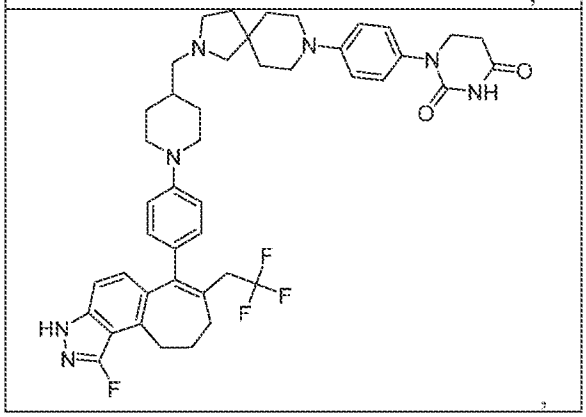

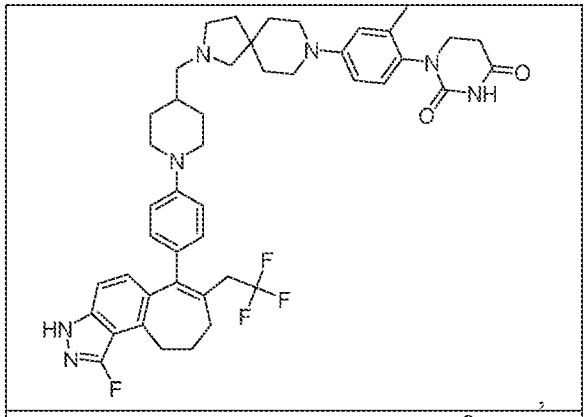

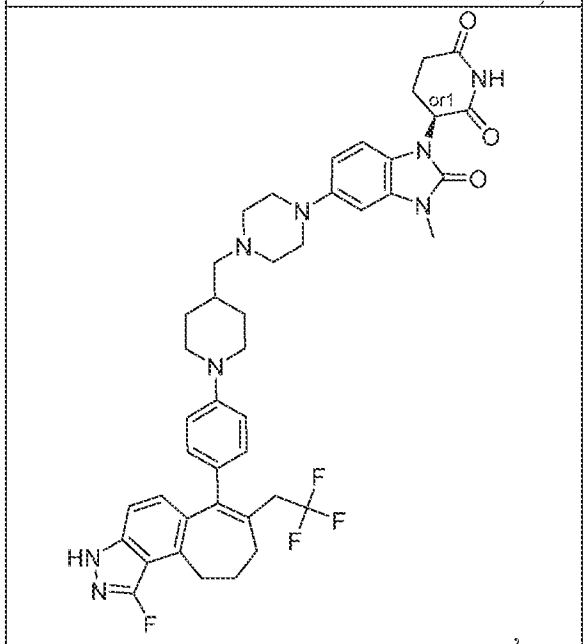

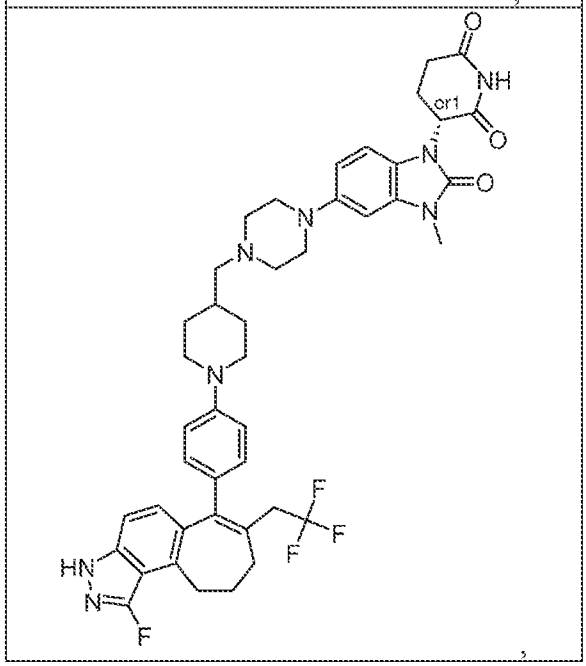

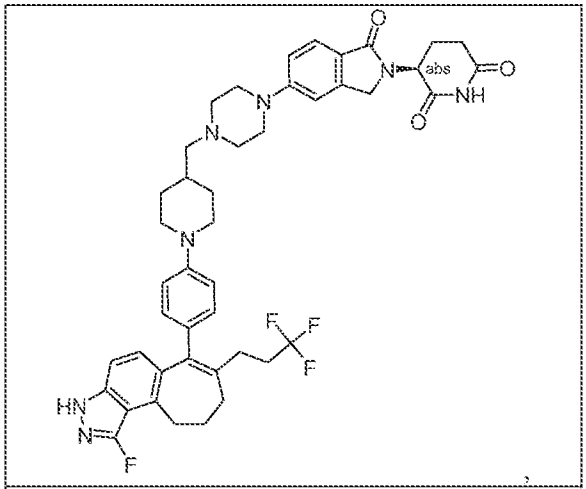

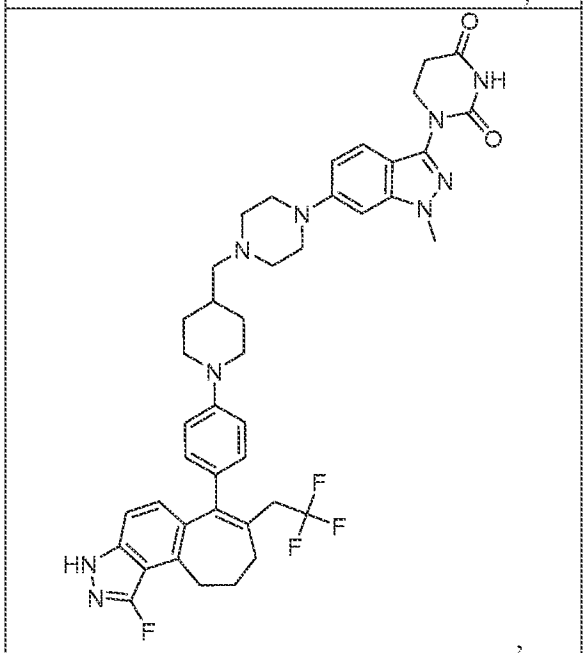

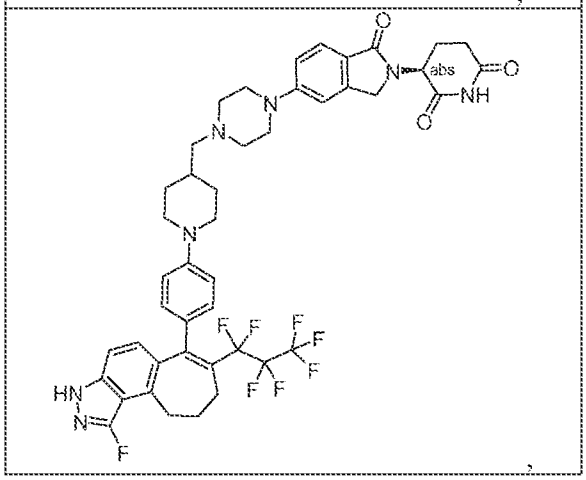

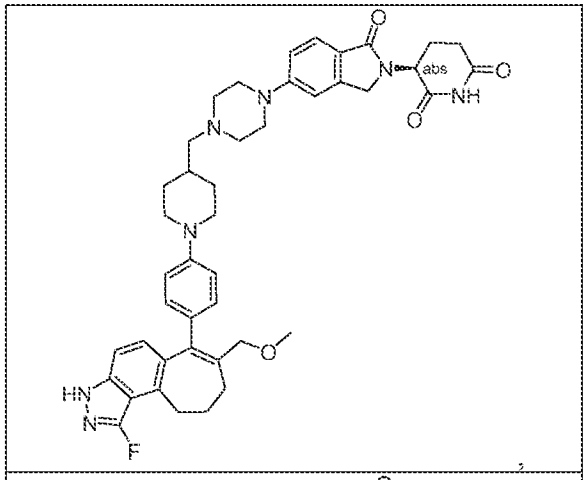

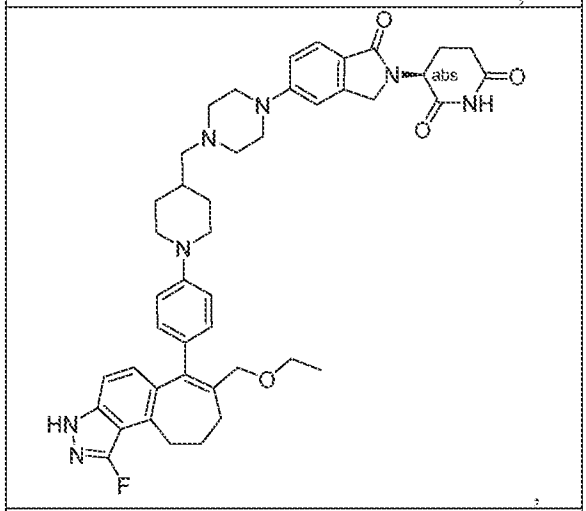

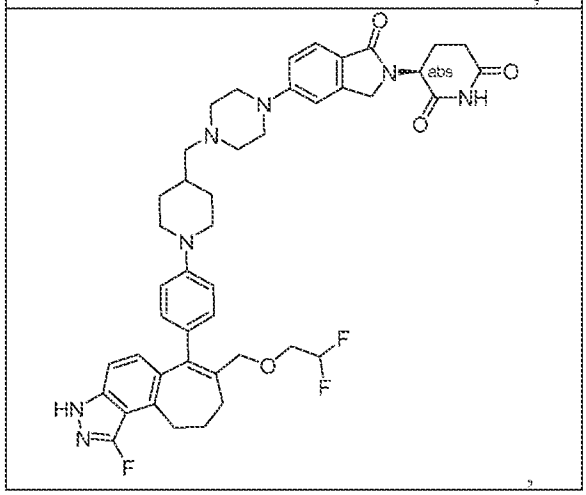

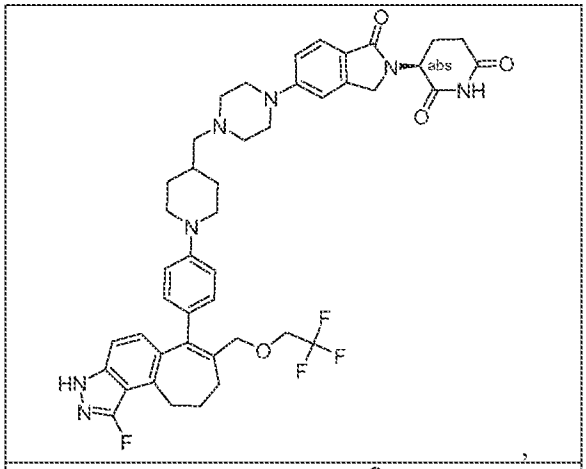

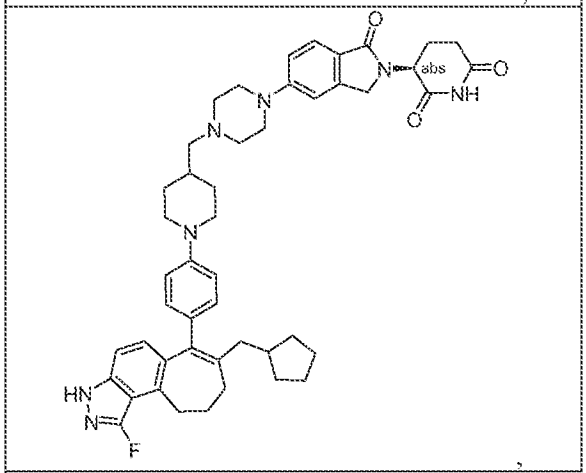

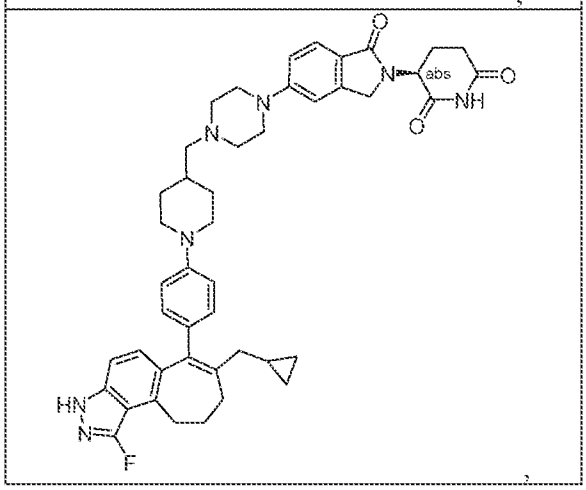

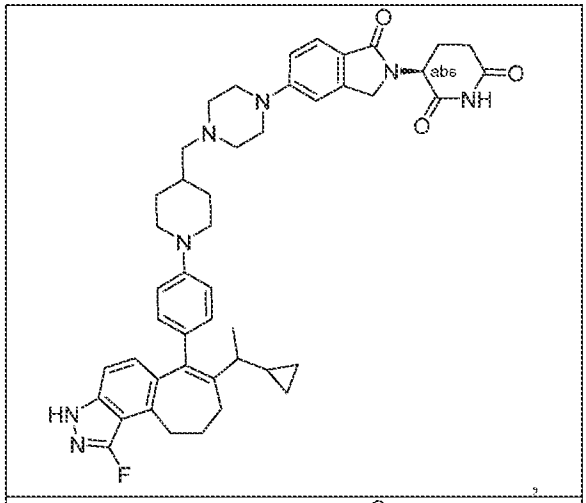

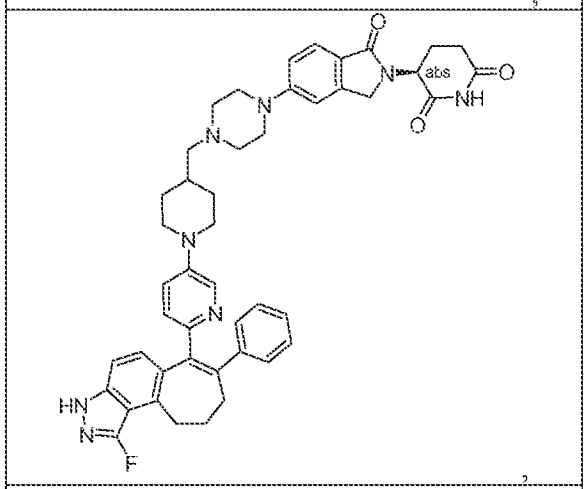

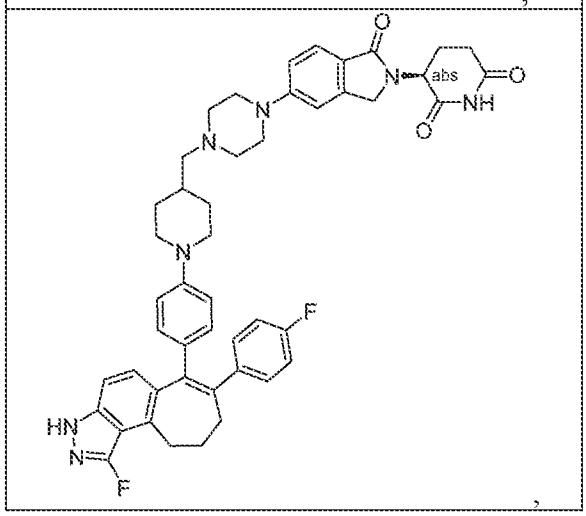

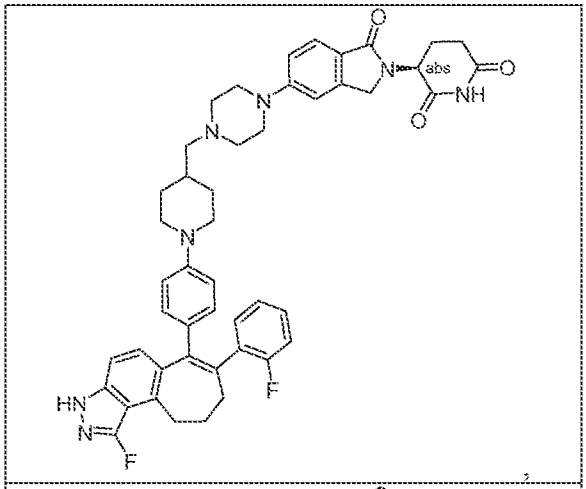

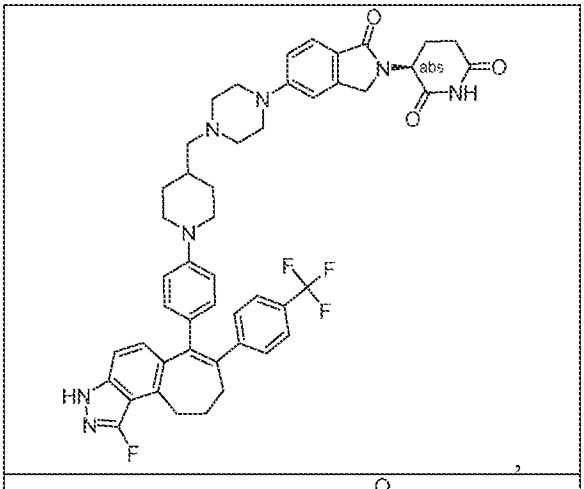

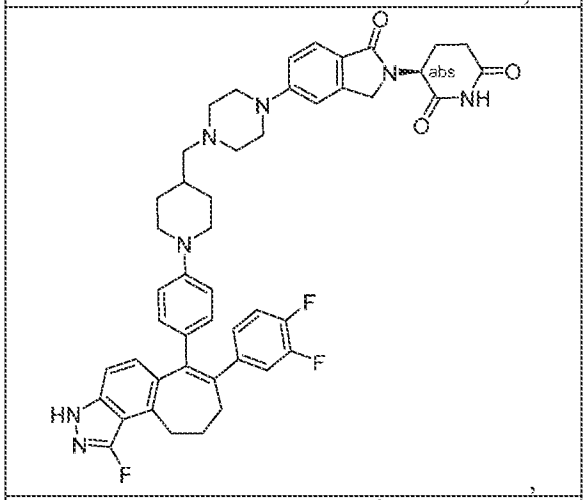

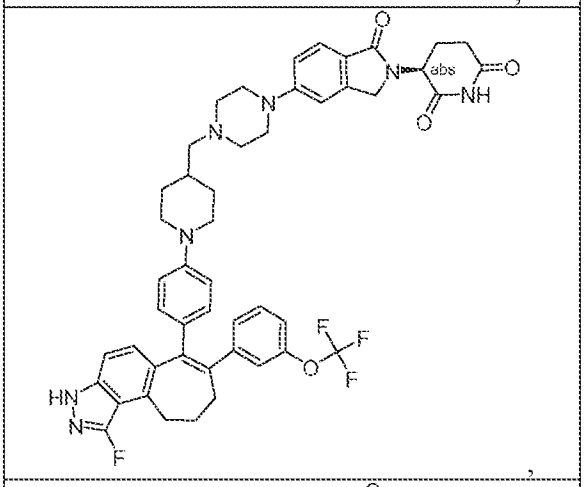

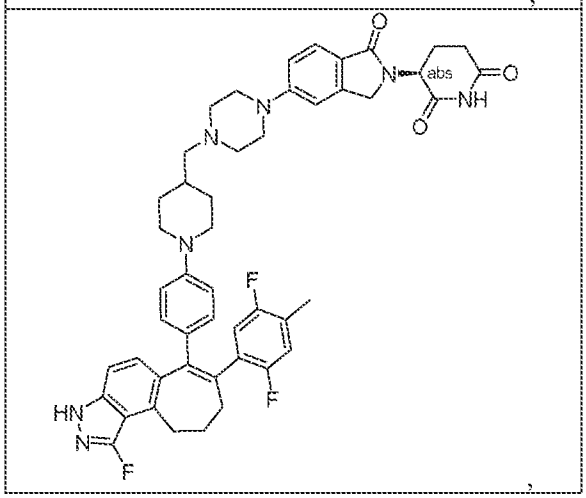

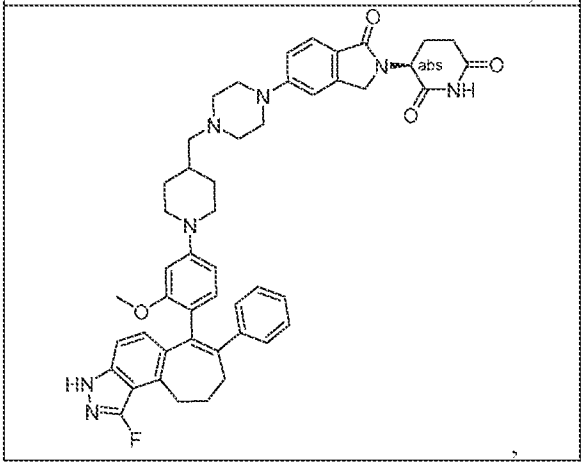

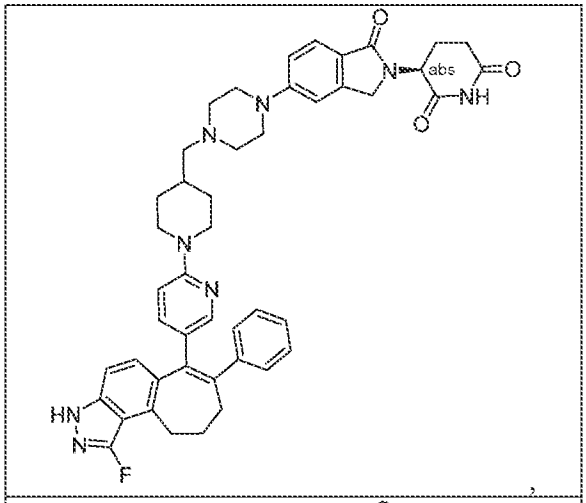

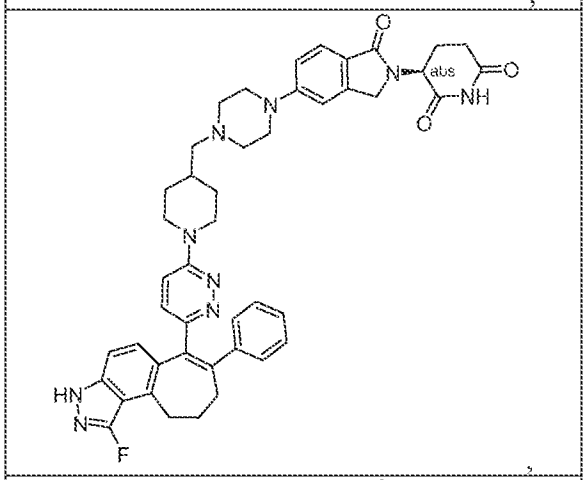

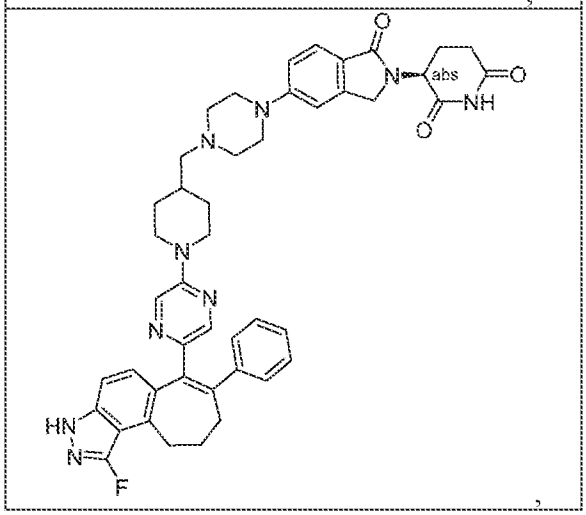

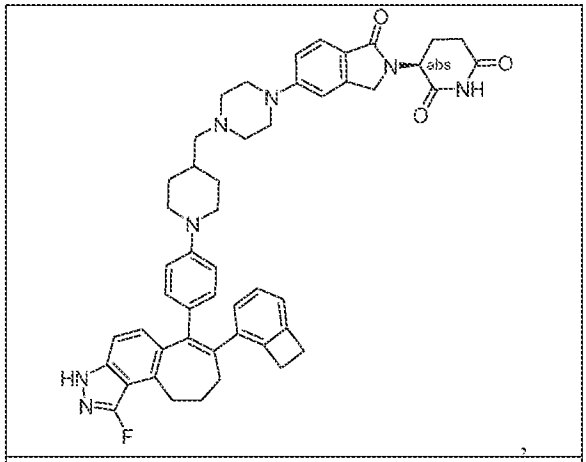

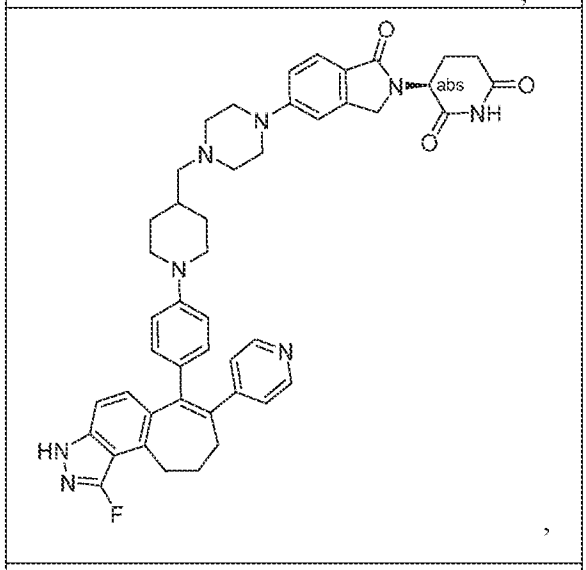

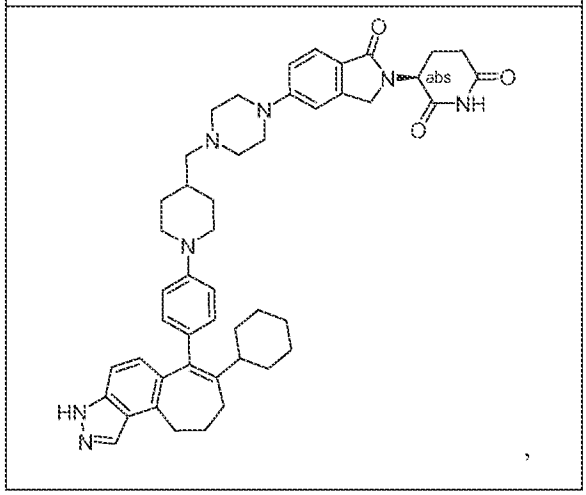

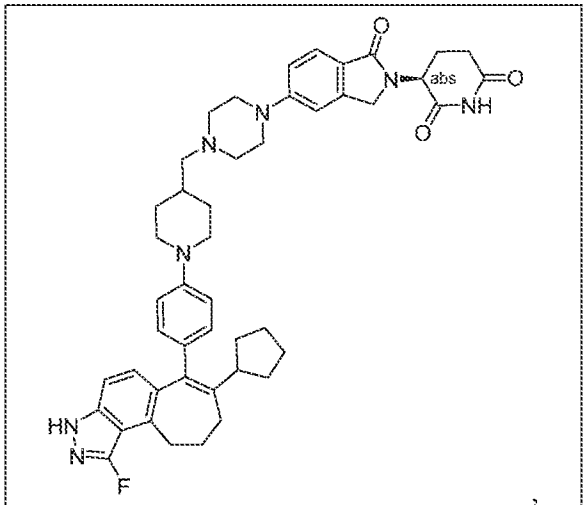

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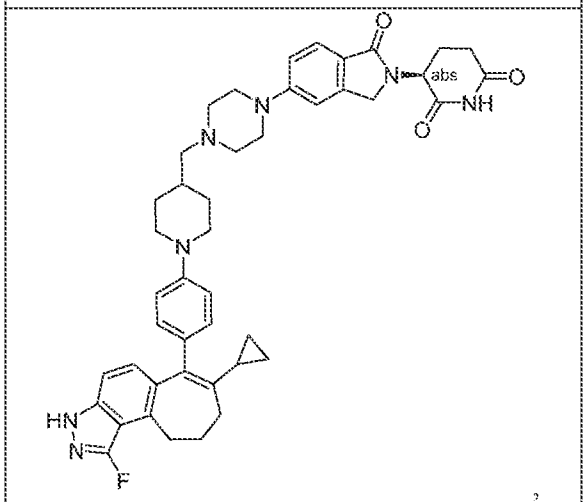

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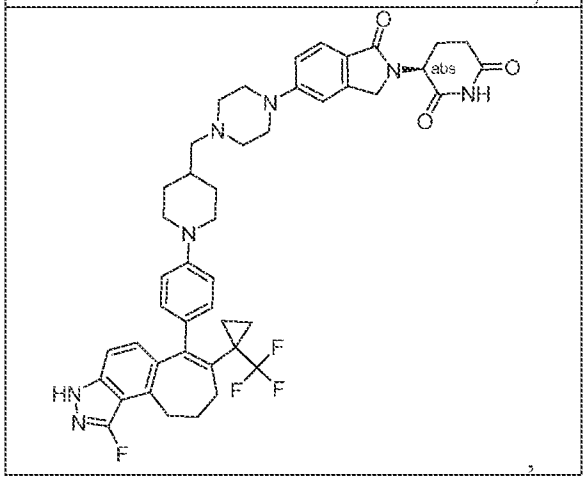

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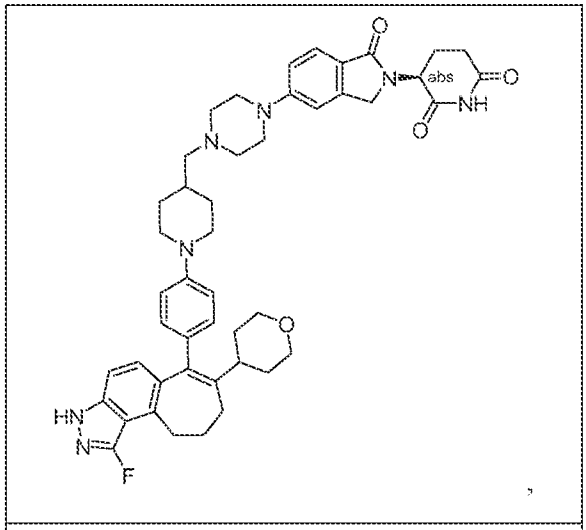

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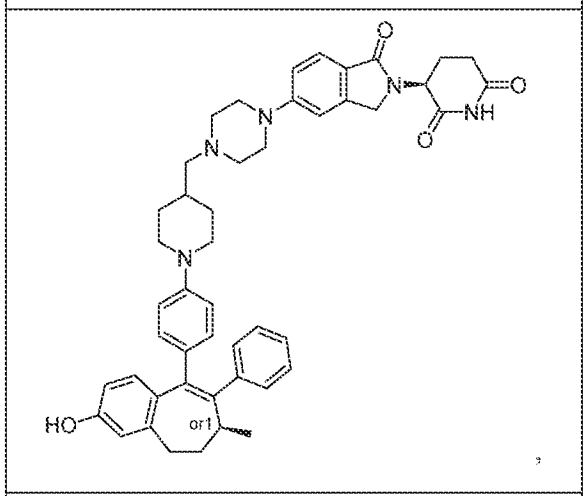

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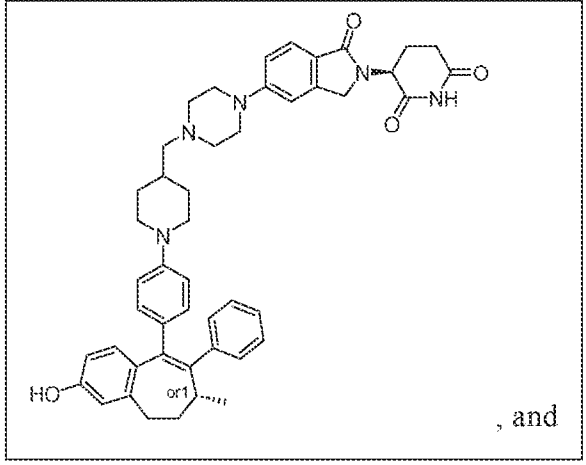

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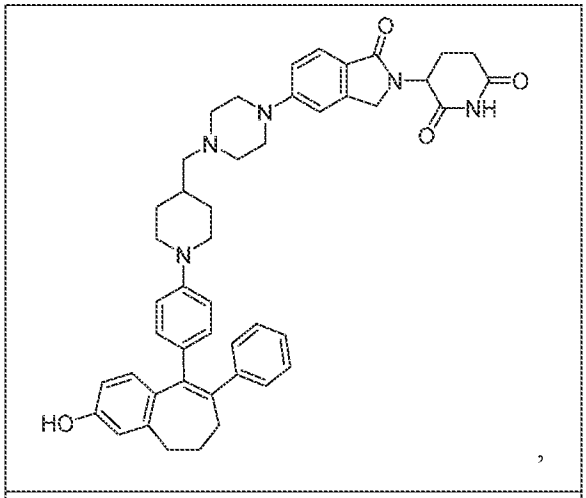

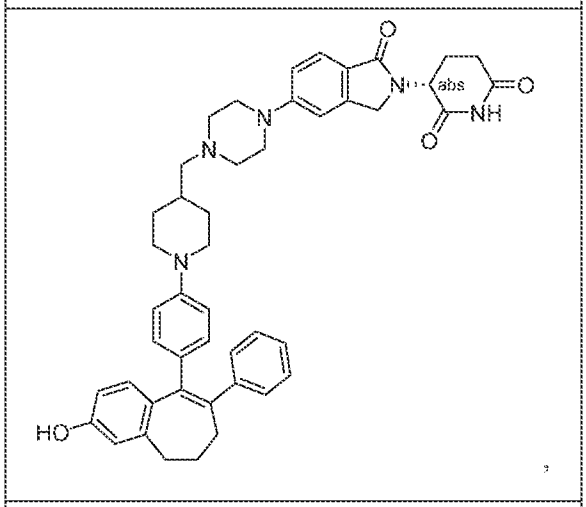

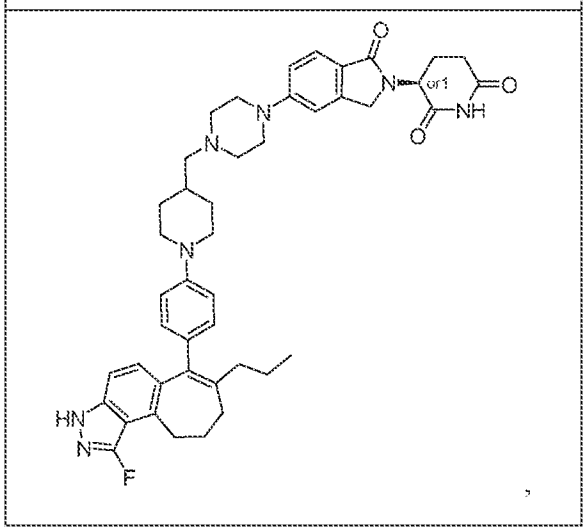

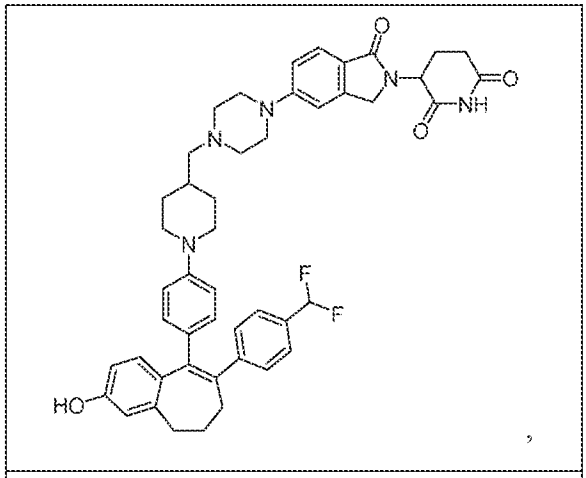

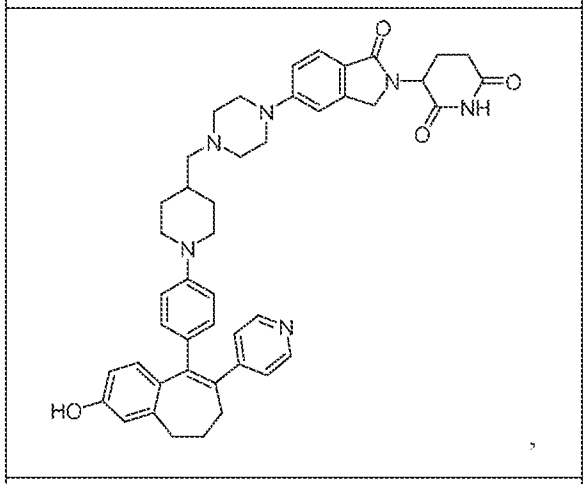

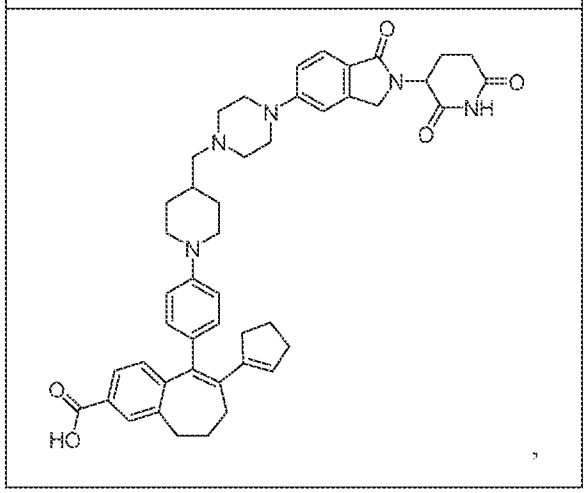

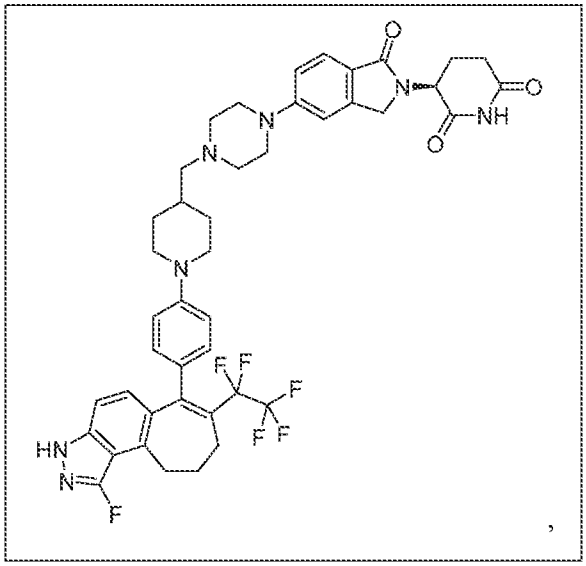

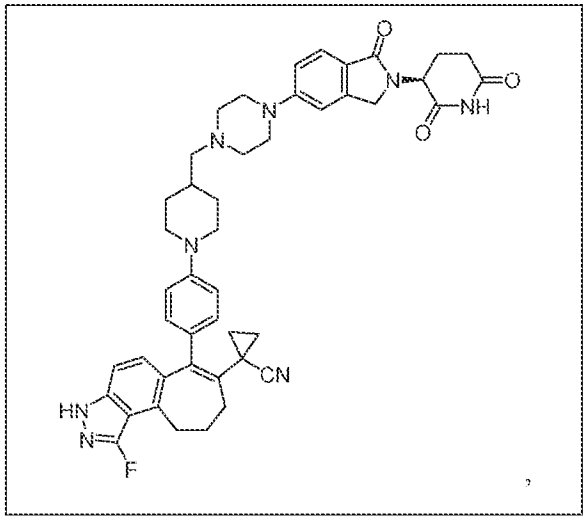

or a pharmaceutically acceptable salt thereof.

118. A pharmaceutical composition comprising a compound of any one of claims 1-117, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

119. A method of inhibiting ERα signaling in a sample, e.g., in vivo or in vitro, by contacting ERα with a compound of any one of claims 1-117, or a pharmaceutically acceptable salt thereof, or a composition of claim 118.

120. The method of claim 119, wherein the inhibiting of ERα signaling comprises reducing the signaling activity of ERα by at least 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, e.g., relative to a reference standard.

121. The method of claim 119, wherein the inhibiting of ERα signaling comprises reducing the signaling activity of ERα by at least 1-fold, 1.5-fold, 2-fold, 3-fold, 5-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold, or more, e.g., relative to a reference standard.

122. A method of treating an ERα-mediated disorder in a patient in need thereof, comprising administering to the patient a compound of any one of claims 1-117, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 118.

123. The method of claim 122, wherein the ERα-mediated disorder is associated with estrogen receptor accumulation and aggregation.

124. The method of any claims 122 or 123, wherein the ERα-mediated disorder is cancer or a neoplasia associated with estrogen receptor accumulation and aggregation.

125. The method of claim 124, wherein the ERα-mediated disorder is a disorder mediated by a ERα containing a D538G, Y537S, or L536R mutation.

126. The method of any one of claims 119-125, wherein the ERα-mediated disorder is cancer.

127. The method of any one of claims 119-125, wherein the method comprises the steps of:
(i) identifying a subject in need of such treatment;
(ii) providing a disclosed compound, or a pharmaceutically acceptable salt thereof; and
(iii) administering said provided compound in a therapeutically effective amount to treat, suppress and/or prevent the disease state or condition in a subject in need of such treatment.

128. The method of any one of claims 119-125, wherein the ERα-mediated disorder is breast cancer or uterine cancer.

129. The method of claim 128, wherein the breast cancer is selected from the group consisting of ER+ breast cancer, ER+/HER2- breast cancer, ER+ advanced/metastatic breast cancer, and ER+/HER2- advanced/metastatic breast cancer.

130. The method of any one of claims 119-125, wherein the ERα-mediated disorder is endometriosis.

131. A compound or pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, according to any one of claims 1-117, or a pharmaceutical composition of claim 118, for use as a medicament.

132. A compound or pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof, according to any one of claims 1-117, or a pharmaceutical composition of claim 118, for use in the treatment of an ERα-mediated disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/069192

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D405/14 C07D471/10 C07D491/044 C07F5/02
A61P35/00 A61K31/496
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D C07F A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2018/102725 A1 (ARVINAS, INC.) 7 June 2018 (2018-06-07) abstract; claims; examples page 496; compound 413	1-132
Y	WO 2019/199816 A1 (ARVINAS OPERATIONS, INC.) 17 October 2019 (2019-10-17) cited in the application abstract; claims; examples claim 18 page 403 - page 412; examples 1-31; table 1	1-132
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[x] Further documents are listed in the continuation of Box C.
[x] See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2023	28/09/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kiernan, Andrea

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Y	WO 2022/084280 A1 (SANOFI) 28 April 2022 (2022-04-28) abstract; claims; examples	1-132
X,P	WO 2022/166879 A1 (CHIA TAI TIANQING PHARMACEUTICAL GROUP CO., LTD. ET AL.) 11 August 2022 (2022-08-11) abstract; claims; examples	1-132
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