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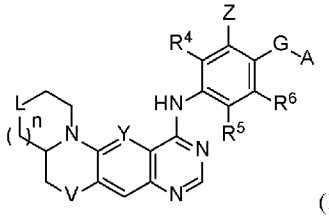
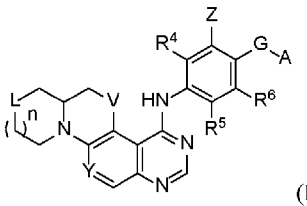
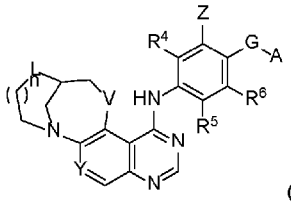


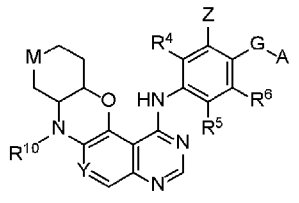
(I-A),



(I-B'),



(I-C'), or



(I-D),

(57) Abstract: The present disclosure relates generally to compounds of Formulae (l-A), (l-B1), (l-C) and ((l-D) and compositions thereof for inhibition of ErbB2, including mutant forms of ErbB2, particularly those harboring an Exon 20 mutation, methods of preparing said compounds and compositions, and their use in the treatment or prophylaxis of various cancers, such as lung, glioma, skin, head neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal, bladder, prostate, or ovarian cancer.

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# POLYCYCLIC QUINAZOLINES FOR INHIBITION OF ERBB2

## CROSS-REFERENCE TO RELATED APPLICATION

**[0001]** This application claims priority to and the benefit of United States Provisional Patent Application No. 63/406,191, filed on September 13, 2022, the disclosure of which is incorporated herein by reference in its entirety.

## FIELD

**[0002]** The present disclosure relates generally to compounds and compositions thereof for inhibition of ErbB2, including mutant forms of ErbB2, particularly those harboring an Exon 20 mutation, methods of preparing said compounds and compositions, and their use in the treatment or prophylaxis of various cancers, such as lung, glioma, skin, head and neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal, bladder, prostate, or ovarian cancer.

## BACKGROUND

**[0003]** ErbB2 (or HER2) is a member of the ErbB receptor tyrosine kinase family consisting of four related receptors, including ErbB1 (also known as epidermal growth factor receptor, or EGFR), ErbB3 and ErbB4. Although there are no known ligands that bind to monomeric ErbB2, it can dimerize with other ErbB receptors, particularly ErbB3, and regulate downstream signaling cascades including, but not limited to, the MAPK and PI3K pathways, that promote cell proliferation and survival. Aberrant overexpression of ErbB2 or certain genetic alterations (including point mutations that lead to certain amino acid substitutions or small in-frame insertions in Exon 20 that lead to the deletion and/or insertion of certain small stretches of amino acids) are known to confer elevated or constitutive tyrosine kinase activation to the receptor. Accordingly, the overexpression or mutation of ErbB2 is highly associated with aggressive forms of solid cancers, including breast, ovarian, stomach, and lung cancer (e.g., NSCLC).

**[0004]** Currently, there are few approved treatments for cancers associated with ErbB2 overexpression, including tyrosine kinase inhibitors (TKIs) such as tucatinib. Although these TKIs can be effective at ameliorating cancers associated with ErbB2 overexpression, their therapeutic utility is often limited by inadequate selectivity for ErbB2 over EGFR, and consequently are dose-limited by toxicity concerns related to EGFR inhibition (especially gastrointestinal and skin-related toxicities). These toxicities necessitate restrictive dosing regimens, leading to suboptimal target engagement and thus limited therapeutic benefit.

Moreover, while current TKIs provide therapeutic benefit for cancers driven by ErbB2 overexpression, they may have limited efficacy in patients harboring specific genetic alterations, such as EGFR or ERBB2 exon 20 insertions, specific point mutations or genetic alterations associated with ErbB family ligands, such as NRG1 gene fusions.

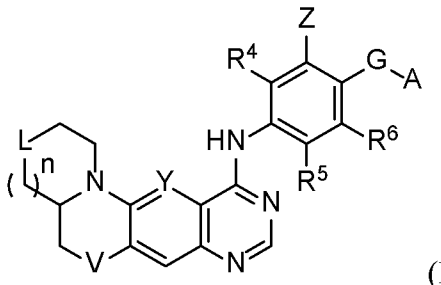
**[0005]** For example, in a small proportion of lung cancer patients, certain especially pernicious mutations in EGFR and ErbB2 known as EGFR exon 20 insertions/ErbB2 insertions are markedly less sensitive to first and second generation reversible TKIs. An added challenge to the development of viable therapies for these specific ErbB Exon 20 mutants (20ins or E20I) is the fact these alterations are heterogeneous, encompassing a diversity of amino acid insertions/deletions. In addition to E20I mutations, a number of other genetic alterations of the receptor, specifically point mutations leading to single amino acid substitutions, have been associated with the development of a variety of cancers, including lung cancer. Although the resistance mechanisms associated with each of these mutations are not fully understood, it is believed that the mutations may share a commonality in promoting ligand-independent activation of the kinases. Further investigation of the underlying mechanisms and development of TKIs tailored to these mutants are needed.

**[0006]** Other aggressive, refractory cancers exhibiting ErbB2 overexpression have been observed to harbor NRG1 gene re-arrangements resulting in novel fusion proteins. NRG1 gene fusions may induce overproduction of neuregulin-1, the cognate ligand for ErbB3. The simultaneous overexpression of ErbB2 and overproduction of neuregulin-1 may lead to excess activation of ErbB2-ErbB3 heterodimers and resultant hyperplasia.

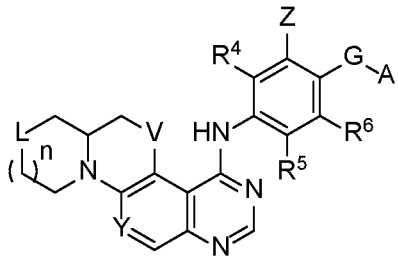
**[0007]** Accordingly, there remains a need for new therapeutics for the treatment of cancers driven by dysregulated ErbB2 receptor kinase activity, not only with improved safety and selectivity for ErbB2 over EGFR, but also for addressing mutation-associated sub-variants of ErbB2 (e.g., E20I mutations and NRG1 gene fusions) with enhanced potency.

## BRIEF SUMMARY

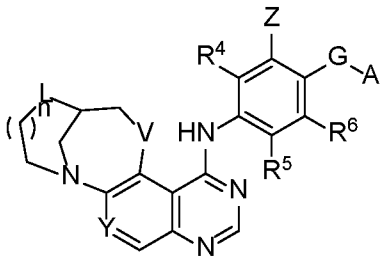
**[0008]** In one aspect, provided herein is a compound of formula (I-A), (I-B'), (I-C'), or (I-D):



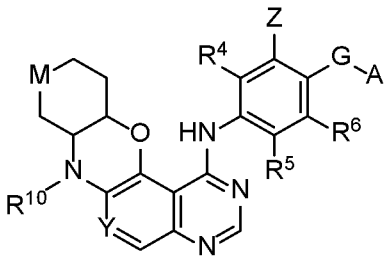
(I-A),



(I-B'),

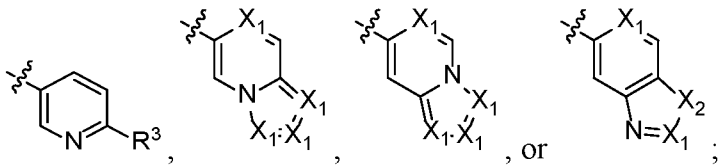


(I-C'), or



(I-D),

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

M is NH or N($C_1$-$C_6$ alkyl);

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -S(O)$_2$-, or $CH_2$;

V is O, S, or $NR^2$;

each $X_1$ is independently N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is optionally substituted by 3-6 membered heterocycle or $-NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

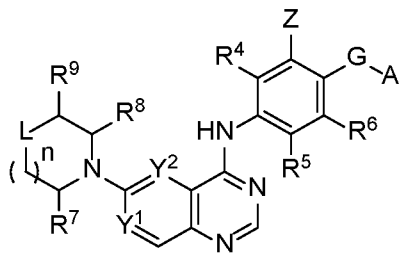
$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, $-CD_3$, or $C_3$-$C_6$ cycloalkyl;

$R^4$, $R^5$, and $R^6$ are each independently -H or halogen; and

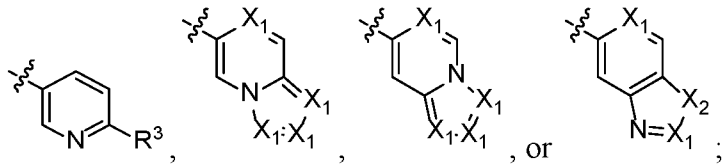
$R^{10}$ is -H or $C_1$-$C_6$ alkyl.

**[0009]** In some embodiments, the compound of formula (I-A), (I-B'), or (I-C') is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

either $Y^1$ is C-$R^{Y1}$, $Y^2$ is Y, $R^8$ is -H, $R^9$ is -H, and $R^{Y1}$ is taken together with $R^7$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^1$,

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$, or

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^8$ is -H, and $R^{Y2}$ is taken together with $R^9$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$;

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, or $CH_2$;

V is O, S, or $NR^2$;

$X_1$ is N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

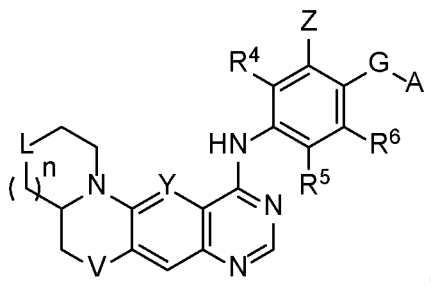
$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is independently optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, -$CD_3$, or $C_3$-$C_6$ cycloalkyl; and

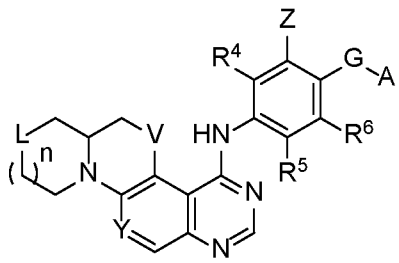
$R^4$, $R^5$, and $R^6$ are each independently -H or halogen.

**[0010]** In some embodiments, provided is a compound of formula (I-A)



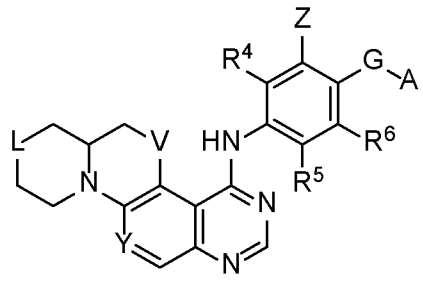

(I-A).

**[0011]** In some embodiments, provided is a compound of formula (I-B')



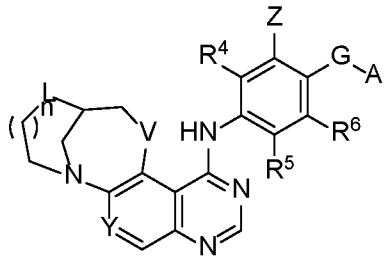
(I-B').

**[0012]** In some embodiments, provided is a compound of formula (I-B)



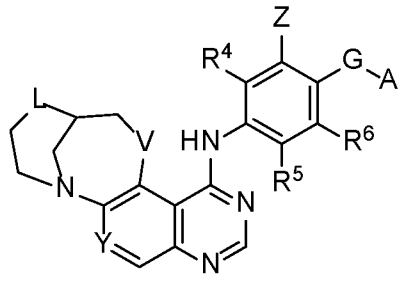
(I-B).

**[0013]** In some embodiments, provided is a compound of formula (I-C')



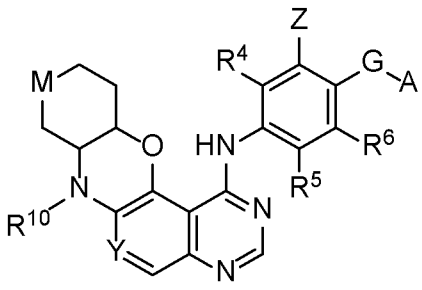
(I-C').

**[0014]** In some embodiments, provided is a compound of formula (I-C)

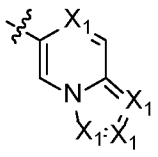
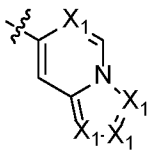
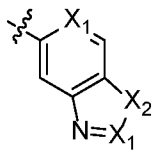
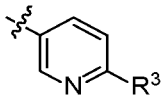
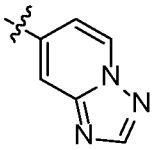
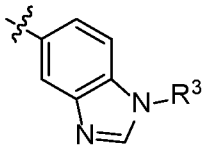
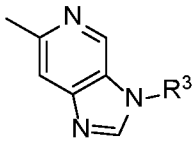
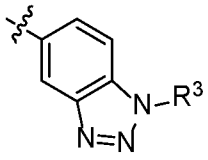


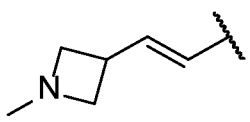
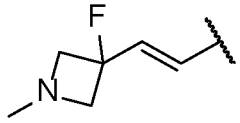
(I-C).

**[0015]** In some embodiments, provided is a compound of formula (I-D)



(I-D).

**[0016]** In some embodiments, A is  ,  , or  . In some embodiments, A is  . In some embodiments, A is  ,  ,  , or  .

**[0017]** In some embodiments, $R^3$ is -H or $-CH_3$. In some embodiments, L is N-E. In some embodiments, E is $-C(O)-R^1$. In some embodiments, $R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 4 membered heterocycle or $-N(CH_3)_2$, wherein the 4 membered heterocycle is optionally substituted by -F or $-CH_3$. In some embodiments, $R^1$ is $C_1$ alkyl, $C_2$-$C_4$ alkenyl, or $C_2$-$C_3$ alkynyl, each of which is independently optionally substituted by 4 membered heterocycle or $-N(CH_3)_2$, wherein the 4 membered heterocycle is optionally substituted by -F or $-CH_3$. In some embodiments, $R^1$ is $-CH_3$ $-CH=CH_2$, $-CH=CH-CH_2-N(CH_3)_2$, $-C\equiv C-CH_3$, $-CH=CH-CH(CH_3)-N(CH_3)_2$,  , or  . In some embodiments, E is -H, $-C(O)O-(C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro. In some embodiments, E is -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_3OCH_3$, or $-C(O)O-CH_3$.

**[0018]** In some embodiments, G is -O-. In some embodiments, G is -C(=O)-. In some embodiments, G is -S-, -S(O)-, or $-S(O)_2$-. In some embodiments, G is $-CH_2$-.

**[0019]** In some embodiments, V is O. In some embodiments, V is S. In some embodiments, V is $NR^2$.

**[0020]** In some embodiments, Y is N. In some embodiments, Y is C-$R^y$. In some embodiments, Y is C-$R^y$, and $R^y$ is -H. In some embodiments, Y is C-$R^y$, and $R^y$ is -F.

**[0021]** In some embodiments, Z is -H, halogen, -C≡CH, $-OCH_3$, or $-CH_3$. In some embodiments, Z is -H, -F, or $-CH_3$. In some embodiments, $R^4$ is -H. In some embodiments, $R^4$ is -F. In some embodiments, $R^5$ is -H. In some embodiments, $R^5$ is -F. In some embodiments, $R^6$ is -H. In some embodiments, $R^6$ is -F.

**[0022]** In some embodiments, $R^{10}$ is -H. In some embodiments, $R^{10}$ is $-CH_3$.

**[0023]** In another aspect, provided is a pharmaceutical composition comprising a compound of formula (I-A), (I-B'), (I-C'), (I-D), (I'), (I''), or (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

**[0024]** In another aspect, provided is a method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2 comprising contacting the ErbB2 or the mutant form with a therapeutically effective amount of a compound of formula (I-A), (I-B'), (I-C'), (I-D), (I'), (I''), or (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the mutant form of human ErbB2 comprises a mutation in Exon 20. In some embodiments, the mutant form of human ErbB2 comprises one or more mutations that introduce amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In some embodiments, the mutant form of human ErbB2 comprises a disease-associated point mutation in ErbB2. In some embodiments, the mutant form of human ErbB2 comprises one or more point mutations in ErbB2 that introduce (a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or (b) a frameshift at A1232.

**[0025]** In another aspect, provided is a method of treating a patient having a cancer, comprising administering to the patient a therapeutically effective amount of a compound of

formula (I-A), (I-B'), (I-C'), (I-D), (I'), (I''), or (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the cancer comprises cells or cell tissue having increased ErbB2 kinase activity as compared to a control. In some embodiments, the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2. In some embodiments, the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2 that introduce amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In some embodiments, the cancer comprises cells or cell tissue having one or more disease-associated point mutations in ErbB2. In some embodiments, the cancer comprises cells or cell tissue having one or more point mutations that introduce an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or a frameshift at A1232. In some embodiments, the cancer is lung, glioma, skin, head and neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal, bladder, prostate, or ovarian cancer. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the patient has received at least one, at least two, or at least three prior therapies for the cancer. In some embodiments, one or more of the prior therapies selected from the group consisting of lapatinib, neratinib, afatinib, pyrotinib, poziotinib, TAK-788, and tucatinib. In some embodiments, the method further comprises administering one or more additional anti-cancer agents.

## DETAILED DESCRIPTION

**[0026]** The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

## I. DEFINITIONS

**[0027]** As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

**[0028]** The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of

the present disclosure as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., carbomers, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc = "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

**[0029]** The terms "individual", "subject" and "patient" refer to mammals and includes humans and non-human mammals. Examples of patients include, but are not limited to, mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, patient refers to a human.

**[0030]** As used herein, the term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep.

**[0031]** "Pharmaceutically acceptable" refers to safe and non-toxic, and suitable for in vivo or for human administration.

**[0032]** As used herein, the term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.*, $C_1$-$C_6$ means one to six carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. In some embodiments, the term "alkyl" may encompass $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkyl, $C_3$-$C_6$ alkyl, $C_4$-$C_6$ alkyl, $C_5$-$C_6$ alkyl, $C_1$-$C_5$ alkyl, $C_2$-$C_5$ alkyl, $C_3$-$C_5$ alkyl, $C_4$-$C_5$ alkyl, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkyl, $C_3$-$C_4$ alkyl, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkyl, or $C_1$-$C_2$ alkyl.

**[0033]** As used herein, the term "alkenyl" refers to an unsaturated branched or straight-chain alkyl group having the indicated number of carbon atoms (e.g., 2 to 8, or 2 to 6 carbon atoms) and at least one carbon-carbon double bond. The group may be in either the cis or trans configuration (Z or E configuration) about the double bond(s). Alkenyl groups include, but are not limited to, ethenyl, propenyl (e.g., prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl), and butenyl (e.g., but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl). In some embodiments, the alkenyl group may be attached to the rest of the molecule by a carbon atom in the carbon-carbon double bond. In other embodiments, the "alkenyl" may be attached to the rest of the molecule by a saturated carbon atom, and the carbon-carbon double bond is located elsewhere along the branched or straight-chain alkyl group.

**[0034]** As used herein, the term "alkynyl"refers to an unsaturated branched or straight-chain alkyl group having the indicated number of carbon atoms (e.g., 2 to 8 or 2 to 6 carbon atoms) and at least one carbon-carbon triple bond. Alkynyl groups include, but are not limited to, ethynyl, propynyl (e.g., prop-1-yn-1-yl, prop-2-yn-1-yl) and butynyl (e.g., but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl). In some embodiments, the alkynyl group may be attached to the rest of the molecule by a carbon atom in the carbon-carbon triple bond. In other embodiments, the "alkynyl" may be attached to the rest of the molecule by a saturated carbon atom, and the carbon-carbon triple bond is located elsewhere along the branched or straight-chain alkyl group.

**[0035]** The term "cycloalkyl", "carbocyclic", or "carbocycle" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, $C_3$-$C_6$ cycloalkyl means 3-6 carbons) and being fully saturated or having no more than one double bond between ring vertices. In some embodiments, "cycloalkyl" encompasses $C_3$-$C_6$ cycloalkyl, $C_4$-$C_6$ cycloalkyl, $C_5$-$C_6$ cycloalkyl, $C_3$-$C_5$ cycloalkyl, $C_4$-$C_5$ cycloalkyl, or $C_3$-$C_4$ cycloalkyl. In some embodiments, the term "cycloalkyl" may be further described as a "spirocycloalkyl" or a "fused cycloalkyl". The term "spirocycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, $C_3$-$C_6$ cycloalkyl means 3-6 carbons) and being fully saturated or having no more than one double bond between ring vertices, wherein the hydrocarbon ring is attached to the rest of the molecule at a single ring vertex (e.g., ring carbon atom) by two covalent bonds. The term "fused "cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, $C_3$-$C_6$ cycloalkyl means 3-6 carbons) and being fully saturated or having no more than one double bond between ring vertices, wherein the hydrocarbon ring is attached to the rest of the molecule at two ring vertices (e.g. two carbon atoms) by two covalent bonds. In some embodiments,

"cycloalkyl", "cycloalkyl", "carbocyclic", or "carbocycle" is also meant to refer to bicyclic, polycyclic and spirocyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, pinane, bicyclo[2.2.2]octane, adamantane, norborene, spirocyclic $C_{5-12}$ alkane, etc. In addition, one ring of a polycyclic cycloalkyl group may be aromatic, provided the polycyclic cycloalkyl group is bound to the parent structure via a non-aromatic carbon. For example, a 1,2,3,4-tetrahydronaphthalen-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is a cycloalkyl group, while 1,2,3,4-tetrahydronaphthalen-5-yl (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a cycloalkyl group.

**[0036]** The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain hydrocarbon radical, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N and S can be placed at any interior position of the heteroalkyl group. The heteroatom Si can be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. A "heteroalkyl" can contain up to three units of unsaturation, and also include mono- and poly-halogenated variants, or combinations thereof. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-O-CF_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH{=}CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH{=}N-OCH_3$, and $-CH{=}CH{=}N(CH_3)-CH_3$. Up to two heteroatoms can be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

**[0037]** The term "heterocycloalkyl", "heterocyclic", "heterocyclyl", or "heterocycle" refers to a cycloalkyl radical group having the indicated number of ring atoms (*e.g.*, 5-6 membered heterocycloalkyl) that contain from one to five heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, nitrogen atom(s) are optionally quaternized, as ring atoms. In some embodiments, a "heterocycloalkyl," "heterocyclic," or "heterocycle" ring can be a monocyclic, a bicyclic, bridged or fused ring system, spirocyclic or a polycylic ring system. Non-limiting examples of "heterocycloalkyl," "heterocyclic," or "heterocycle" rings include pyrrolidine, piperidine, N-methylpiperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, pyrimidine-2,4(1H,3H)-dione, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-5-oxide, thiomorpholine-S,S-oxide, piperazine, pyran,

pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrhydrothiophene, quinuclidine, tropane and the like. A "heterocycloalkyl," "heterocyclic," or "heterocycle" group can be attached to the remainder of the molecule through one or more ring carbons or heteroatoms. In some embodiments, "heterocycloalkyl" encompasses3- to 10-membered heterocycloalkyl, 4- to 10-membered heterocycloalkyl, 5- to 10-membered heterocycloalkyl, 6- to 10-membered heterocycloalkyl, 7- to 10-membered heterocycloalkyl, 8- to 10-membered heterocycloalkyl, 9- to 10-membered heterocycloalkyl, 3- to 9-membered heterocycloalkyl, 4- to 9-membered heterocycloalkyl, 5- to 9-membered heterocycloalkyl, 6- to 9-membered heterocycloalkyl, 7- to 9-membered heterocycloalkyl, 8- to 9-membered heterocycloalkyl, 3- to 8-membered heterocycloalkyl, 4- to 8-membered heterocycloalkyl, 5- to 8-membered heterocycloalkyl, 6- to 8-membered heterocycloalkyl, 7- to 8-membered heterocycloalkyl, 3- to 7-membered heterocycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 7-membered heterocycloalkyl, 6- to 7-membered heterocycloalkyl, 3- to 6-membered heterocycloalkyl, 4- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkyl, 3- to 10-membered heterocycloalkyl, 4- to 5-membered heterocycloalkyl, or 3- to 4-membered heterocycloalkyl. In other embodiments, "heterocycloalkyl" may be characterized by the number of carbon atoms in the ring, provided that the ring contains at least one heteroatom. For example, in some embodiments, "heterocycloalkyl" encompasses $C_3$-$C_9$ heterocycloalkyl, $C_3$-$C_8$ heterocycloalkyl, $C_3$-$C_7$ heterocycloalkyl, $C_3$-$C_6$ heterocycloalkyl, $C_3$-$C_5$ heterocycloalkyl, $C_3$-$C_4$ heterocycloalkyl, $C_4$-$C_9$ heterocycloalkyl, $C_4$-$C_8$ heterocycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_4$-$C_6$ heterocycloalkyl, $C_4$-$C_5$ heterocycloalkyl, $C_5$-$C_9$ heterocycloalkyl, $C_5$-$C_8$ heterocycloalkyl, $C_5$-$C_7$ heterocycloalkyl, $C_5$-$C_6$ heterocycloalkyl, $C_6$-$C_9$ heterocycloalkyl, $C_6$-$C_8$ heterocycloalkyl, $C_6$-$C_7$ heterocycloalkyl, $C_7$-$C_9$ heterocycloalkyl, $C_7$-$C_8$ heterocycloalkyl, or $C_8$-$C_9$ heterocycloalkyl. It should be recognized that "heterocycloalkyl" as described by the number of ring atoms may also be described by number of carbon atoms in the ring. For example, a piperazinyl ring may be described as a $C_4$ heterocycloalkyl ring or a 6-membered heterocycloalkyl ring; an azetidinyl or oxetanyl ring may each be described as a $C_3$ heterocycloalkyl ring or a 4-membered heterocycloalkyl ring.

**[0038]** The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms. In some embodiments, an alkyl (or alkylene) group will have 10 or fewer carbon atoms.

**[0039]** The term "heteroalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heteroalkyl, as exemplified by

-$CH_2$-$CH_2$-S-$CH_2CH_2$-, -$CH_2$-S-$CH_2$-$CH_2$-NH-$CH_2$-, -O-$CH_2$-CH=CH-, -$CH_2$-CH=C(H)$CH_2$-O-$CH_2$- and -S-$CH_2$-C≡C-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like).

**[0040]** The term "heterocycloalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heterocycloalkyl. For heterocycloalkylene groups, heteroatoms can also occupy either or both of the chain termini.

**[0041]** The terms "alkoxy" and "alkylamino" are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom or an amino group, respectively.

**[0042]** The term "heterocycloalkoxy" refers to a heterocycloalkyl-O- group in which the heterocycloalkyl group is as previously described herein.

**[0043]** The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "$C_1$-$C_4$ haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, difluoromethyl, and the like.

**[0044]** The term "haloalkyl-OH" refers to a haloalkyl group as described above which is also substituted by one or more hydroxyl groups. The term "haloalkyl-OH" is meant to include haloalkyl substituted by one hydroxyl group, as well as haloalkyl substituted by multiple hydroxyl groups. For example, the term "haloalkyl-OH" includes -CH(F)OH, -$CH_2$CFH$CH_2$OH, -CH(OH)$CF_3$, and the like.

**[0045]** The term "alkyl-OH" refers to an alkyl substituted by one or more hydroxyl groups. The term "alkyl-OH" is meant to include alkyl substituted by one hydroxyl group, as well as alkyl substituted by multiple hydroxyl groups. For example, the term "alkyl-OH" includes -$CH_2$OH, -CH(OH)$CH_3$, -$CH_2CH_2$OH, and the like.

**[0046]** The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group, which can be a single ring or multiple rings (up to three rings) which are fused together. In some embodiments, "aryl" encompasses $C_6$-$C_{14}$ aryl, $C_8$-$C_{14}$ aryl, $C_{10}$-$C_{14}$ aryl, $C_{12}$-$C_{14}$ aryl, $C_6$-$C_{12}$ aryl, $C_8$-$C_{12}$ aryl, $C_{10}$-$C_{12}$ aryl, $C_6$-$C_{10}$ aryl, $C_8$-$C_{10}$ aryl, or $C_6$-$C_8$

aryl. In some instances, both rings of a polycyclic aryl group are aromatic (e.g., naphthyl). In other instances, polycyclic aryl groups may include a non-aromatic ring fused to an aromatic ring, provided the polycyclic aryl group is bound to the parent structure via an atom in the aromatic ring. Thus, a 1,2,3,4-tetrahydronaphthalen-5-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydronaphthalen-1-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered an aryl group. Similarly, a 1,2,3,4-tetrahydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is not considered an aryl group. However, the term "aryl" does not encompass or overlap with "heteroaryl," as defined herein, regardless of the point of attachment (e.g., both quinolin-5-yl and quinolin-2-yl are heteroaryl groups). In some instances, aryl is phenyl or naphthyl. In certain instances, aryl is phenyl.

**[0047]** The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom as valency permits. In some instances, both rings of a polycyclic heteroaryl group are aromatic. In other instances, polycyclic heteroaryl groups may include a non-aromatic ring (e.g., cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl) fused to a heteroaryl ring, provided the polycyclic heteroaryl group is bound to the parent structure via an atom in the aromatic ring. For example, a 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered a heteroaryl group, while 4,5,6,7-tetrahydrobenzo[d]thiazol-5-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered a heteroaryl group.

**[0048]** Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. In

some embodiments, the term "heteroaryl" encompasses 5- to 10-membered heteroaryl, 6- to 10-membered heteroaryl, 7- to 10-membered heteroaryl, 8- to 10-membered heteroaryl, 9- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 6- to 9-membered heteroaryl, 7- to 9-membered heteroaryl, 8- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 6- to 8-membered heteroaryl, 7- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, 6- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl.

**[0049]** The above terms (*e.g.*, "alkyl," "aryl" and "heteroaryl"), in some embodiments, will include both substituted and unsubstituted forms of the indicated radical. The term "substituted" means that the specified group or moiety bears one or more substituents including, but not limited to, substituents such as alkoxy, acyl, acyloxy, alkoxycarbonyl, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, aryl, heteroaryl, aryloxy, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, alkyl, alkenyl, alkynyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo and the like. The term "unsubstituted" means that the specified group bears no substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. When a group or moiety bears more than one substituent, it is understood that the substituents may be the same or different from one another. In some embodiments, a substituted group or moiety bears from one to five substituents. In some embodiments, a substituted group or moiety bears one substituent. In some embodiments, a substituted group or moiety bears two substituents. In some embodiments, a substituted group or moiety bears three substituents. In some embodiments, a substituted group or moiety bears four substituents. In some embodiments, a substituted group or moiety bears five substituents.

**[0050]** By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined herein. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible, and/or inherently unstable. It will also be understood that where a group or moiety is optionally substituted, the disclosure includes both embodiments in which the group or moiety is substituted and embodiments in which the group or moiety is unsubstituted.

**[0051]** As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), boron (B), and silicon (Si).

**[0052]** As used herein, the term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

**[0053]** As used herein, the term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

**[0054]** As used herein, a wavy line "〰" that intersects a bond in a chemical structure indicates the point of attachment of the atom to which the wavy bond is connected in the chemical structure to the remainder of a molecule, or to the remainder of a fragment of a molecule.

**[0055]** As used herein, the representation of a group (*e.g.*, $X^a$) in parenthesis followed by a subscript integer range (*e.g.*, $(X^a)_{0-1}$) means that the group can have the number of occurrences as designated by the integer range. For example, $(X^a)_{0-1}$ means the group $X^a$ can be absent or can occur one time.

**[0056]** "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.* melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers can separate under high resolution analytical procedures such as electrophoresis and chromatography.

**[0057]** "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

**[0058]** Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the present disclosure can contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the present disclosure, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present disclosure. Many organic compounds exist in

optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (−) are employed to designate the sign of rotation of plane-polarized light by the compound, with (−) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

**[0059]** As used herein, the term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

**[0060]** As used herein, the term "solvate" refers to an association or complex of one or more solvent molecules and a compound of the present disclosure. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water. Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present disclosure.

**[0061]** The term "co-crystal" as used herein refers to a solid that is a crystalline single phase material composed of two or more different molecular or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. A co-crystal consists of two or more components that form a unique crystalline structure having unique properties. Co-crystals are typically characterized by a crystalline structure, which is generally held together by freely reversible, non-covalent interactions. As used herein, a co-crystal refers to a compound of the

present disclosure and at least one other component in a defined stoichiometric ratio that form a crystalline structure.

**[0062]** As used herein, the term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functional group on a compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonylethyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see P. G. M. Wuts and T. W. Greene, Greene's Protective Groups in Organic Synthesis 4$^{th}$ edition, Wiley-Interscience, New York, 2006.

**[0063]** As used herein, the term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N′-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a

sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

**[0064]** The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present disclosure.

**[0065]** Certain compounds of the present disclosure possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (*e.g.*, separate enantiomers) are all intended to be encompassed within the scope of the present disclosure.

**[0066]** The compounds of the present disclosure can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present disclosure also embraces isotopically-labeled variants of the present disclosure which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the present disclosure and include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as $^{2}H$ ("D"), $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{13}N$, $^{15}N$, $^{15}O$, $^{17}O$, $^{18}O$, $^{32}P$, $^{33}P$, $^{35}S$, $^{18}F$, $^{36}Cl$, $^{123}I$ and $^{125}I$. Certain isotopically labeled compounds of the present disclosure (*e.g.*, those labeled with $^{3}H$ or $^{14}C$) are useful in compound and/or substrate tissue distribution assays. Tritiated ($^{3}H$)

and carbon-14 ($^{14}C$) isotopes are useful for their ease of preparation and detectability. Further substitution with heavier isotopes such as deuterium (*i.e.*, $^{2}H$) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as $^{15}O$, $^{13}N$, $^{11}C$, and $^{18}F$ are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

**[0067]** "Treating" or "treatment" of a disease in a patient refers to inhibiting the disease or arresting its development; or ameliorating or causing regression of the disease. As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (e.g., preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delay or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by "treatment" is a reduction of pathological consequence of the disease or disorder. The methods of the present disclosure contemplate any one or more of these aspects of treatment.

**[0068]** "Preventing", "prevention", or "prophylaxis" of a disease in a patient refers to preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease.

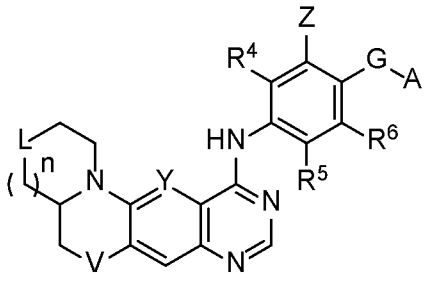
**[0069]** The phrase "therapeutically effective amount" means an amount of a compound of the present disclosure that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

**[0070]** The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth.

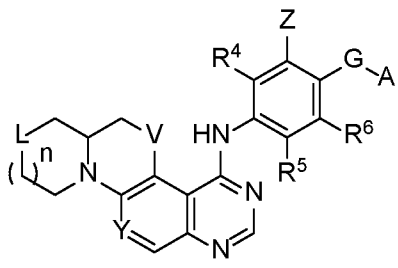
**[0071]** It is appreciated that certain features of the present disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (*i.e.*, compounds that can be isolated, characterized, and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

## II. COMPOUNDS

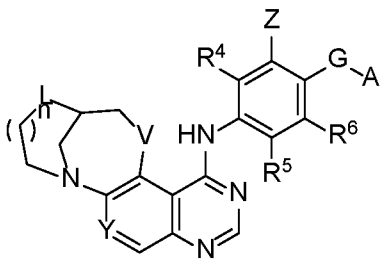
**[0072]** In one aspect, provided herein is a compound of formula (I-A), (I-B'), (I-C'), or (I-D):



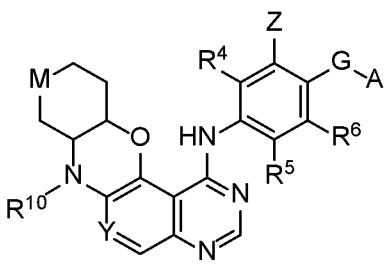
(I-A),



(I-B'),

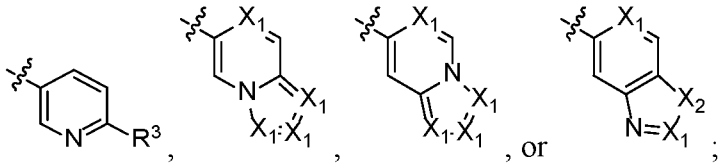


(I-C'), or



(I-D),

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

M is NH or N($C_1$-$C_6$ alkyl);

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -S(O)$_2$-, or $CH_2$;

V is O, S, or $NR^2$;

each $X_1$ is independently N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

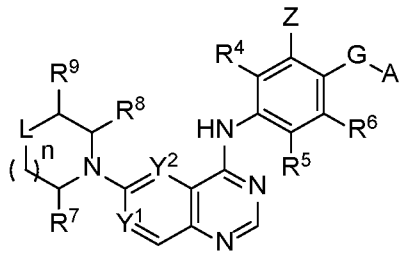
$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, -$CD_3$, or $C_3$-$C_6$ cycloalkyl;

$R^4$, $R^5$, and $R^6$ are each independently -H or halogen; and

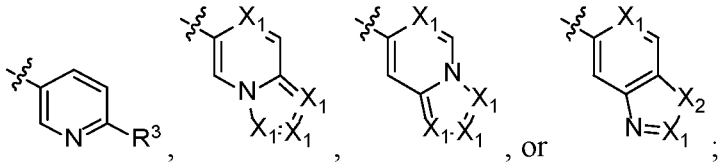
$R^{10}$ is -H or $C_1$-$C_6$ alkyl.

**[0073]** In one aspect, provided herein is a compound of formula (I)



(I),

or a pharmaceutically acceptable salt thereof wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

either $Y^1$ is C-$R^{Y1}$, $Y^2$ is Y, $R^8$ is -H, $R^9$ is -H, and $R^{Y1}$ is taken together with $R^7$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^1$,

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$, or

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^8$ is -H, and $R^{Y2}$ is taken together with $R^9$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$;

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -S(O)$_2$-, or $CH_2$;

V is O, S, or $NR^2$;

$X_1$ is N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

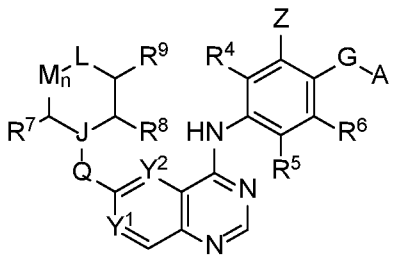
$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or $-NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is independently optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, $-CD_3$, or $C_3$-$C_6$ cycloalkyl; and

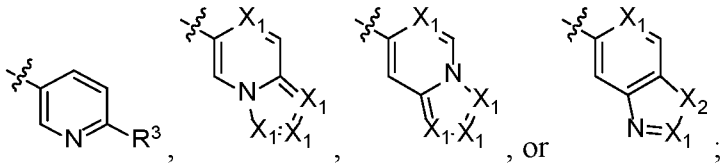
$R^4$, $R^5$, and $R^6$ are each independently -H or halogen.

**[0074]** In some embodiments, the compound is a compound of formula (I'')



(I''),

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

J is N or CH;

L is N-E, $CH_2$, O, or a bond;

M is N-E or $CH_2$;

either Q is a bond, $Y^1$ is C-$R^{Y1}$, $Y^2$ is Y, $R^8$ is -H, $R^9$ is -H, and $R^{Y1}$ is taken together with $R^7$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^1$,

Q is a bond, $Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$,

Q is a bond, $Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^8$ is -H, and $R^{Y2}$ is taken together with $R^9$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$, or

Q is $NR^{10}$, $Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -O-;

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, or $CH_2$;

V is O, S, or $NR^2$;

$X_1$ is N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

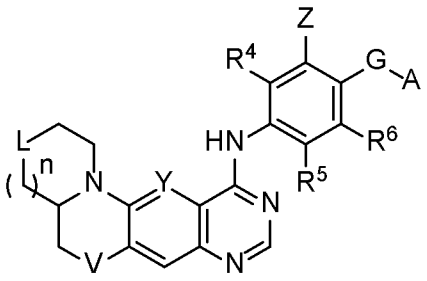
$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is independently optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, -$CH_3$, or $C_3$-$C_6$ cycloalkyl;

$R^4$, $R^5$, and $R^6$ are each independently -H or halogen; and

$R^{10}$ is -H or $C_1$-$C_6$ alkyl.

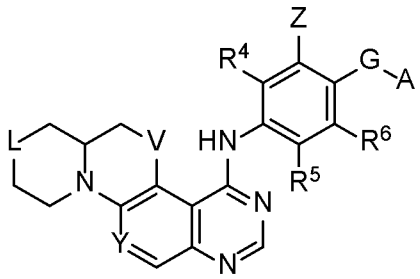
**[0075]** In some embodiments, the compound or the compound of formula (I) is a compound of formula (I-A)



(I-A)

wherein A, L, n, G, V, Y, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I).

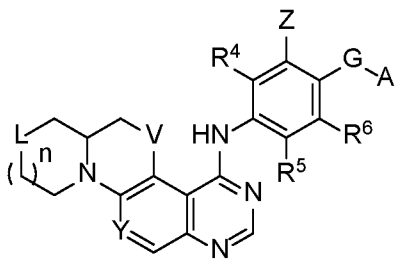
**[0076]** In some embodiments, the compound or the compound of formula (I) is a compound of formula (I-B)



(I-B)

wherein A, L, G, V, Y, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I).

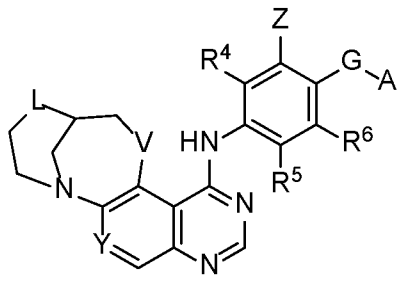
**[0077]** In some aspect, the compound or the compound of formula (I) is a compound of formula (I-B'):



(I-B'),

wherein A, L, G, V, Y, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I).

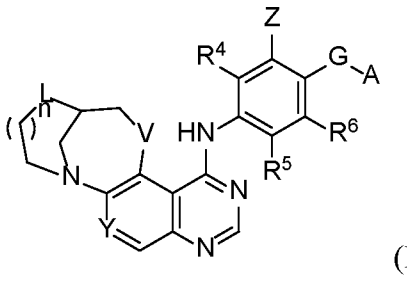
**[0078]** In some embodiments, the compound or the compound of formula (I) is a compound of formula (I-C)



(I-C)

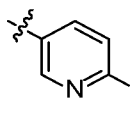
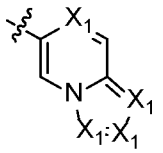
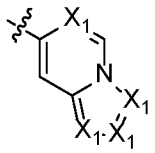
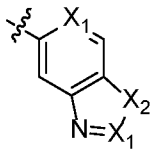
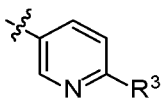
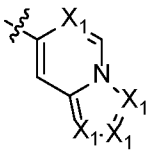
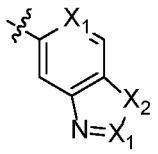
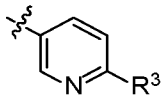
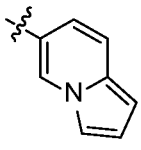
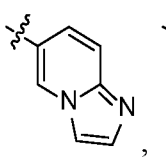
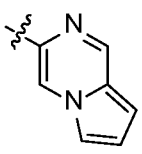
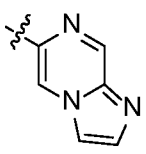
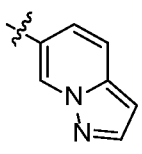
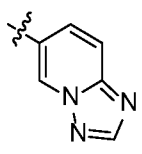
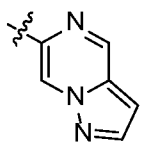
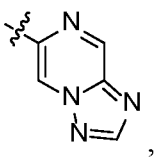
wherein A, L, G, V, Y, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I).

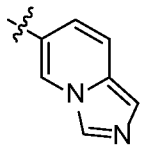
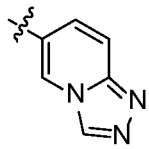
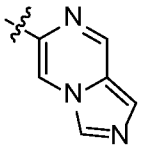
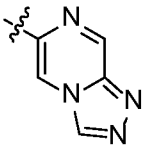
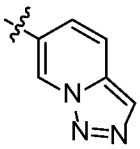
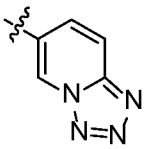
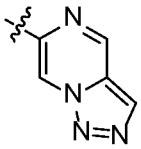
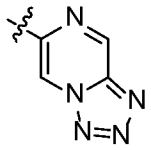
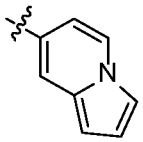
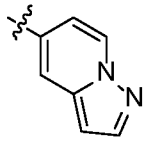
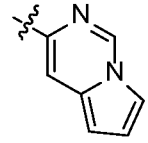
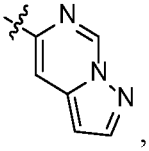
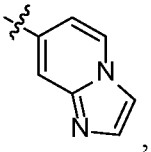
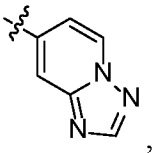
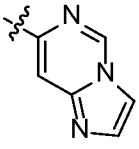
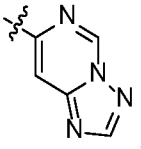
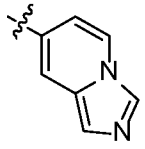
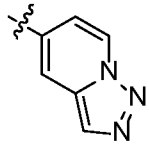
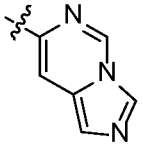
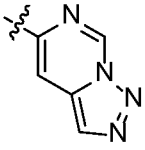
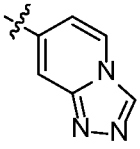
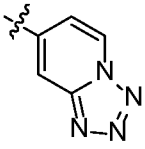
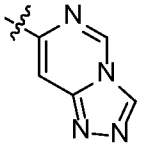
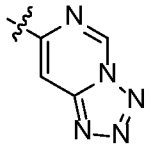
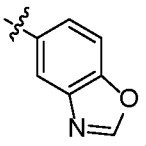
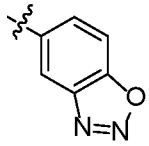
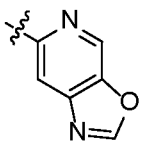
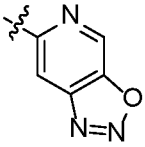
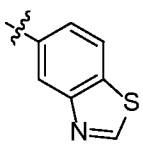
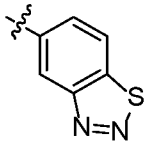
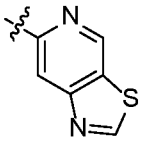
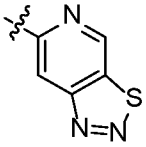
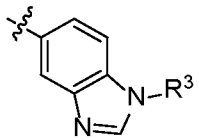
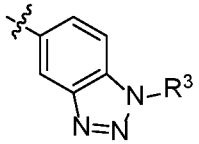
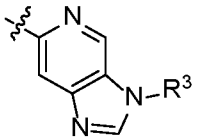
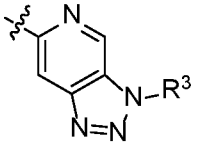
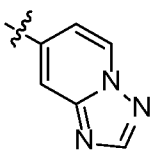
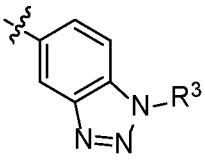
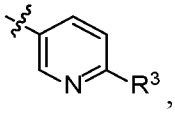
**[0079]** In some embodiments, the compound or the compound of formula (I) is a compound of formula (I-C'):

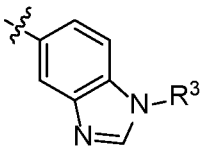
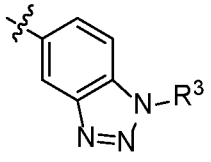
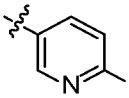
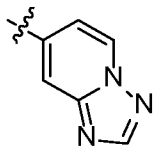
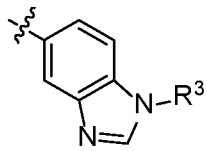
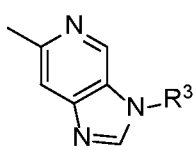
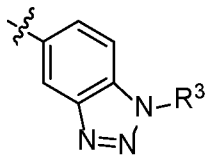


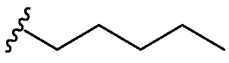
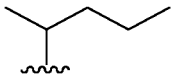
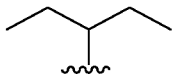
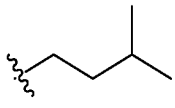
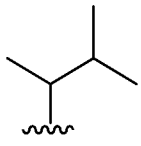
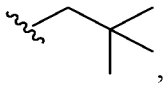
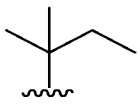
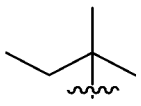
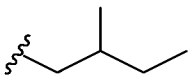
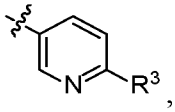
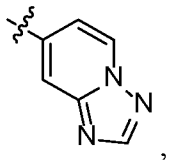
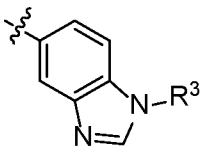
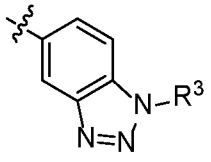
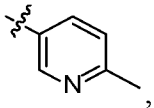
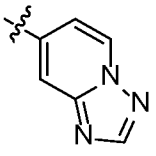
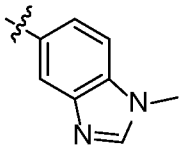
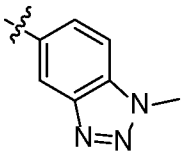
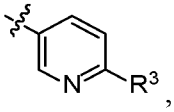
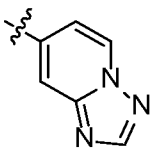
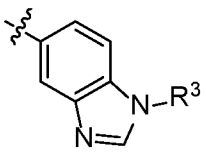
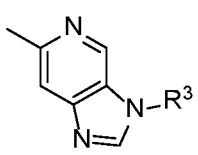
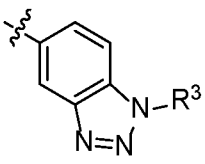
(I-C'),

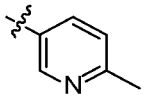
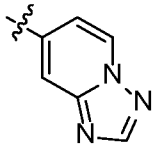
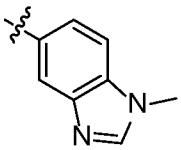
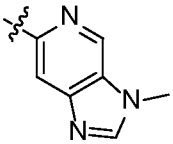
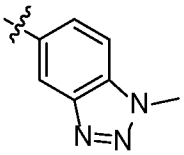
wherein A, L, G, V, Y, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I).

**[0080]** In some embodiments, A is selected from the group consisting of  ,  ,  , and  . In some embodiments, A is selected from the group consisting of  ,  , and  . In some embodiments, A is  . In some embodiments A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,

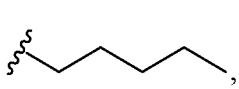
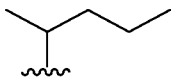
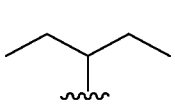
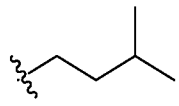
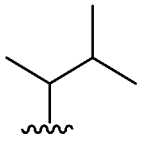
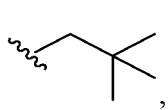
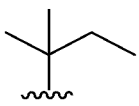
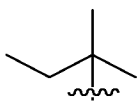
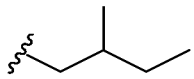
 ,  ,  ,  ,  ,  ,  , and  . In some embodiments A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiment, A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, A is  . In some embodiments, A is  , or  . In some embodiments, A is selected from the group consisting of  , ,


, and  . In some embodiments, A is selected from the group consisting of  ,  ,  ,  , and  .

**[0081]** In some embodiments, $R^3$ is selected from the group consisting of -H, $C_1$-$C_6$ alkyl, -$CD_3$, and $C_3$-$C_6$ cycloalkyl. In some embodiments, $R^3$ is $C_3$-$C_6$ cycloalkyl. In some embodiments, $R^3$ is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In some embodiments, $R^3$ is $C_1$-$C_6$ alkyl. In some embodiments, $R^3$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, $R^3$ is -$CH_3$. In some embodiments, A is selected from the group consisting of  ,  ,  , and  , and $R^3$ is $C_1$-$C_6$ alkyl. In some embodiments, A is selected from the group consisting of  ,  ,  , and  . In some embodiments, A is selected from the group consisting of  ,  ,  ,  , and  , and $R^3$ is $C_1$-$C_6$ alkyl. In

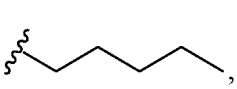
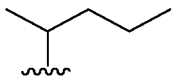
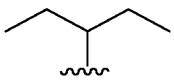
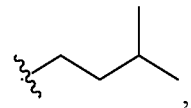
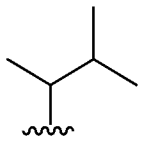
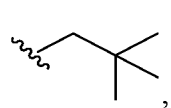
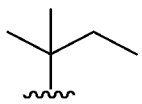
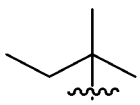
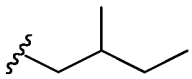
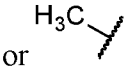
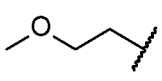
some embodiments, A is selected from the group consisting of  ,  ,  ,  , and  .

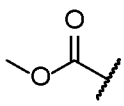
**[0082]** In some embodiments, G is selected from the group consisting of -O-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, and -$CH_2$-. In some embodiments, G is -O-. In some embodiments, G is -C(O)-. In some embodiments, G is selected from the group consisting of -S-, -S(O)-, and -$S(O)_2$-. In some embodiments, G is -$CH_2$-. In some embodiments, G is selected from the group consisting of -O-, -S-, and -$CH_2$-. In some embodiments, G is selected from the group consisting of -C(O)-, -S(O)-, and -$S(O)_2$-. In some embodiments, G is -C(O)- or -$CH_2$-.

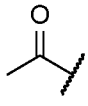
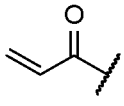
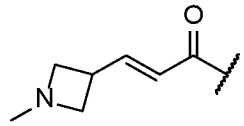
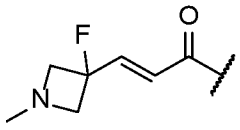
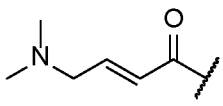
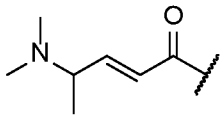
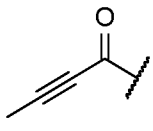
**[0083]** In some embodiments, V is selected from the group consisting of O, S, and $NR^2$. In some embodiments, V is $NR^2$ and $R^2$ is $C_1$-$C_6$ alkyl optionally substituted by 1, 2, 3, or 4 fluoro. In some embodiments, V is $NR^2$ and $R^2$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl,  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is independently optionally substituted by 1, 2, 3, or 4 fluoro. In some embodiments, V is $NR^2$ and $R^2$ is $C_3$-$C_6$ cycloalkyl optionally substituted by 1, 2, 3, or 4 fluoro. In some embodiments, V is $NR^2$ and $R^2$ is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is independently optionally substituted by 1, 2, 3, or 4 fluoro.

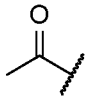
**[0084]** In some embodiments, Z is -H. In some embodiments, Z is halogen. In some embodiments, Z is selected from the group consisting of -F, -Cl, -Br, and -I. In some embodiments, Z is -F or -Cl. In some embodiments, Z is -F. In some embodiments, Z is -C≡CH. In some embodiments, Z is -$OCH_3$. In some embodiments, Z is $C_1$-$C_2$ alkyl. In some embodiments, Z is -$CH_3$. In some embodiments, Z is -$CH_2CH_3$. In some embodiments, Z is selected from the group consisting of -H, -$CH_3$, and -F.

**[0085]** In some embodiments, $R^4$ is -H. In some embodiments $R^4$ is halogen. In some embodiments, $R^4$ is selected from the group consisting of -F, -Cl, -Br, and -I. In some embodiments, $R^4$ is -F or -Cl. In some embodiments, $R^4$ is -F. In some embodiments, $R^5$ is -H. In some embodiments $R^5$ is halogen. In some embodiments, $R^5$ is selected from the group consisting of -F, -Cl, -Br, and -I. In some embodiments, $R^5$ is -F or -Cl. In some embodiments, $R^5$ is -F. In some embodiments, $R^6$ is -H. In some embodiments $R^6$ is halogen. In some embodiments, $R^6$ is selected from the group consisting of -F, -Cl, -Br, and -I. In some embodiments, $R^6$ is -F or -Cl. In some embodiments, $R^6$ is -F. In some embodiments, $R^4$, $R^5$ and $R^6$ are -H. In some embodiments, $R^4$ is -F, $R^5$ is -H, and $R^6$ is -H. In some embodiments, $R^4$ is -H, $R^5$ is -F, and $R^6$ is -H. In some embodiments, $R^4$ is -H, $R^5$ is -H, and $R^6$ is -F. In some embodiments, $R^4$ is -F, $R^5$ is -F, and $R^6$ is -H. In some embodiments, $R^4$ is -F, $R^5$ is -H, and $R^6$ is -F. In some embodiments, $R^4$ is -H, $R^5$ is -F, and $R^6$ is -F. In some embodiments, $R^4$, $R^5$ and $R^6$ are -F.

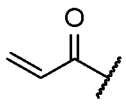
**[0086]** In some embodiments, E is -H. In some embodiments, E is $C_1$-$C_6$ alkyl optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro. In some embodiments, E is unsubstituted $C_1$-$C_6$ alkyl. In some embodiments, E is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, E is unsubstituted $C_1$-$C_3$ alkyl. In some embodiments, E is  or  . In some embodiments, E is $C_1$-$C_6$ alkyl substituted by 1 to 4 fluoro. In some embodiments, E is $C_1$-$C_6$ alkyl substituted by 1, 2, 3, or 4 fluoro. In some embodiments, E is $C_1$-$C_6$ alkyl substituted by $C_1$-$C_6$ alkoxy. In some embodiments, E is $C_1$-$C_6$ alkyl substituted by $-OCH_3$. In some embodiments, E is $C_1$-$C_3$ alkyl substituted by $-OCH_3$. E is $C_1$-$C_2$ alkyl substituted by $-OCH_3$. In some embodiments E is  .

**[0087]** In some embodiments, E is -C(O)O-($C_1$-$C_6$ alkyl). In some embodiments, E is -C(O)O-($C_1$-$C_3$ alkyl). In some embodiments, E is  .

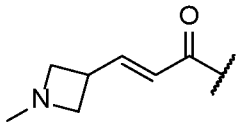
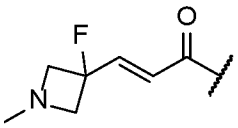
**[0088]** In some embodiments, E is -C(O)-$R^1$, wherein $R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

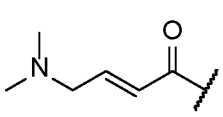
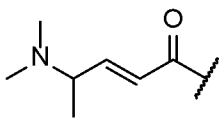
**[0089]** In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_1$-$C_6$ alkyl, optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is unsubstituted $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is unsubstituted $C_1$-$C_3$ alkyl. In some embodiments, E is  .

**[0090]** In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl, optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl.

**[0091]** In some embodiments, E is -C(O)-$R^1$ and $R^1$ is unsubstituted $C_2$-$C_6$ alkenyl. E is -C(O)-$R^1$ and $R^1$ is unsubstituted $C_2$-$C_3$ alkenyl. In some embodiments, E is  . In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl.

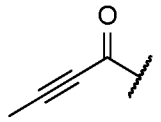
**[0092]** In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 3-6 membered heterocycle optionally substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$ alkenyl substituted by 3-6 membered heterocycle optionally substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 3-6 membered heterocycle comprising at least one N heteroatom and

optionally substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by unsubstituted 3-6 membered heterocycle. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by unsubstituted 4-membered heterocycle. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 3-6 membered heterocycle substituted by halogen or $C_1$-$C_6$ alkyl. E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 4-membered heterocycle substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 3-6 membered heterocycle substituted by -F, -Cl, -Br, -I, or $C_1$-$C_3$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 3-6 membered heterocycle substituted by -F or -$CH_3$. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 4-membered heterocycle substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 4-membered heterocycle substituted by -F, -Cl, -Br, -I, or $C_1$-$C_3$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by 4-membered heterocycle substituted by -F or -$CH_3$. In some embodiments, E is  or  .

**[0093]** In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkenyl substituted by -$N(CH_3)_2$. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_3$-$C_4$ alkenyl substituted by -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_4$ alkenyl substituted by -$N(CH_3)_2$. In some embodiments, E is  or  .

**[0094]** In some embodiments, E is -C(O)-$R^1$ and $R^1$ is $C_2$-$C_6$ alkynyl, optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl. In some embodiments, E is -C(O)-$R^1$ and $R^1$ is unsubstituted $C_2$-$C_6$ alkynyl. In some

embodiments, E is -C(O)-$R^1$ and $R^1$ is unsubstituted $C_2$-$C_3$ alkynyl. In some embodiments, E is



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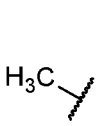
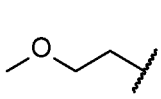
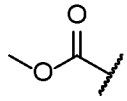
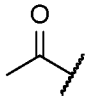
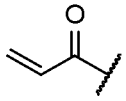
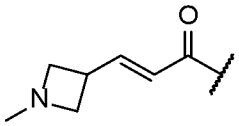
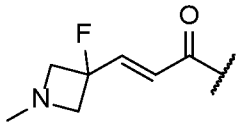
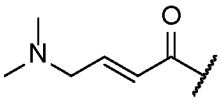
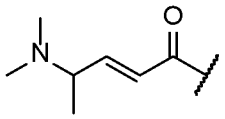
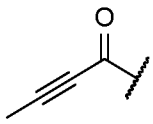
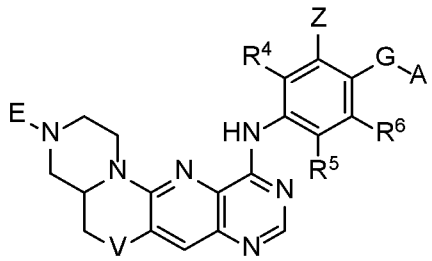
**[0095]** In some embodiments, E is selected from the group consisting of -H,  ,

 ,  ,  ,  ,  ,  ,  ,

 ,  , and  .

**[0096]** In some embodiments, the compound of formula (I) or formula (I-A) is a compound of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10),



(I-A-1)

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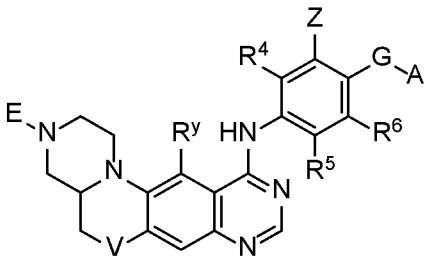

(I-A-2)

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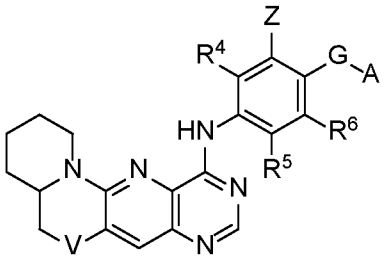

(I-A-3)

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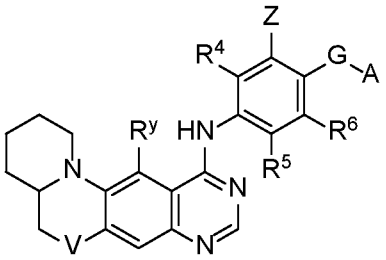

(I-A-4)

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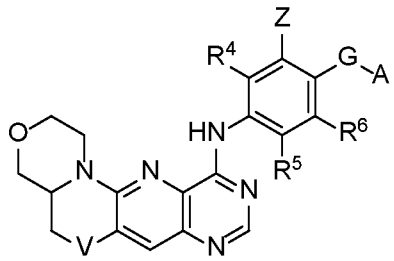

(I-A-5)

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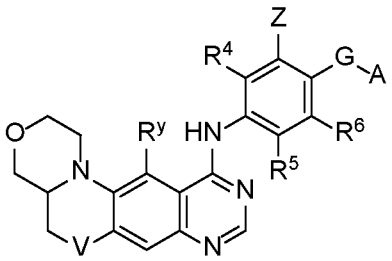

(I-A-6)

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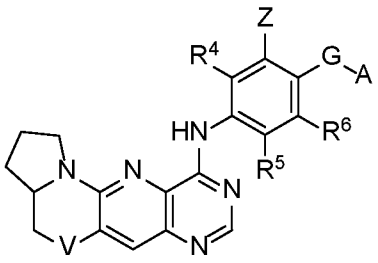

(I-A-7)

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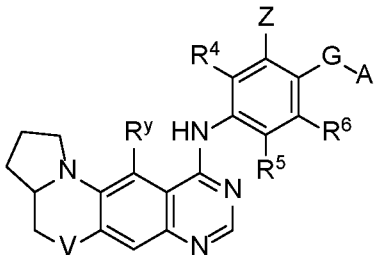

(I-A-8)

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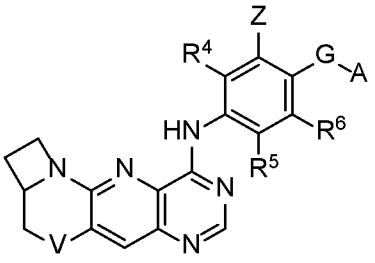
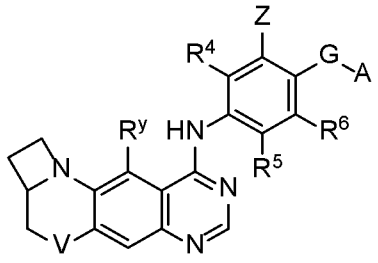


(I-A-9)

, or



(I-A-10)

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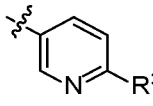
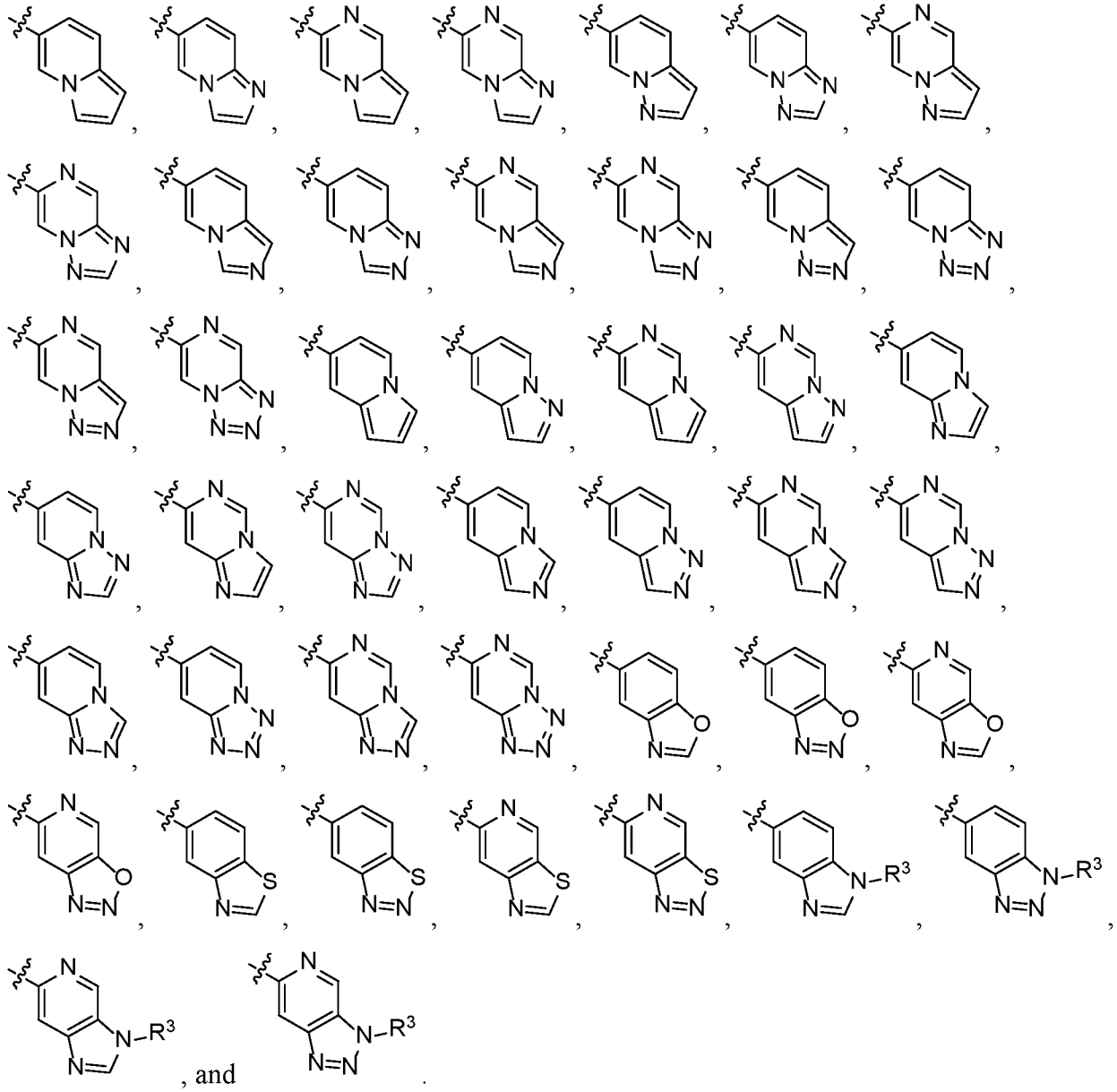
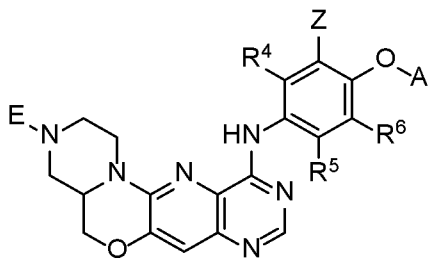
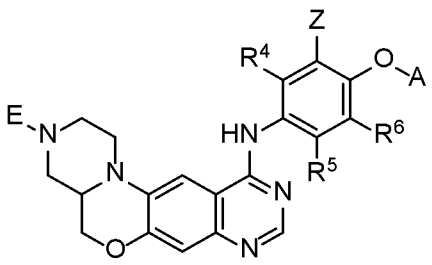
wherein A, E, G, V, Z, $R^4$, $R^5$, $R^6$, and $R^y$ are as defined for formula (I) or formula (I-A). In some embodiments, the compound is a compound of formula (I-A-1). In some embodiments, the compound is a compound of formula (I-A-2). In some embodiments, the compound is a compound of formula (I-A-3). In some embodiments, the compound is a compound of formula (I-A-4). In some embodiments, the compound is a compound of formula (I-A-5). In some embodiments, the compound is a compound of formula (I-A-6). In some embodiments, the compound is a compound of formula (I-A-7). In some embodiments, the compound is a compound of formula (I-A-8). In some embodiments, the compound is a compound of formula (I-A-9). In some embodiments, the compound is a compound of formula (I-A-10). In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), V is O. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), V is S. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), V is $NR^2$. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), G is O. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), $R^y$ is -H. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), $R^y$ is -F. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), A is selected from the group consisting of  ,



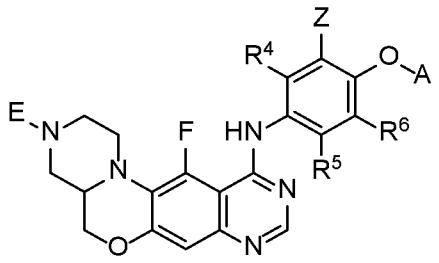
**[0097]** In some embodiments, the compound of formula (I) or formula (I-A) is a compound of formula (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), or (I-A-9a),



(I-A-1a)



(I-A-2a)



(I-A-2b)

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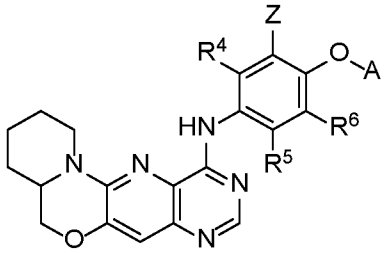

(I-A-3a)

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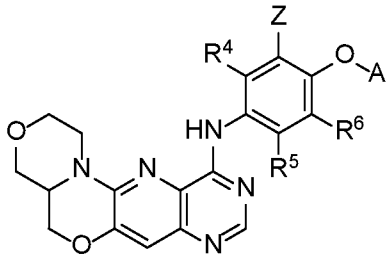

(I-A-5a)

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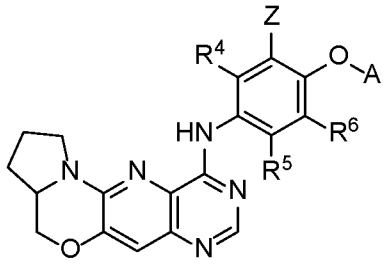
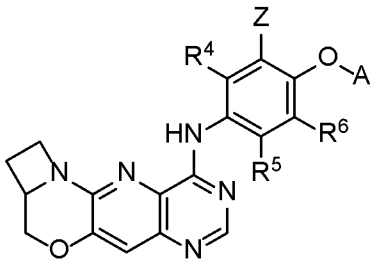


(I-A-7a)

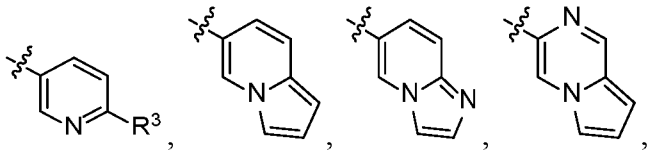
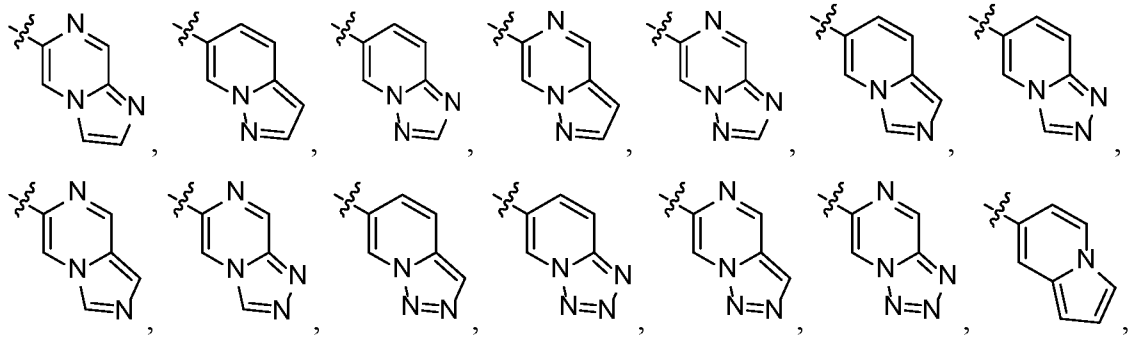
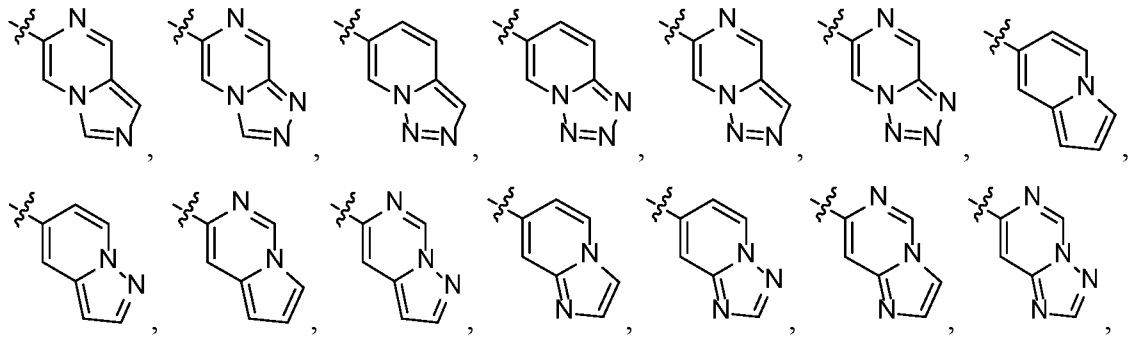
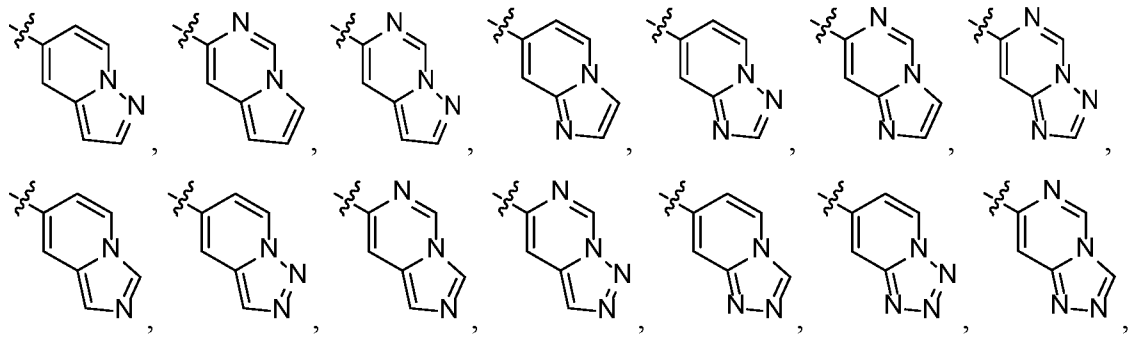
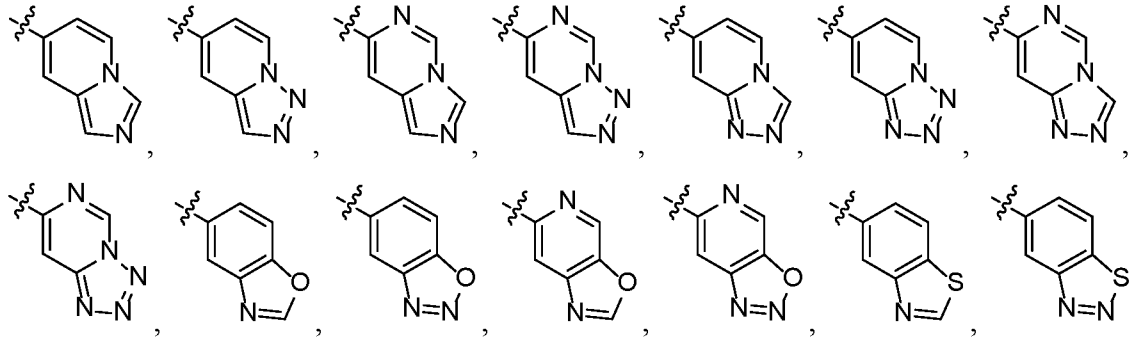
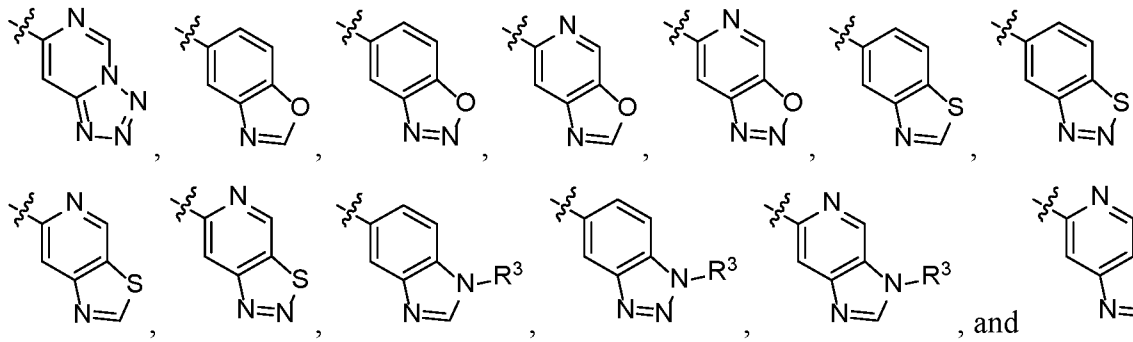
, or

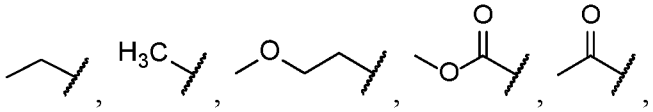
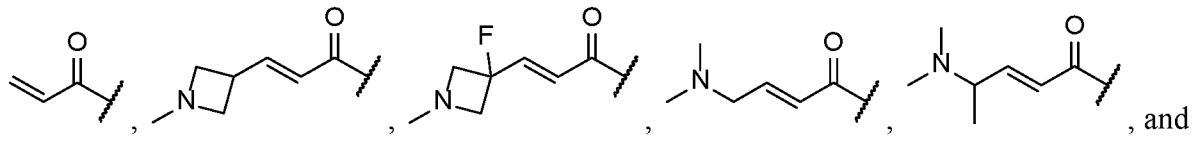
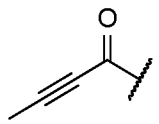


(I-A-9a)

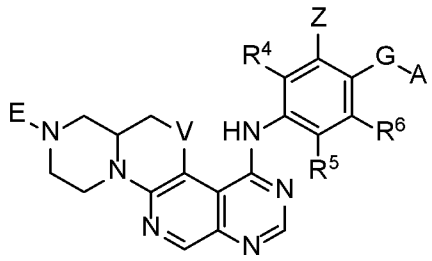
,

wherein A, E, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I) or formula (I-A). In some embodiments, the compound is a compound of formula (I-A-1a). In some embodiments, the compound is a compound of formula (I-A-2a). In some embodiments, the compound is a compound of formula (I-A-2b). In some embodiments, the compound is a compound of formula (I-A-3a). In some embodiments, the compound is a compound of formula (I-A-5a). In some embodiments, the compound is a compound of formula (I-A-7a). In some embodiments, the compound is a compound of formula (I-A-9a). In some variations of formula (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), or (I-A-9a), Z is selected from the group consisting of -H, -F, and $-CH_3$. In some variations of formula (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), or (I-A-9a), $R^4$ is -H or -F. In some variations of formula (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), or (I-A-9a), $R^5$ is -H or -F. In some variations of formula (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), or (I-A-9a), $R^6$ is -H or -F. In some variations of formula (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), or (I-A-9a), A is

selected from the group consisting of  ,  ,  ,  ,  ,  , , and .

**[0098]** In some variations of formula (I-A-1) (I-A-2), (I-A-1a), (I-A-2a), or (I-A-2b), E is selected from the group consisting of -H,  ,  , and  .

**[0099]** In some embodiments, the compound of formula (I) or formula (I-B') is a compound of formula (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8),



(I-B-1)

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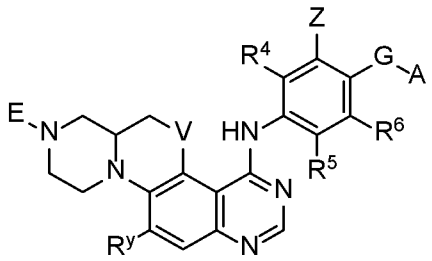

(I-B-2)

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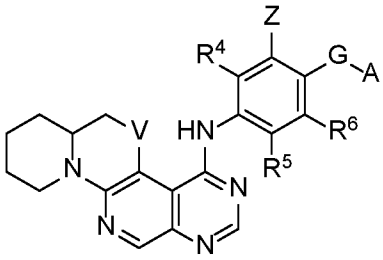

(I-B-3)

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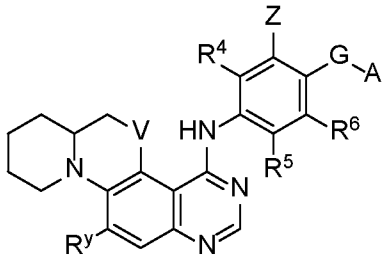

(I-B-4)

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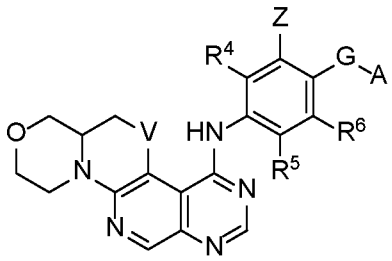

(I-B-5)

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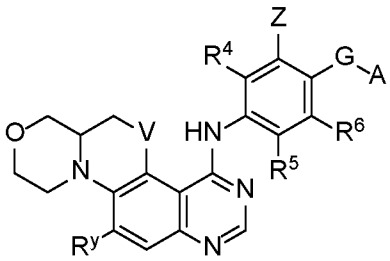

(I-B-6)

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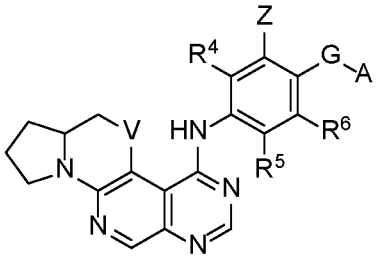
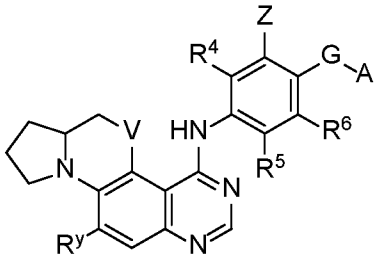


(I-B-7)

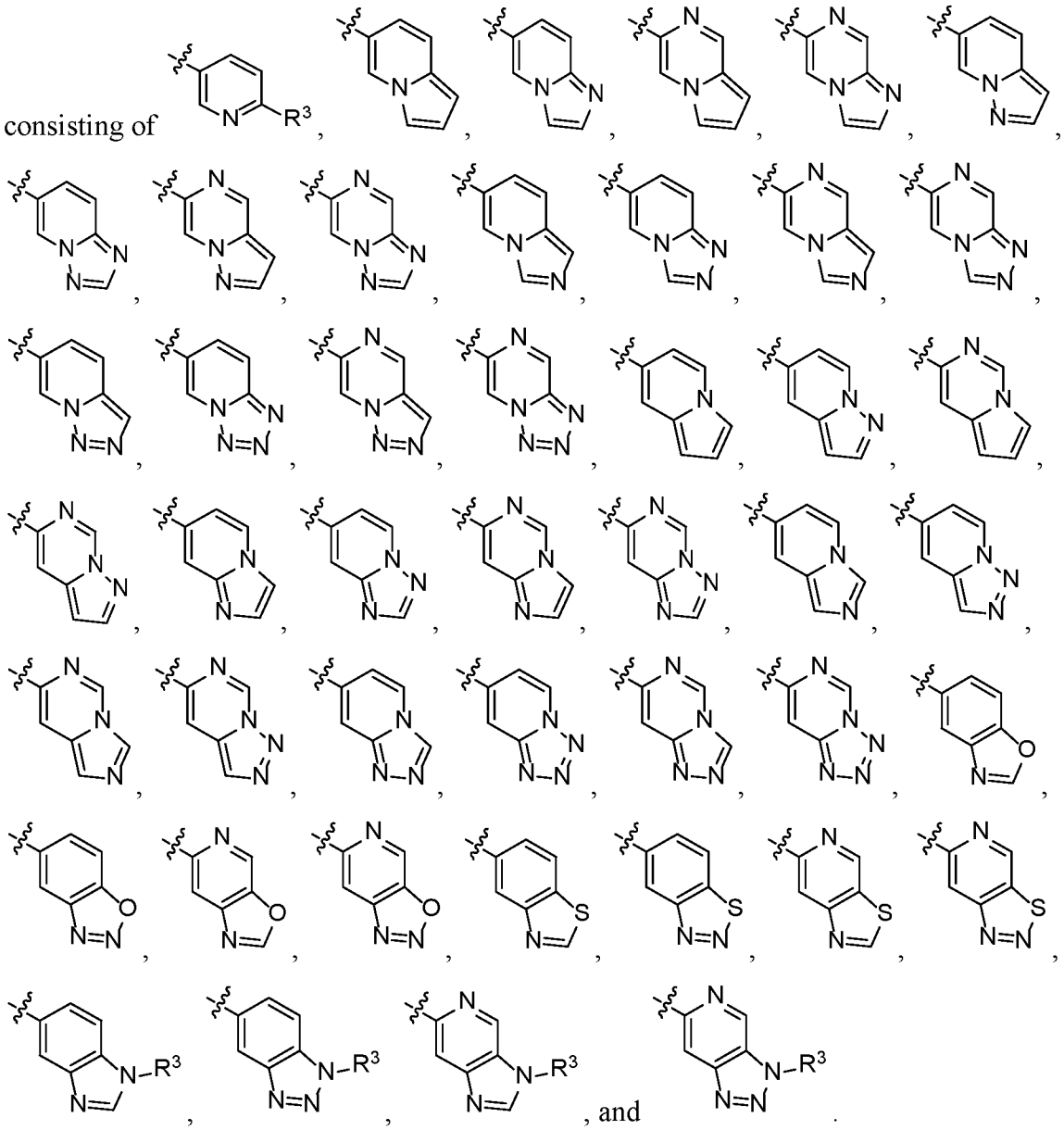
, or



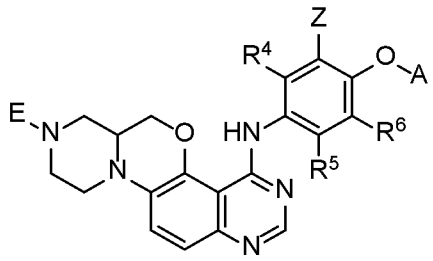
(I-B-8)

,

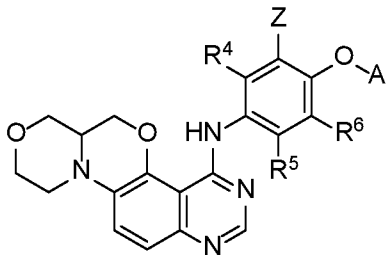
wherein A, E, G, V, Z, $R^4$, $R^5$, $R^6$, and $R^y$ are as defined for formula (I) or formula (I-B'). In some embodiments, the compound is a compound of formula (I-B-1). In some embodiments, the compound is a compound of formula (I-B-2). In some embodiments, the compound is a compound of formula (I-B-3). In some embodiments, the compound is a compound of formula (I-B-4). In some embodiments, the compound is a compound of formula (I-B-5). In some embodiments, the compound is a compound of formula (I-B-6). In some embodiments, the compound is a compound of formula (I-B-7). In some embodiments, the compound is a compound of formula (I-B-8). In some variations of formula (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8), V is O. In some variations of formula (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8), V is S. In some variations of formula

(I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8), V is $NR^2$. In some variations of formula (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8), G is O. In some variations of formula (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8), $R^y$ is -H. In some variations of formula (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), or (I-B-8), $R^y$ is -F. In some variations of formula (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), or (I-A-10), A is selected from the group consisting of  , and .

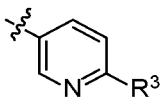
**[0100]** In some embodiments, the compound of formula (I) or formula (I-B') is a compound of formula (I-B-1a) or (I-B-5a),

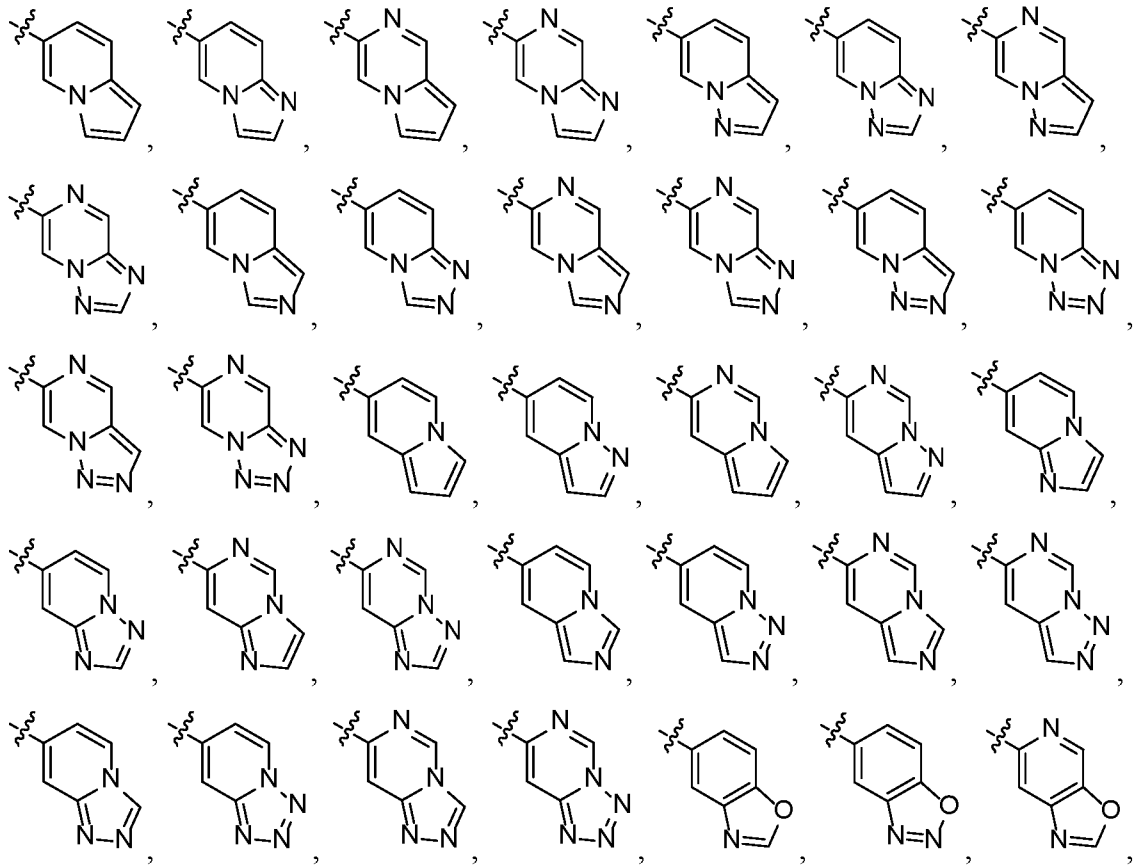


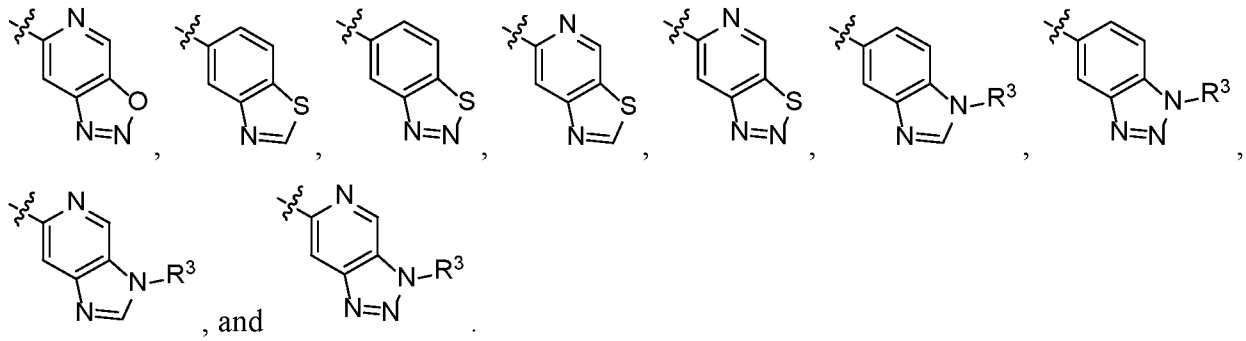
or



(I-B-1a) (I-B-5a)

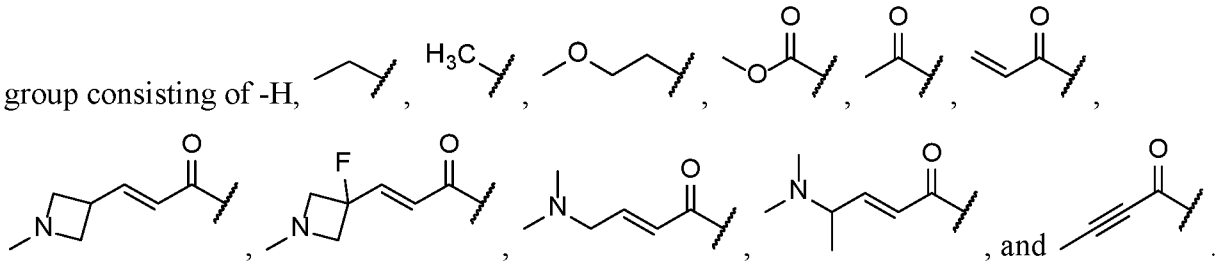
wherein A, E, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I) or formula (I-B'). In some embodiments, the compound is a compound of formula (I-B-1a). In some embodiments, the compound is a compound of formula (I-B-5a). In some variations of formula (I-B-1a) or (I-B-5a), Z is selected from the group consisting of -H, -F, and $-CH_3$. In some variations of formula (I-B-1a) or (I-B-5a), $R^4$ is -H or -F. In some variations of formula (I-B-1a) or (I-B-5a), $R^5$ is -H or -F. In some variations of formula (I-B-1a) or (I-B-5a), $R^6$ is -H or -F. In some variations of formula (I-B-1a) or (I-B-5a), A is selected from the group consisting of  ,





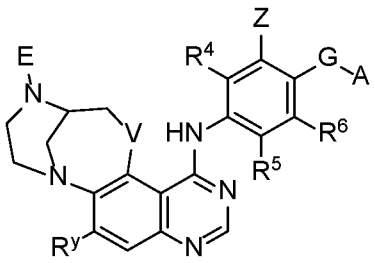
, and .

**[0101]** In some variations of formula (I-B-1), (I-B-2), or (I-B-1a), E is selected from the group consisting of -H,



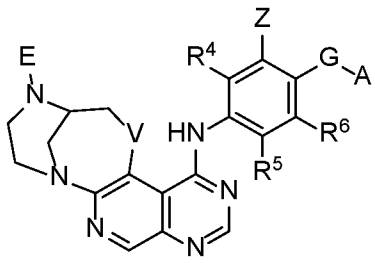
, and .

**[0102]** In some embodiments, the compound of formula (I) or formula (I-C') is a compound of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), or (I-C-6),



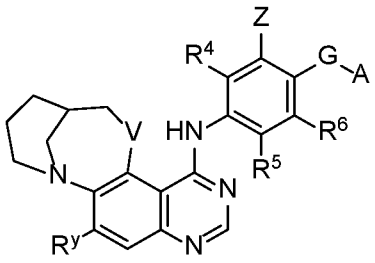
(I-C-1)

,



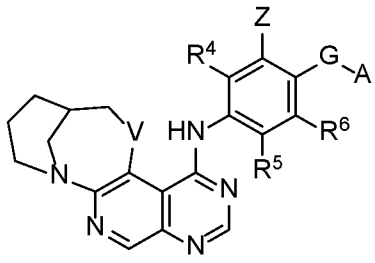
(I-C-2)

,



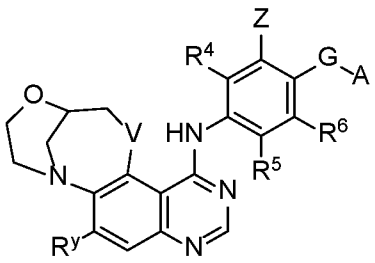
(I-C-3)

,

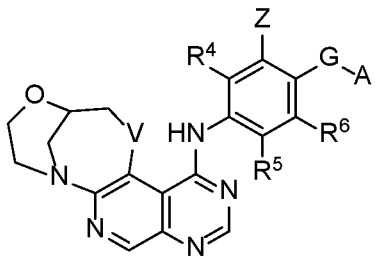


(I-C-4)

,



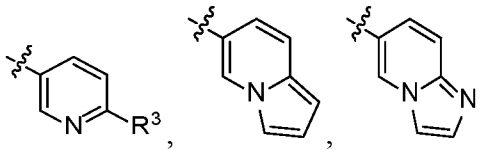
, or

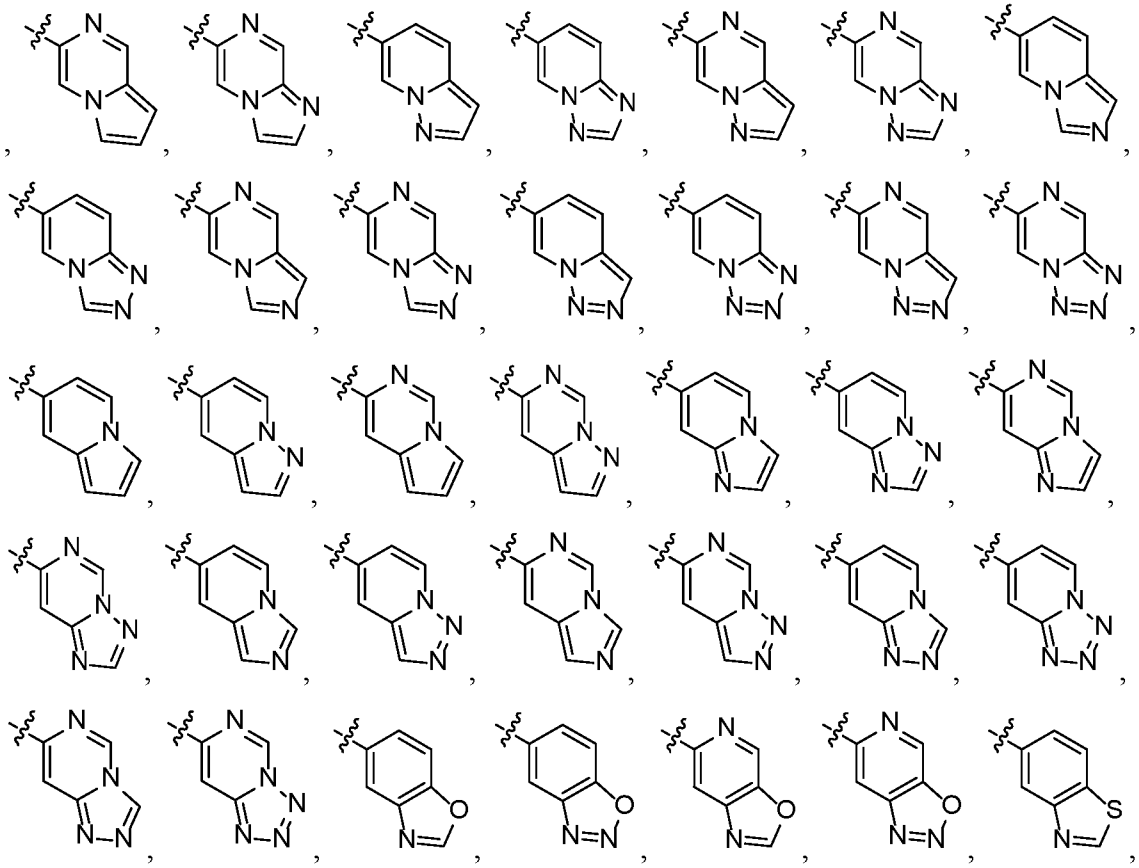


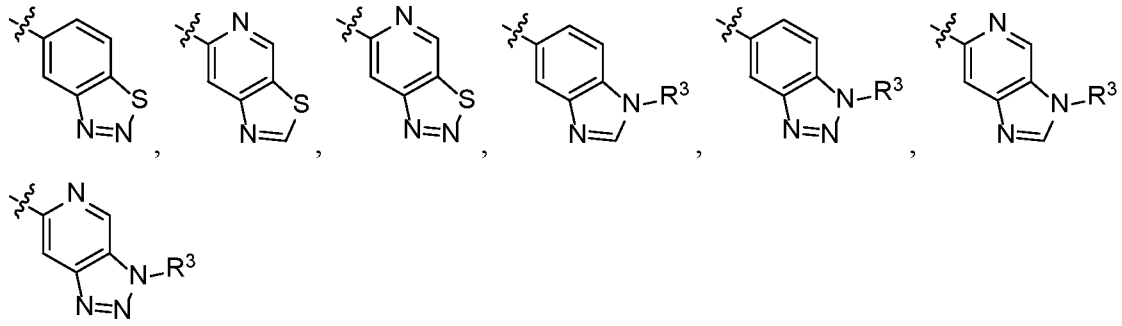
,

(I-C-5) (I-C-6)

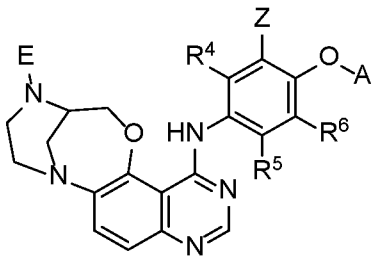
wherein A, E, G, V, Z, $R^4$, $R^5$, $R^6$, and $R^y$ are as defined for formula (I) or formula (I-C'). In some embodiments, the compound is a compound of formula (I-C-1). In some embodiments, the compound is a compound of formula (I-C-2). In some embodiments, the compound is a compound of formula (I-C-3). In some embodiments, the compound is a compound of formula (I-C-4). In some embodiments, the compound is a compound of formula (I-C-5). In some embodiments, the compound is a compound of formula (I-C-6). In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), V is O. In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), V is S. In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), V is $NR^2$. In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), G is O. In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), $R^y$ is -H. In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), $R^y$ is -F. In some variations of formula (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), A is selected from the group consisting of



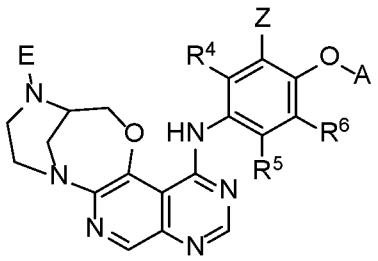




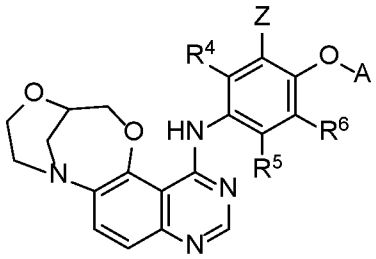
**[0103]** In some embodiments, the compound of formula (I) or formula (I-C') is a compound of formula (I-C-1a), (I-C-2a), or (I-C-5a),



(I-C-1a)

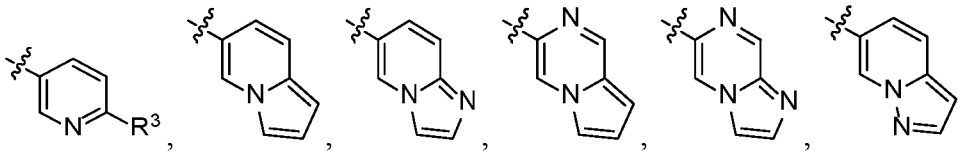


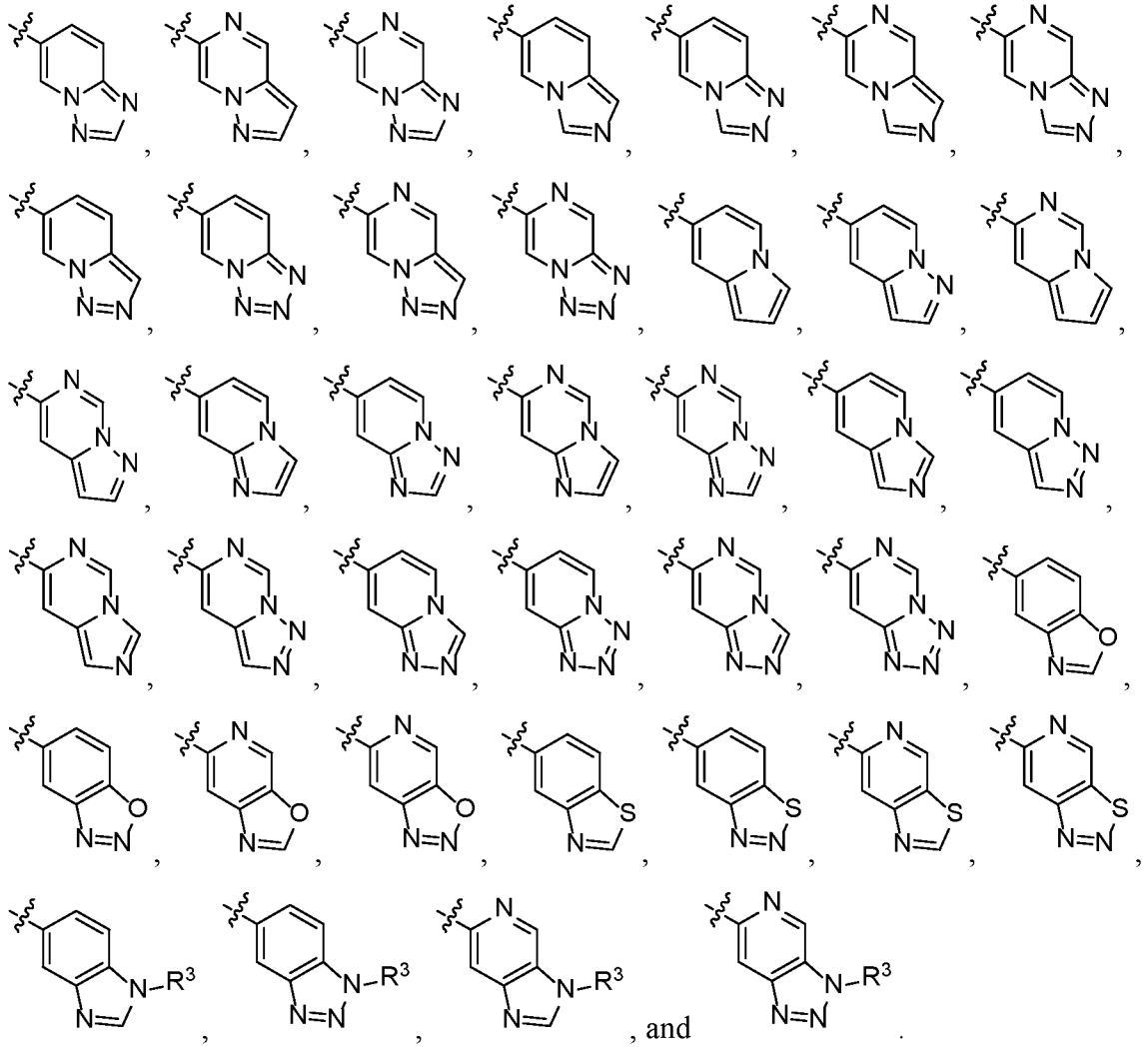
(I-C-2a)



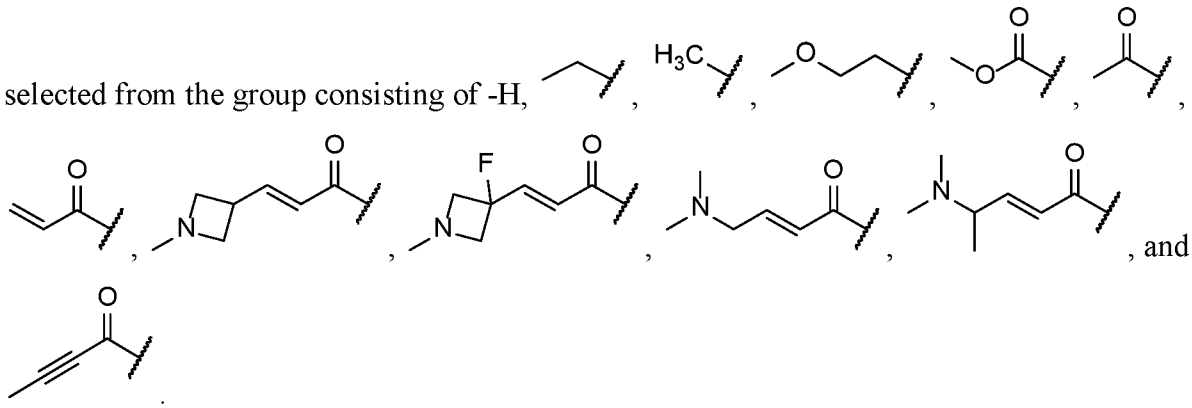
(I-C-5a)

wherein A, E, Z, $R^4$, $R^5$, and $R^6$ are as defined for formula (I) or formula (I-C'). In some embodiments, the compound is a compound of formula (I-C-1a). In some embodiments, the compound is a compound of formula (I-C-2a). In some embodiments, the compound is a compound of formula (I-C-5a). In some variations of formula (I-C-1a), (I-C-2a), or (I-C-5a), Z is selected from the group consisting of -H, -F, and -$CH_3$. In some variations of formula (I-C-1a), (I-C-2a), or (I-C-5a), $R^4$ is -H or -F. In some variations of formula (I-C-1a), (I-C-2a), or (I-C-5a), $R^5$ is -H or -F. In some variations of formula (I-C-1a), (I-C-2a), or (I-C-5a), $R^6$ is -H or -F. In some variations of formula (I-C-1a), (I-C-2a), or (I-C-5a), A is selected from the group consisting of

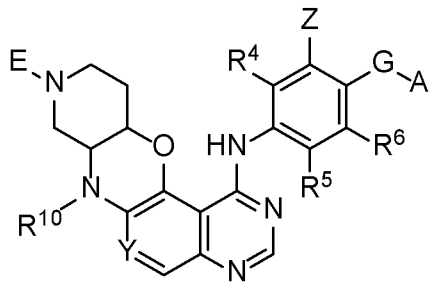




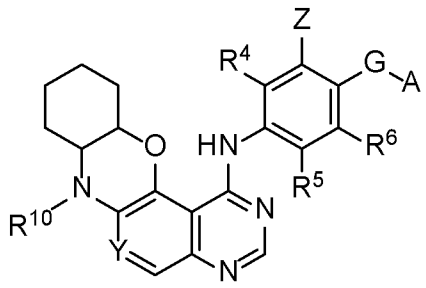
**[0104]** In some variations of formula (I-C-1), (I-C-2), (I-C-1a), (I-C-2a), or (I-C-5a), E is selected from the group consisting of -H,



**[0105]** In some embodiments, the compound of formula (I-D) is a compound of formula (I-D-1) or (I-D-2),

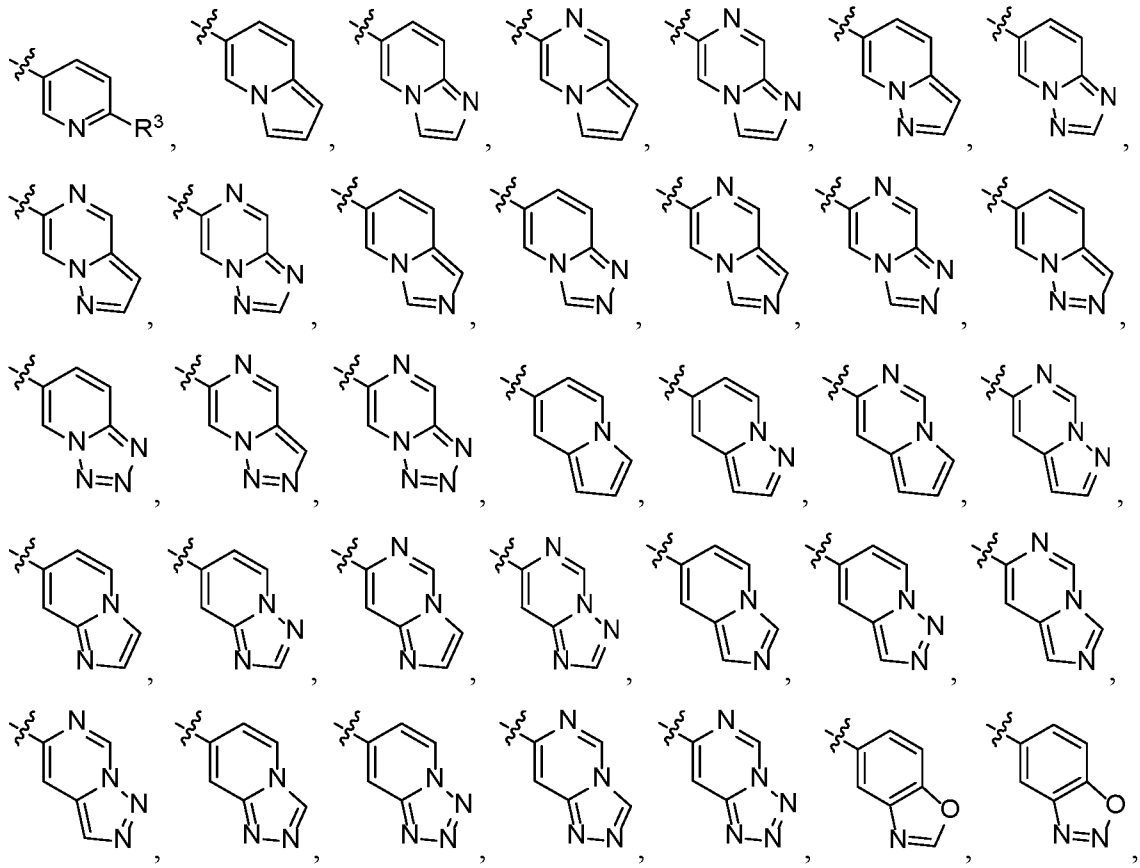


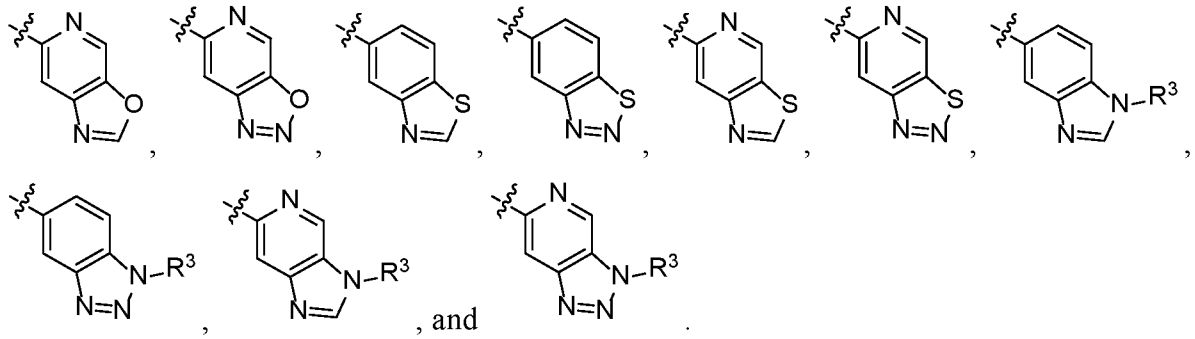
or



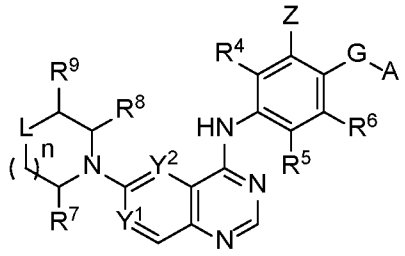
(I-D-1) (I-D-2)

**[0106]** wherein A, G, Y, Z, $R^4$, $R^5$, $R^6$, and $R^{10}$ are as defined for formula (I-D). In some embodiments, the compound is a compound of formula (I-D-1). In some embodiments, the compound is a compound of formula (I-D-2). In some variations of formula (I-D-1) or (I-D-2), $R^{10}$ is -H. In some variations of formula (I-D-1) or (I-D-2), $R^{10}$ is $C_1$-$C_6$ alkyl. In some variations of formula (I-D-1) or (I-D-2), $R^{10}$ is $-CH_3$. In some variations of formula (I-D-1) or (I-D-2), G is O. In some variations of formula (I-D-1) or (I-D-2), A is selected from the group consisting of



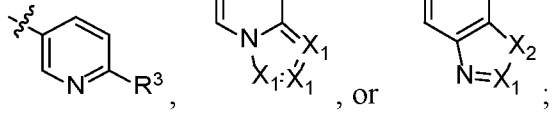


**[0107]** In one aspect, provided herein is a compound of formula (I')



(I')

or a pharmaceutically acceptable salt thereof wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

either $Y^1$ is C-$R^{Y1}$, $Y^2$ is Y, $R^8$ is -H, $R^9$ is -H, and $R^{Y1}$ is taken together with $R^7$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^1$,

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$, or

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^8$ is -H, and $R^{Y2}$ is taken together with $R^9$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$;

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy;

G is -O-;

V is O;

$X_1$ is N or CH;

$X_2$ is N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, or $C_1$-$C_2$ alkyl;

$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

$R^3$ is -H or $C_1$-$C_6$ alkyl; and

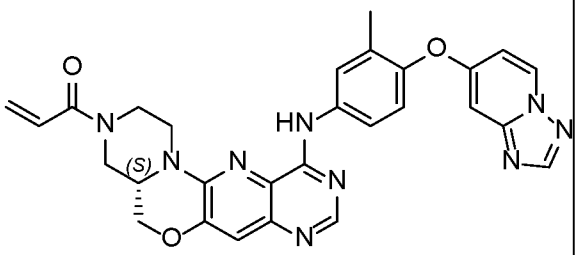
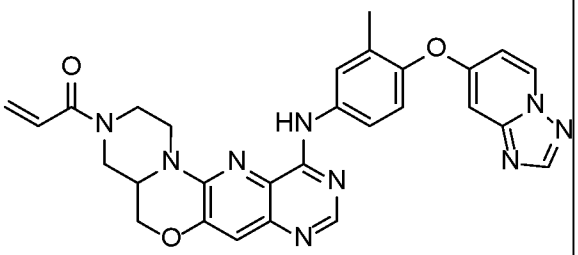
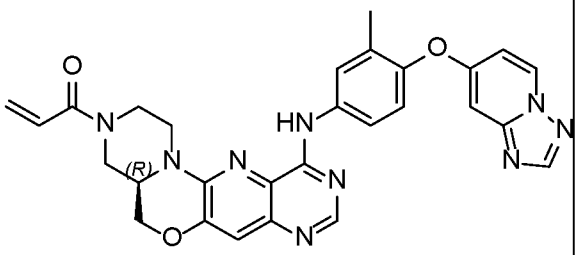
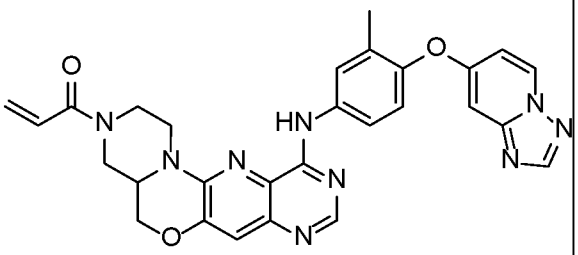
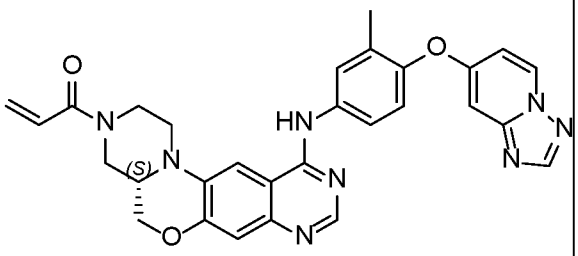
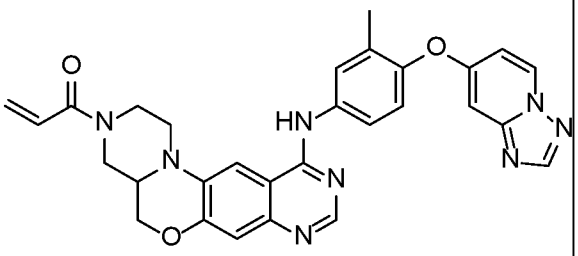
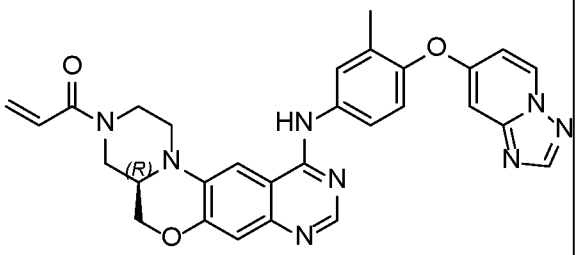
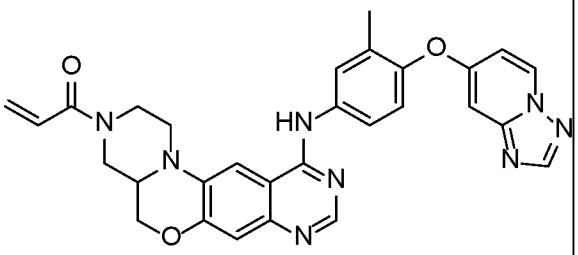
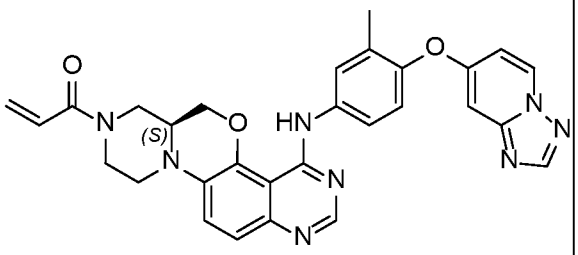
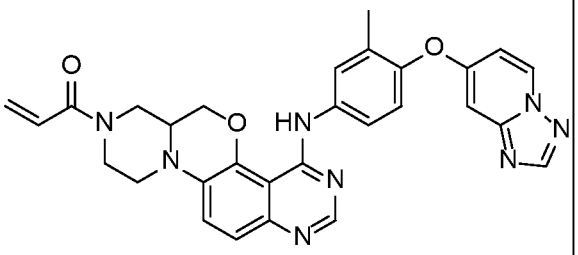
$R^4$, $R^5$, and $R^6$ are each independently -H or halogen.

**[0108]** In some embodiments, a compound of formula (I) is a compound of formula (I').

**[0109]** In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), selected from the compounds in Table 1, or pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

**Table 1**

| Compound No. | Structure | Compound No. | Structure. |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **1** |  | 1-1 |  |
| **2** |  | 2-1 |  |
| **3** |  | 3-1 |  |
| **4** |  | 4-1 |  |
| **5** |  | 5-1 |  |

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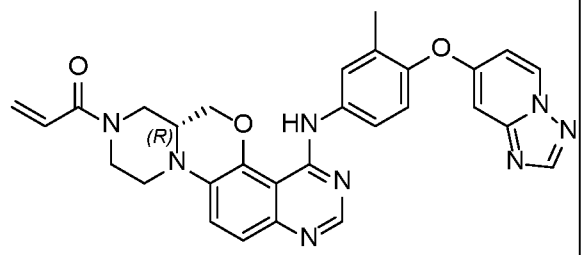
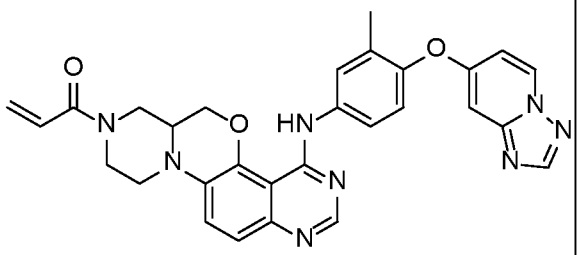
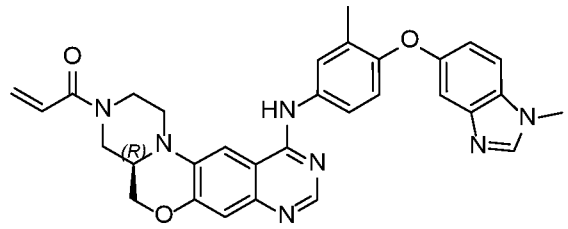
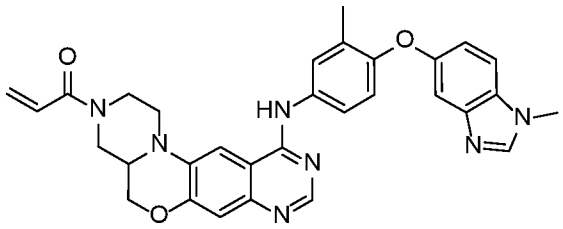
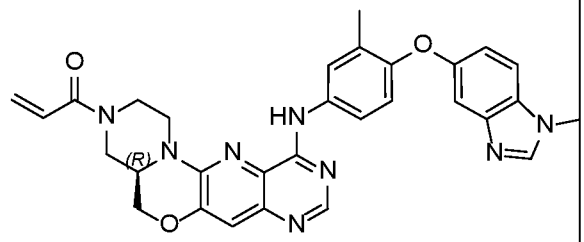
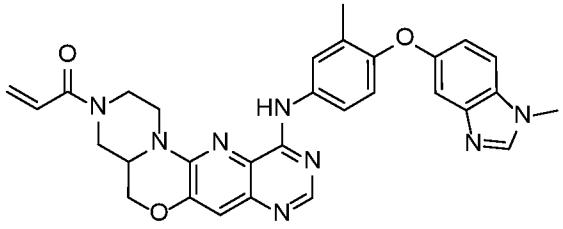
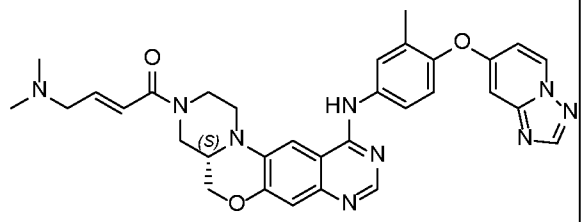
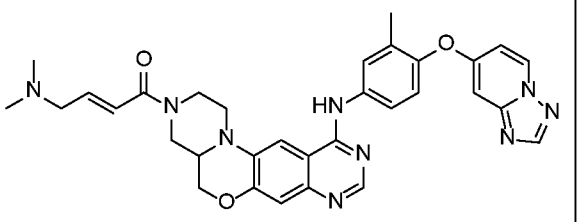
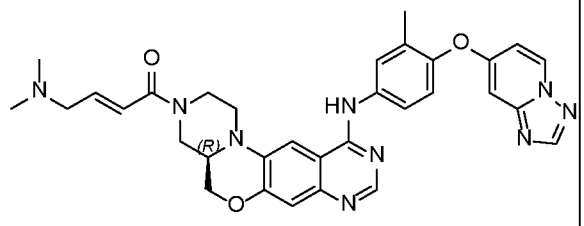
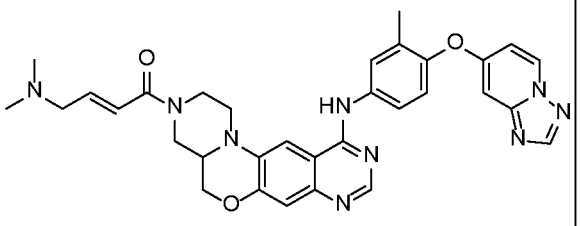
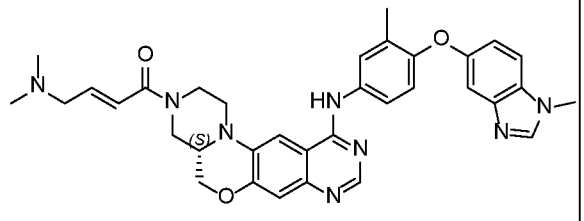
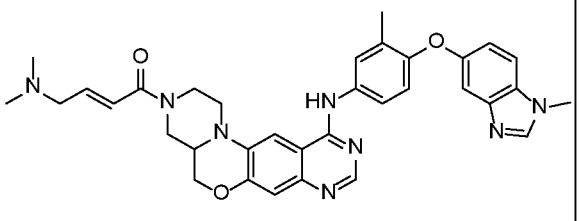
| **6** |  | 6-1 |  |
| **7** |  | 7-1 |  |
| **8** |  | 8-1 |  |
| **9** |  | 9-1 |  |
| **10** |  | 10-1 |  |
| **11** |  | 11-1 |  |

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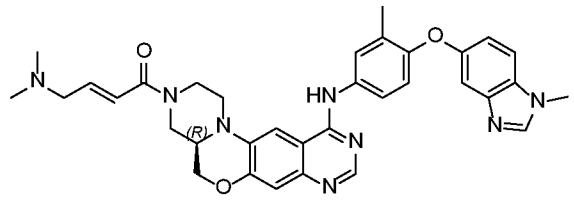
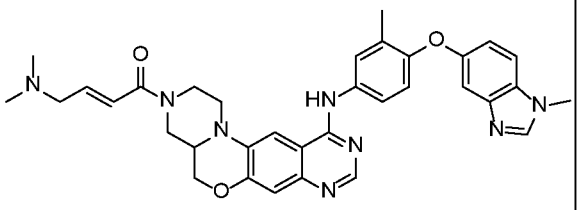
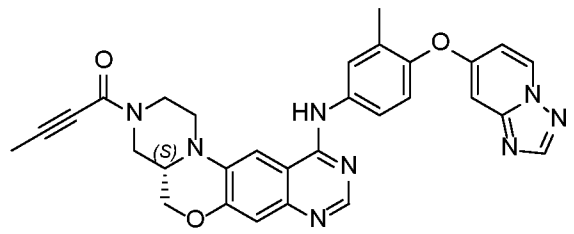
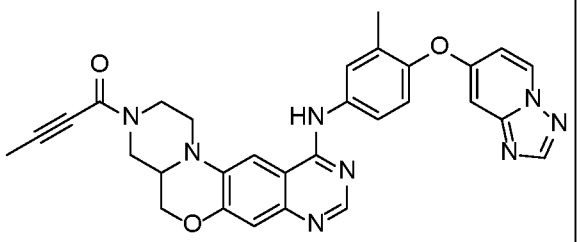
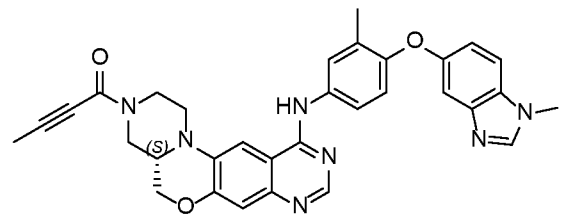
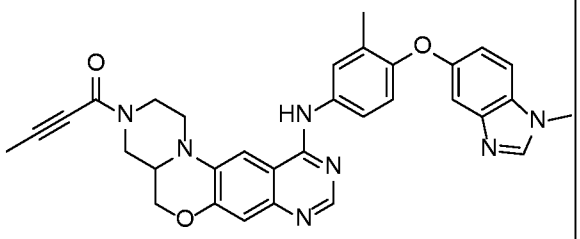
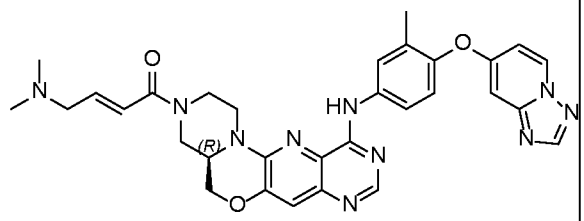
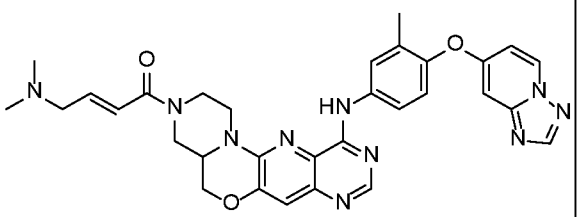
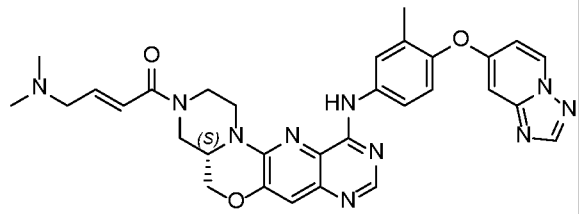
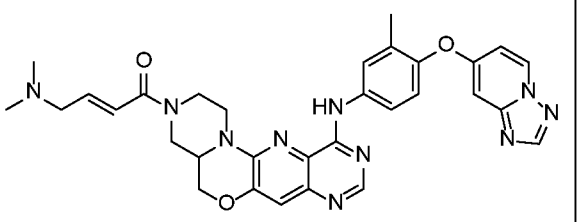
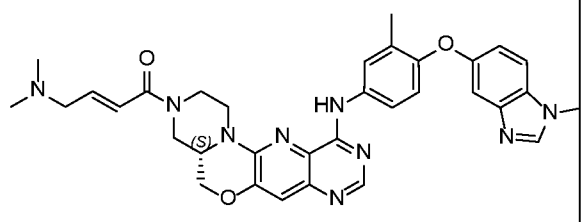
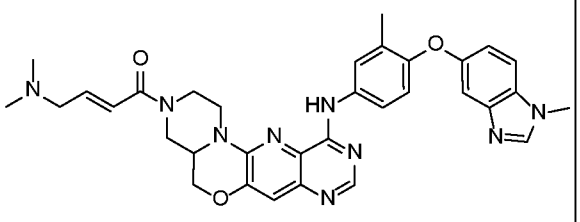
| **12** |  | 12-1 |  |
| **13** |  | 13-1 |  |
| **14** |  | 14-1 |  |
| **15** |  | 15-1 |  |
| **16** |  | 16-1 |  |
| **17** |  | 17-1 |  |

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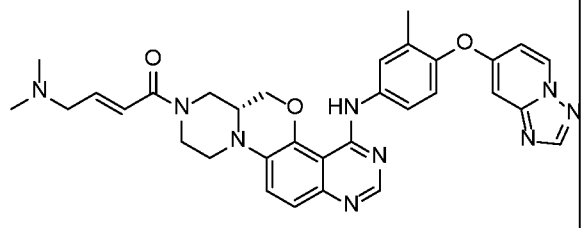
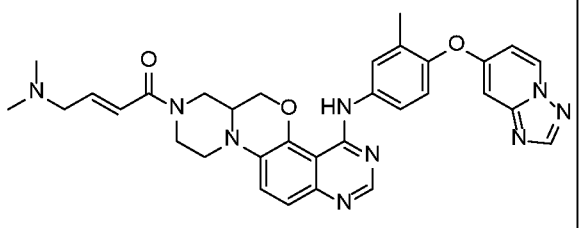
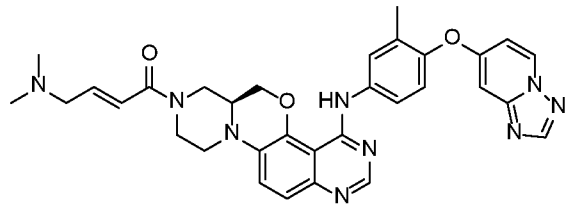
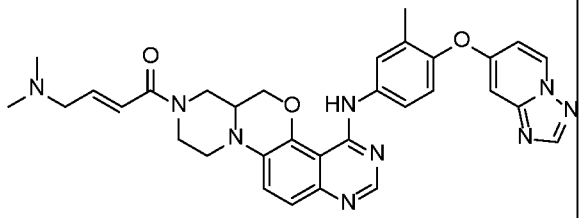
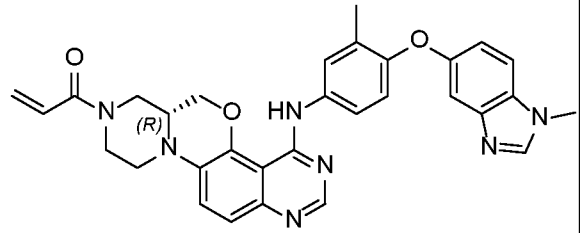
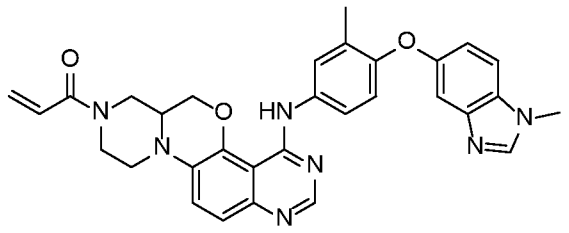
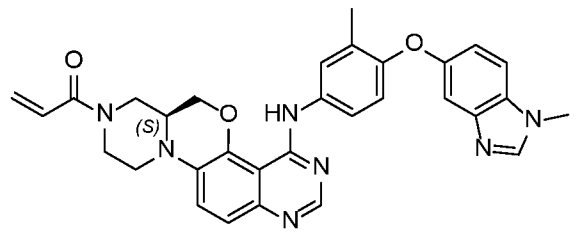
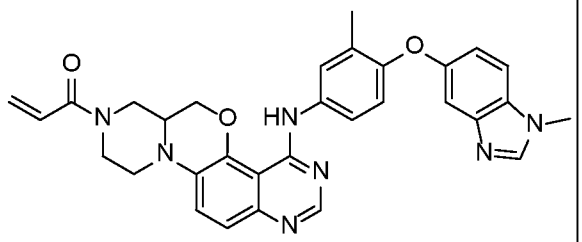
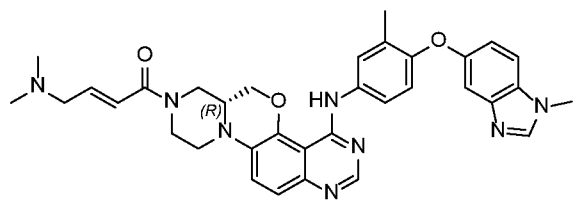
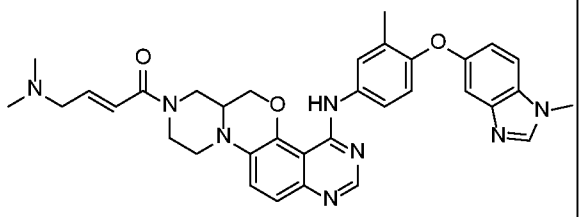
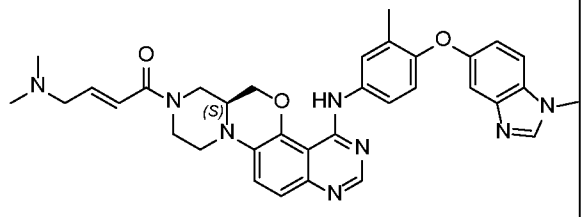
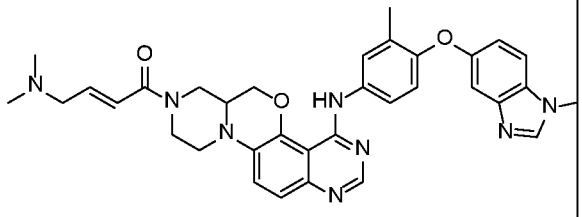
| **18** |  | 18-1 |  |
| **19** |  | 19-1 |  |
| **20** |  | 20-1 |  |
| **21** |  | 21-1 |  |
| **22** |  | 22-1 |  |
| **23** |  | 23-1 |  |

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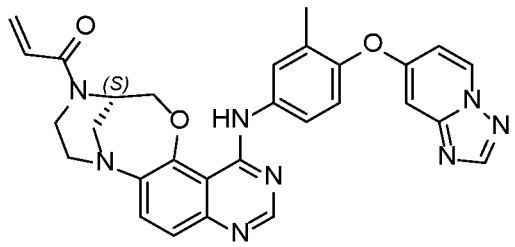
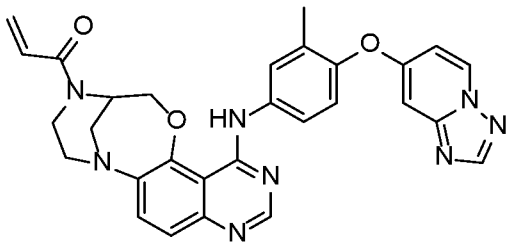
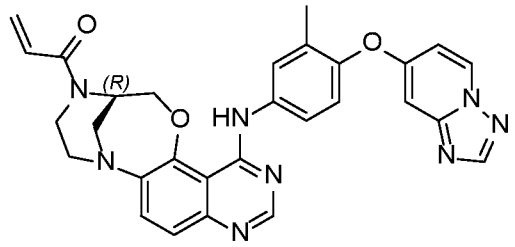
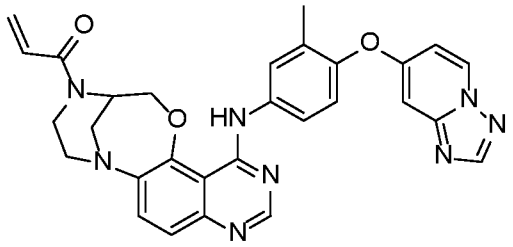
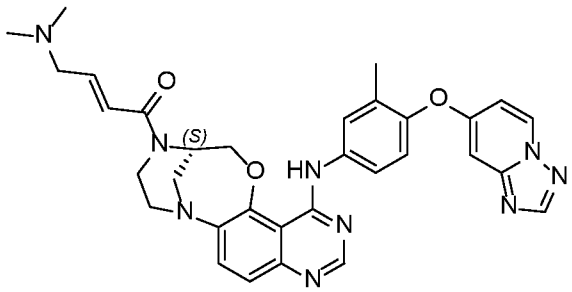
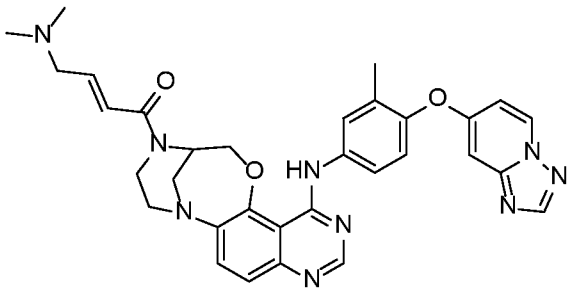
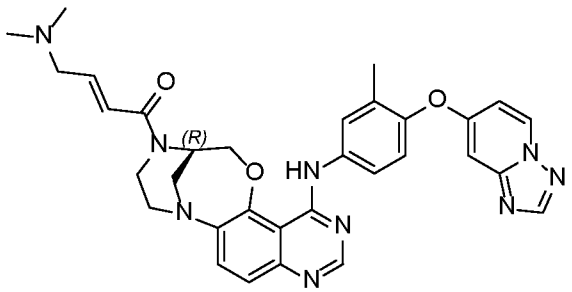
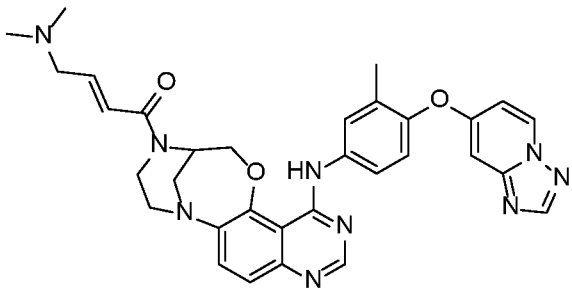
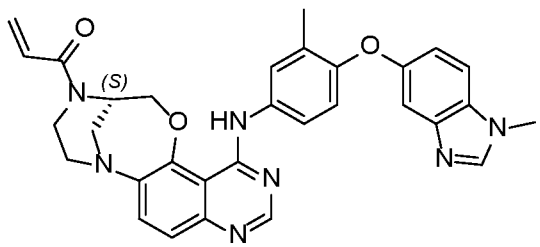
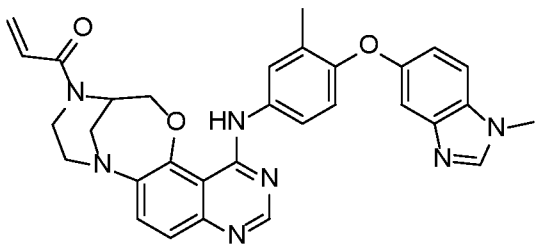
| **24** |  | 24-1 |  |
| **25** |  | 25-1 |  |
| **26** |  | 26-1 |  |
| **27** |  | 27-1 |  |
| **28** |  | 28-1 |  |

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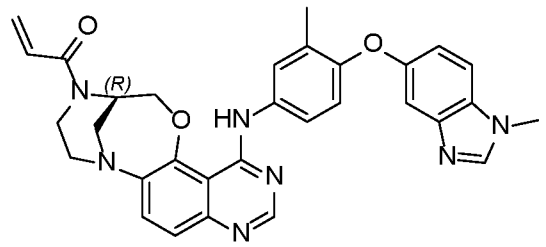
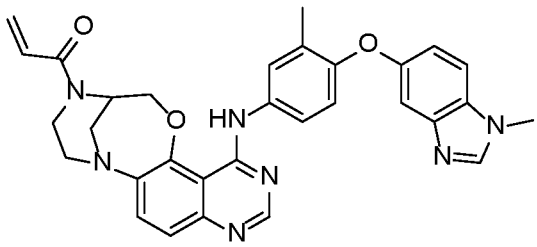
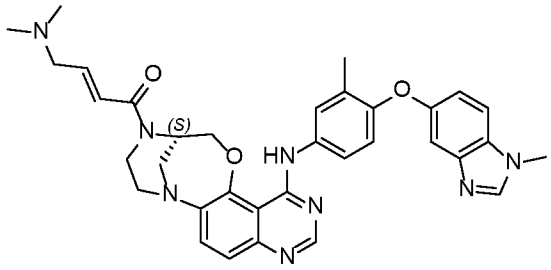
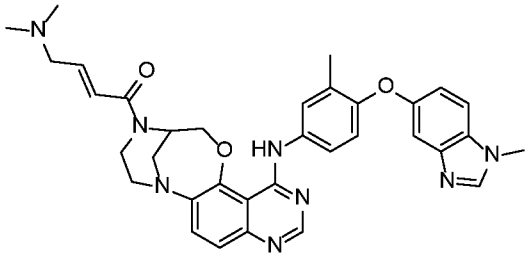
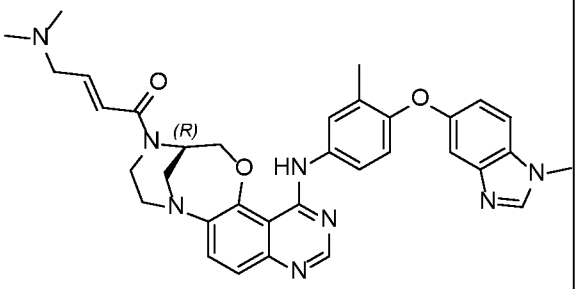
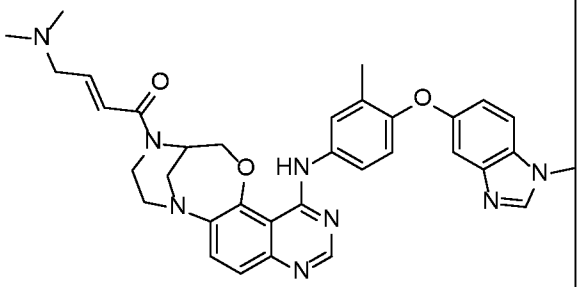
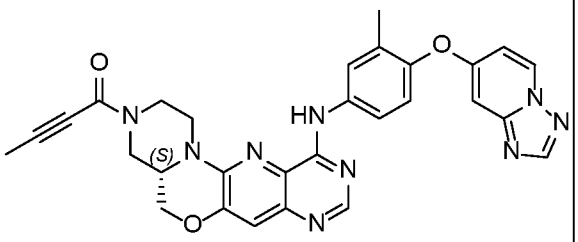
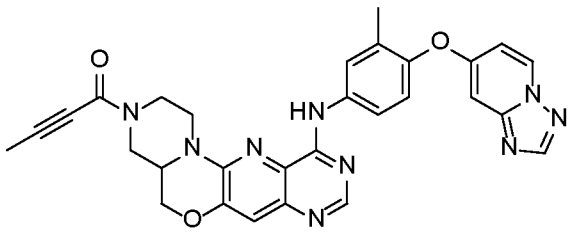
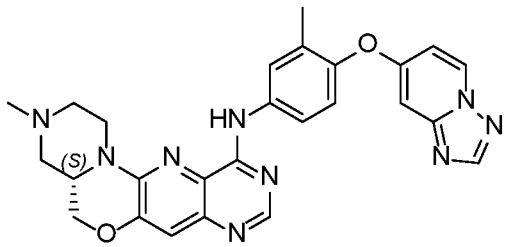
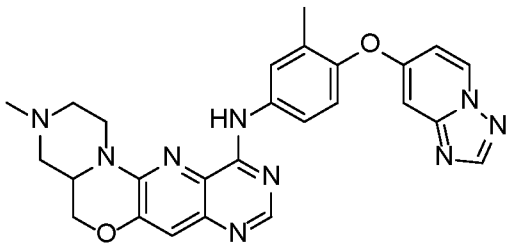
| **29** |  | 29-1 |  |
| **30** |  | 30-1 |  |
| **31** |  | 31-1 |  |
| **32** |  | 32-1 |  |
| **33** |  | 33-1 |  |

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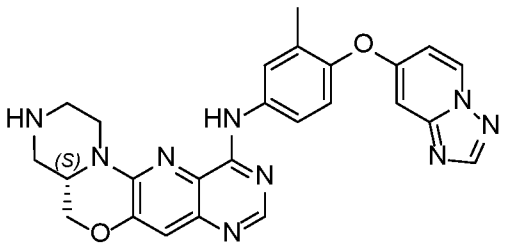
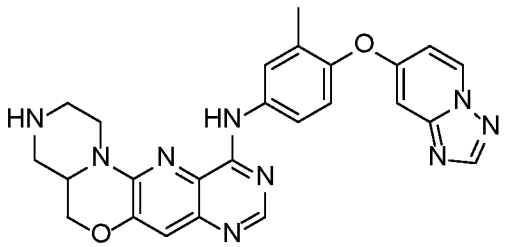
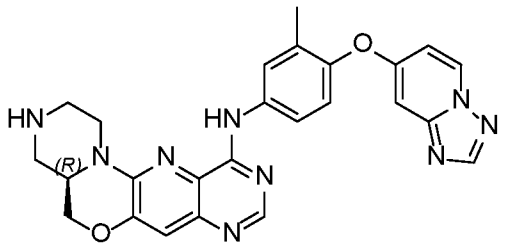
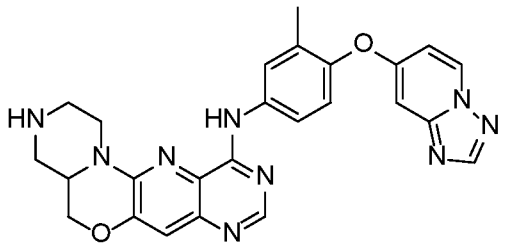
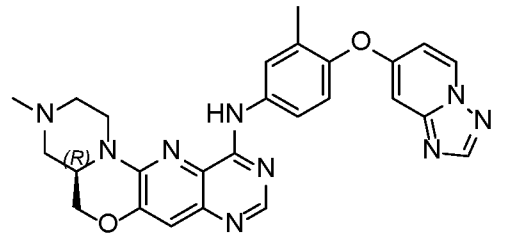
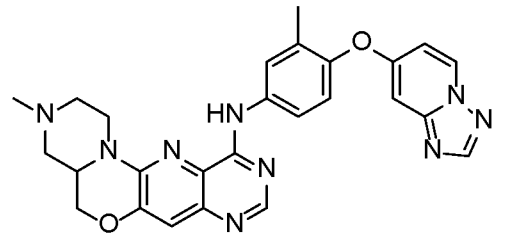
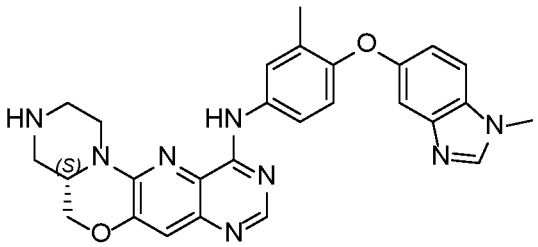
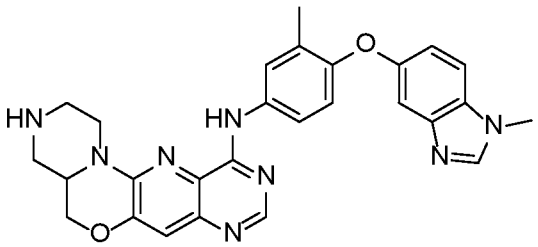
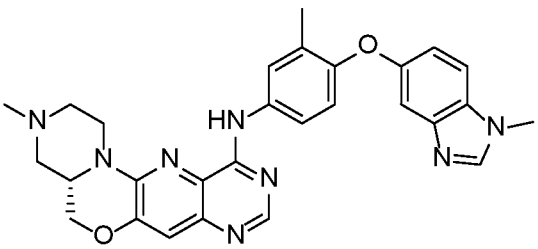
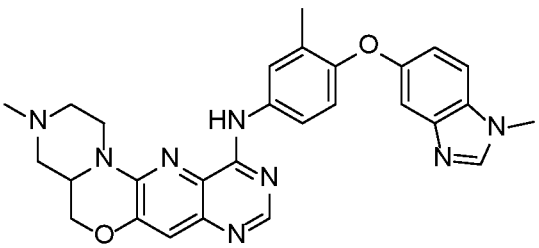
| **34** |  | 34-1 |  |
| **35** |  | 35-1 |  |
| **36** |  | 36-1 |  |
| **37** |  | 37-1 |  |
| **38** |  | 38-1 |  |

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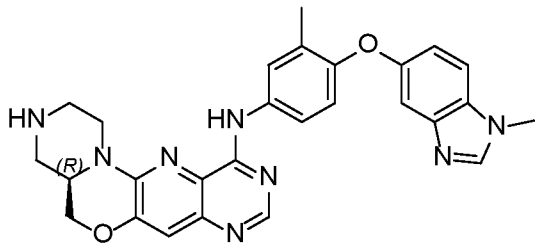
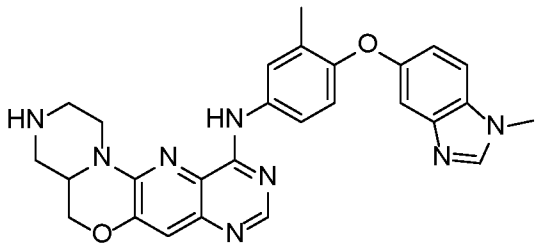
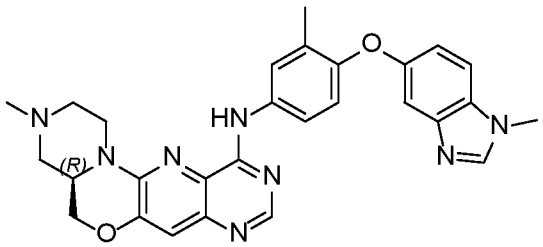
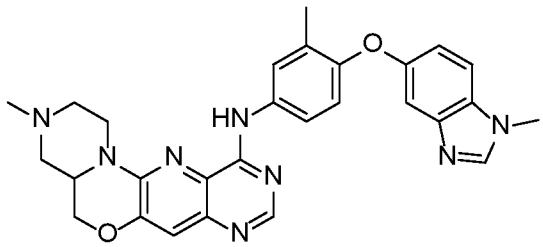
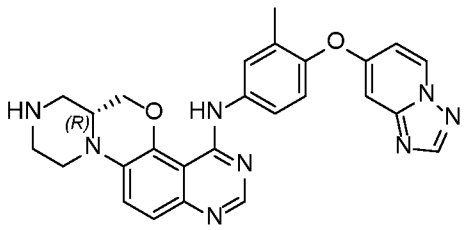
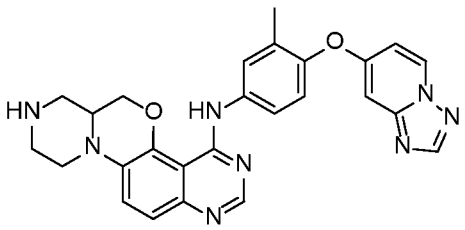
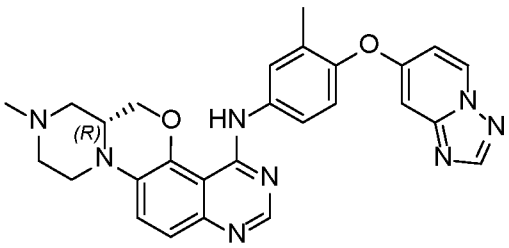
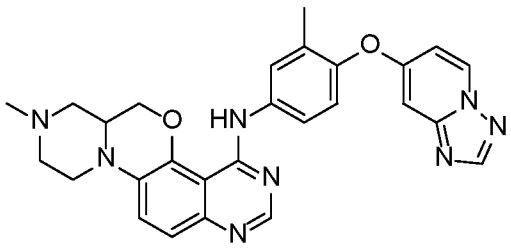
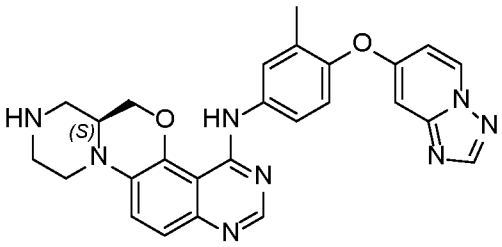
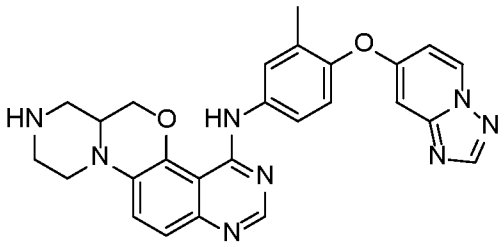
| **39** |  | 39-1 |  |
| **40** |  | 40-1 |  |
| **41** |  | 41-1 |  |
| **42** |  | 42-1 |  |
| **43** |  | 43-1 |  |

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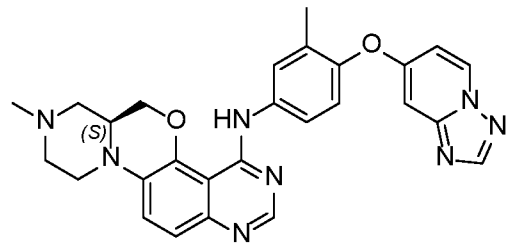
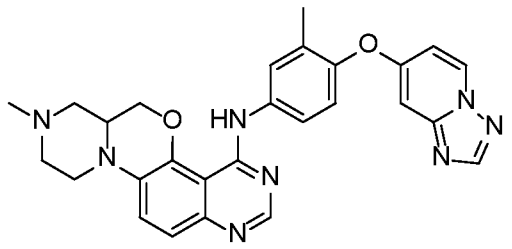
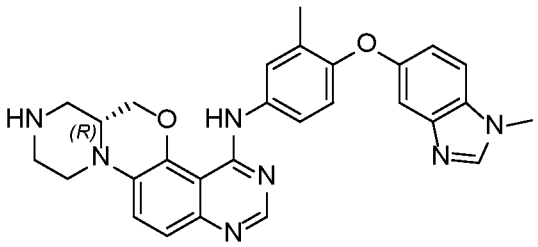
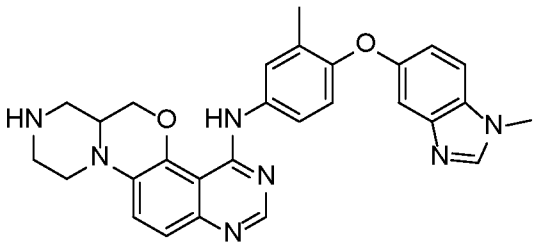
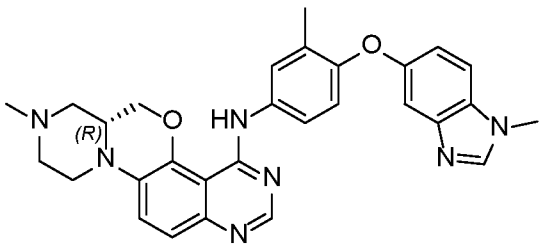
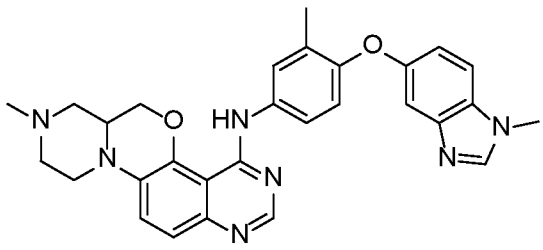
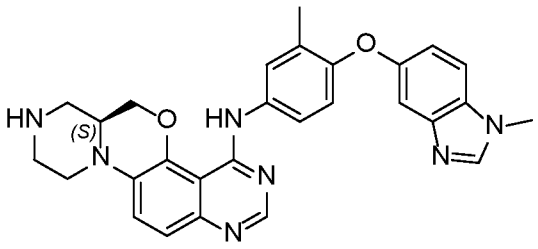
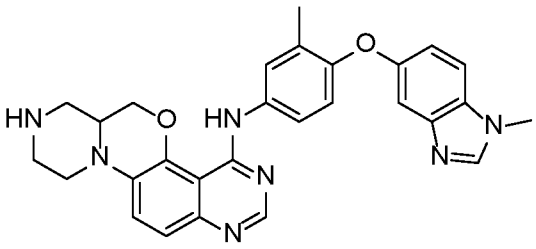
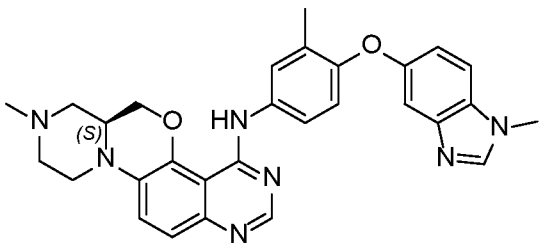
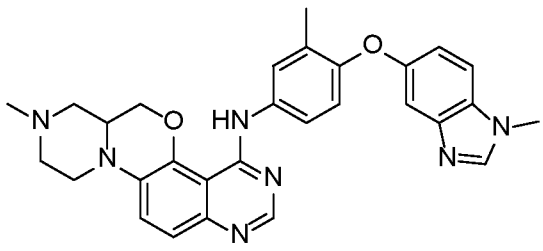
| **44** |  | 44-1 |  |
| **45** |  | 45-1 |  |
| **46** |  | 46-1 |  |
| **47** |  | 47-1 |  |
| **48** |  | 48-1 |  |

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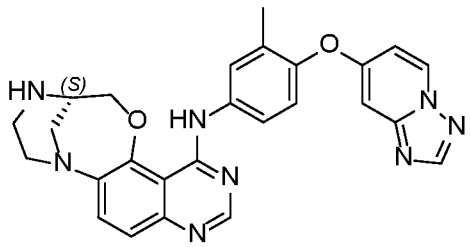
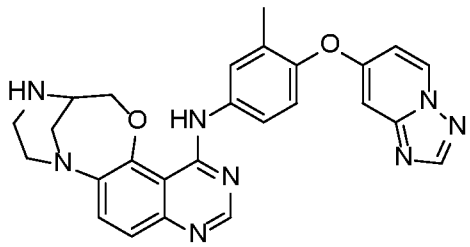
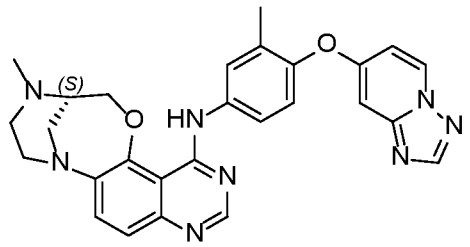
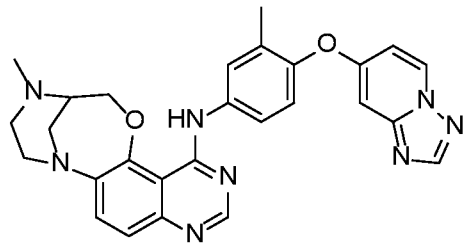
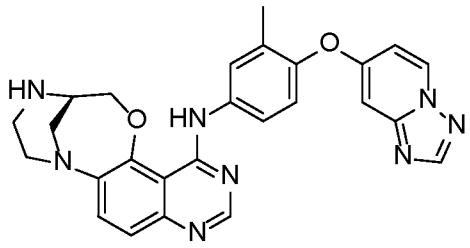
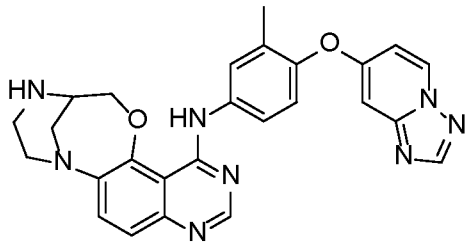
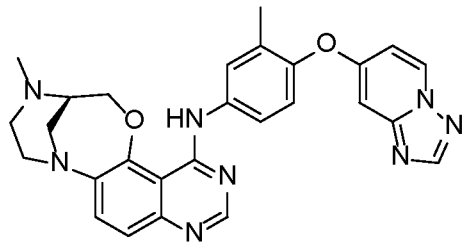
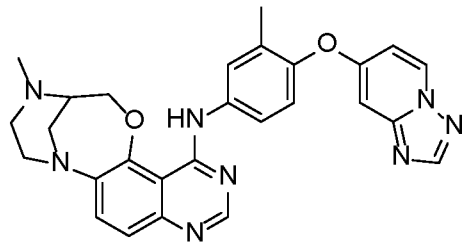
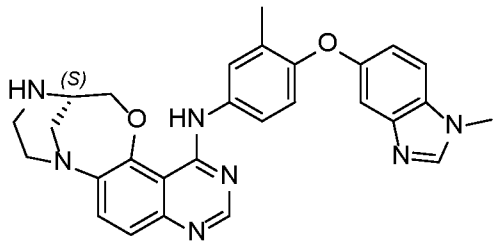
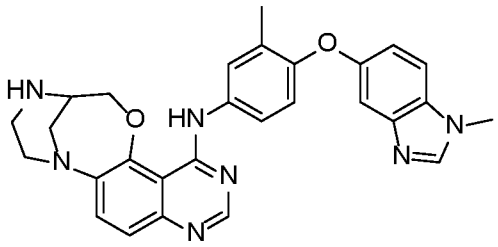
| **49** |  | 49-1 |  |
| **50** |  | 50-1 |  |
| **51** |  | 51-1 |  |
| **52** |  | 52-1 |  |
| **53** |  | 53-1 |  |

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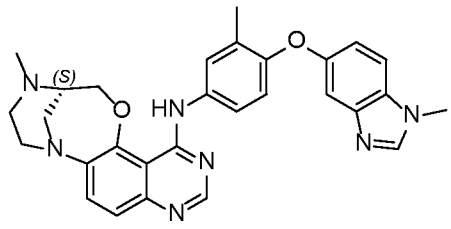
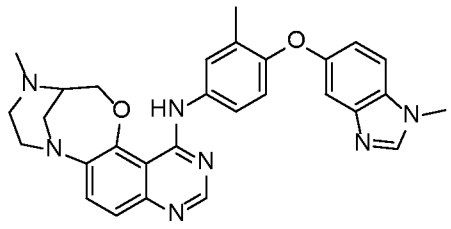
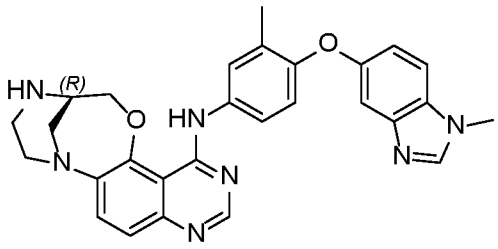
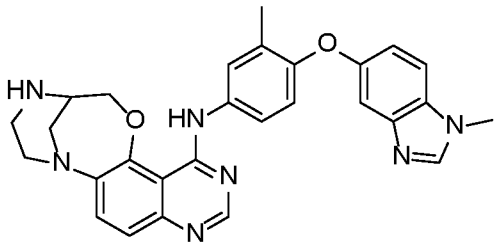
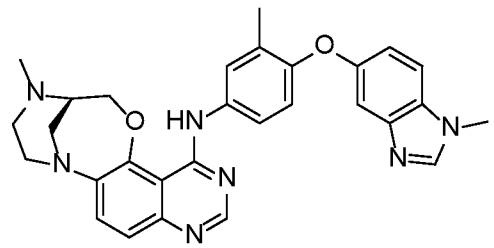
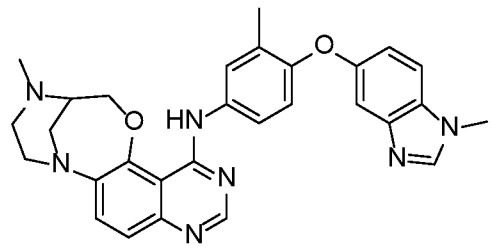
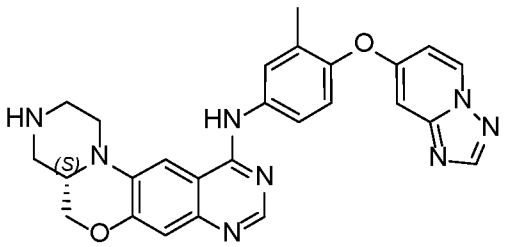
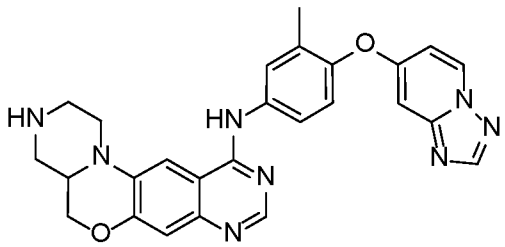
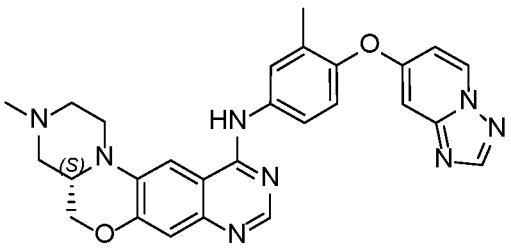
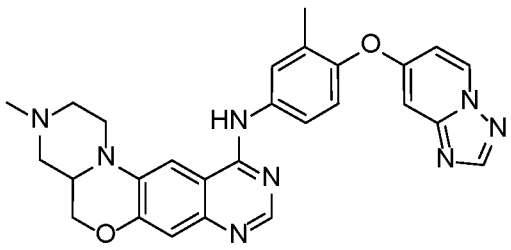
| **54** |  | 54-1 |  |
| **55** |  | 55-1 |  |
| **56** |  | 56-1 |  |
| **57** |  | 57-1 |  |
| **58** |  | 58-1 |  |

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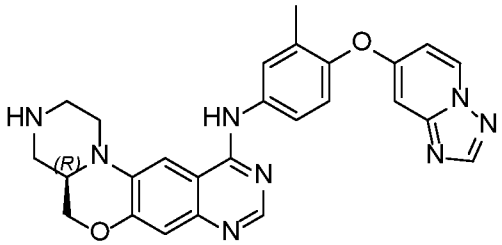
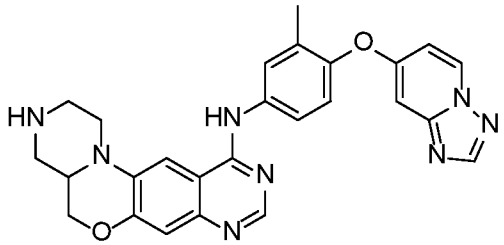
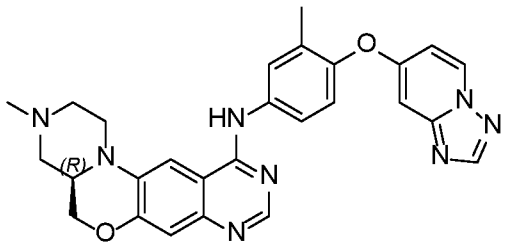
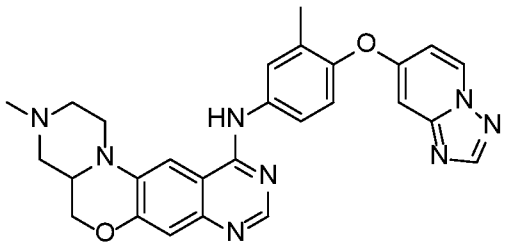
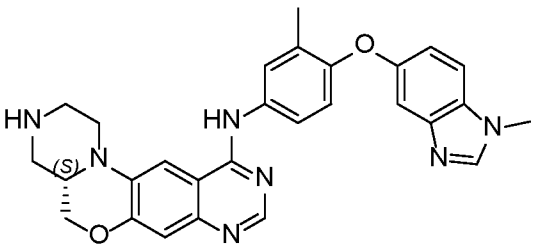
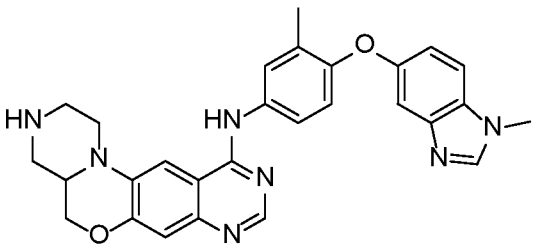
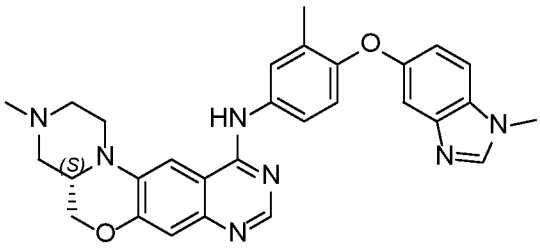
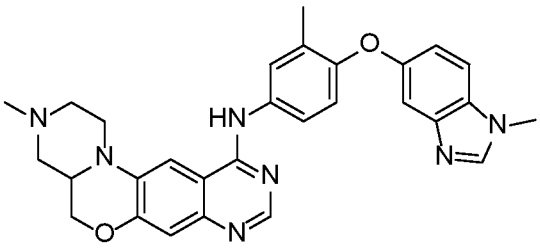
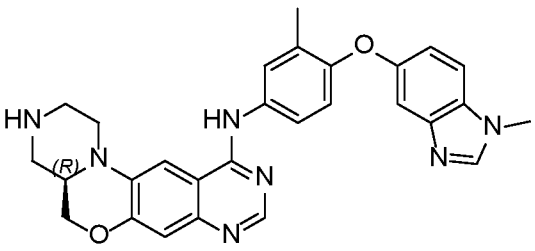
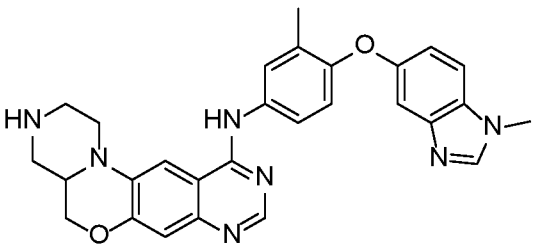
| **59** |  | 59-1 |  |
| **60** |  | 60-1 |  |
| **61** |  | 61-1 |  |
| **62** |  | 62-1 |  |
| **63** |  | 63-1 |  |

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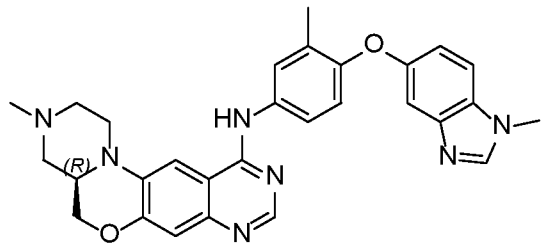
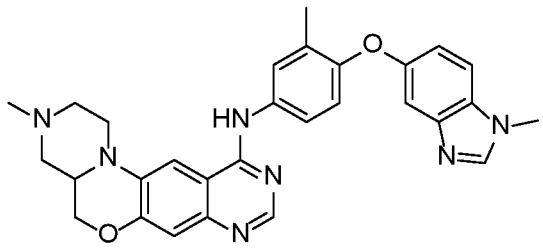
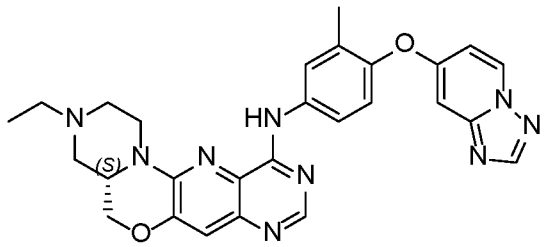
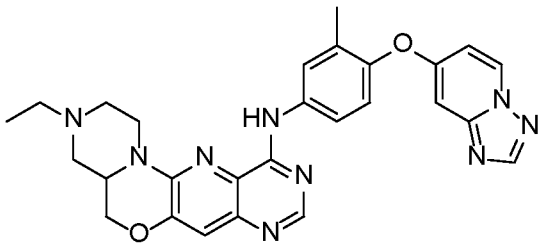
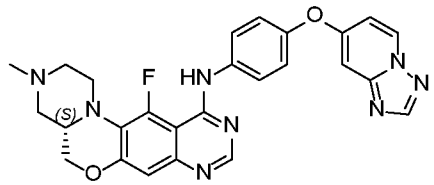
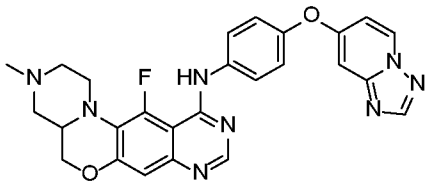
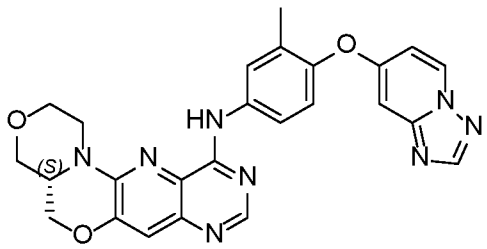
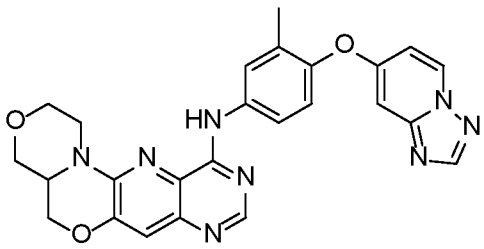
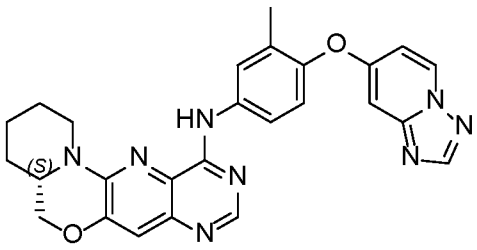
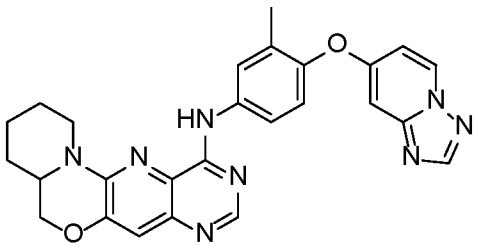
| **64** |  | 64-1 |  |
| **65** |  | 65-1 |  |
| **66** |  | 66-1 |  |
| **67** |  | 67-1 |  |
| **68** |  | 68-1 |  |

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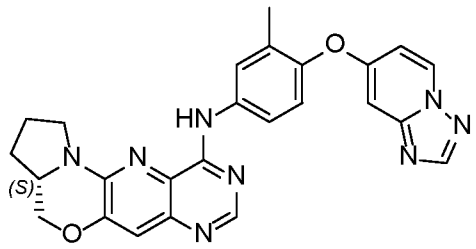
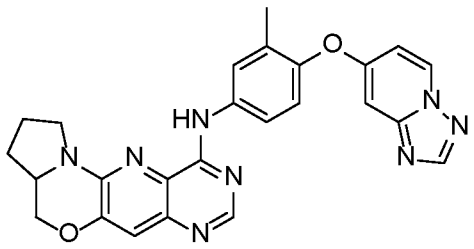
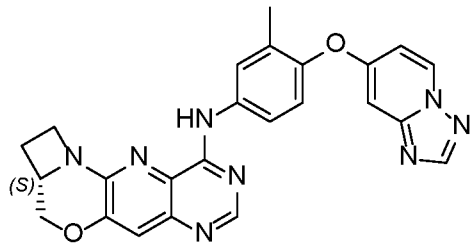
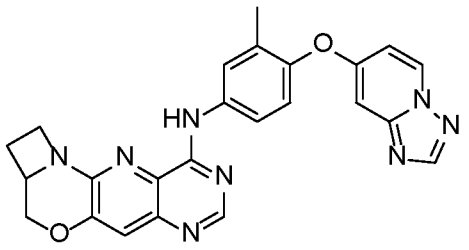
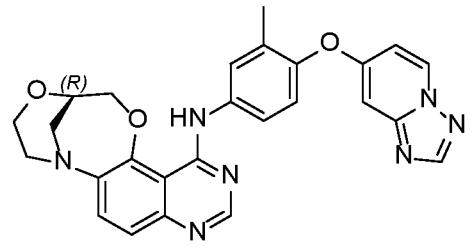
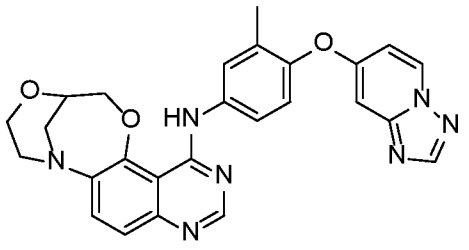
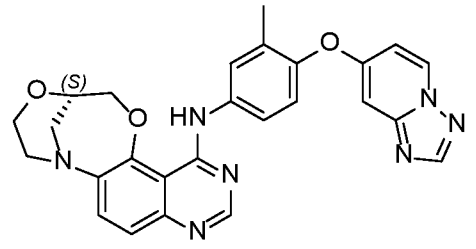
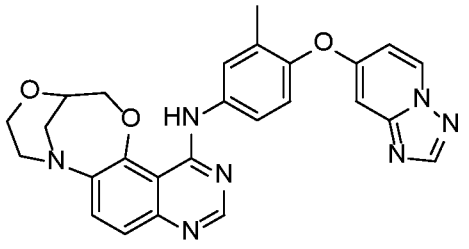
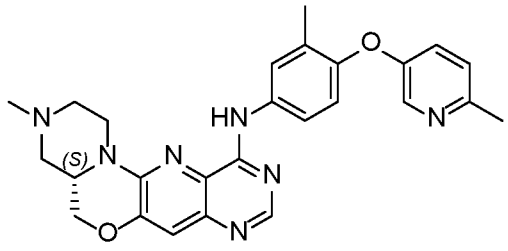
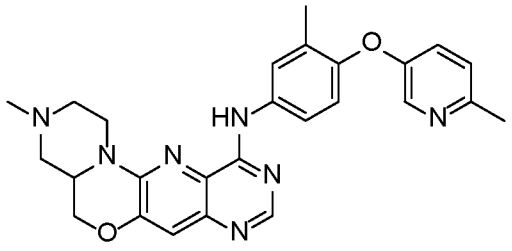
| **69** |  | 69-1 |  |
| **70** |  | 70-1 |  |
| **71** |  | 71-1 |  |
| **72** |  | 72-1 |  |
| **73** |  | 73-1 |  |

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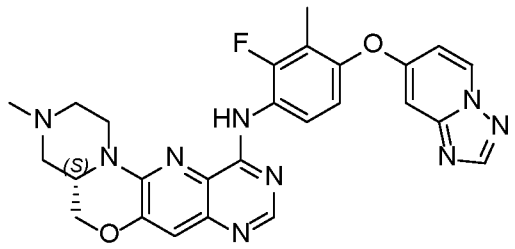
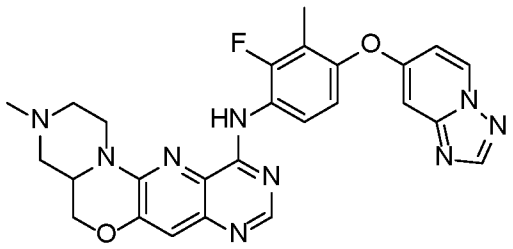
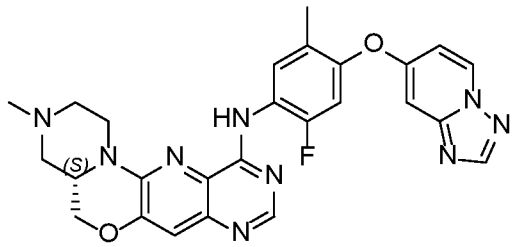
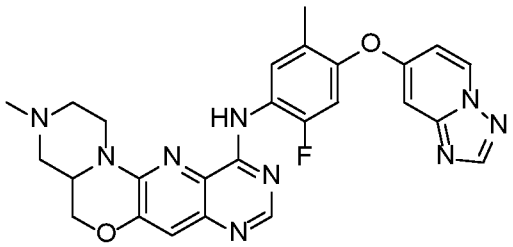
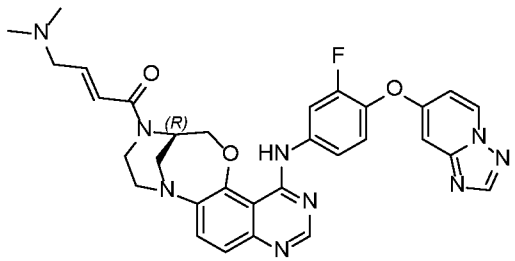
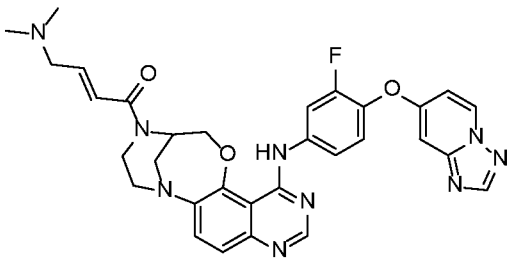
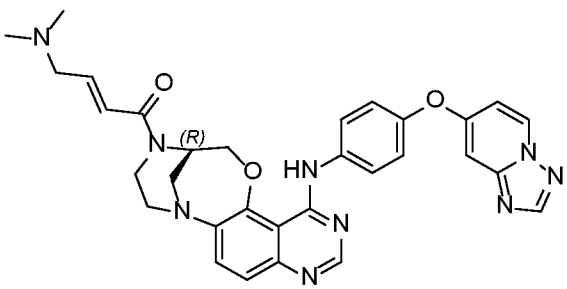
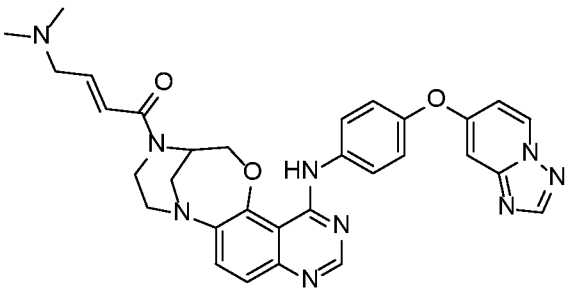
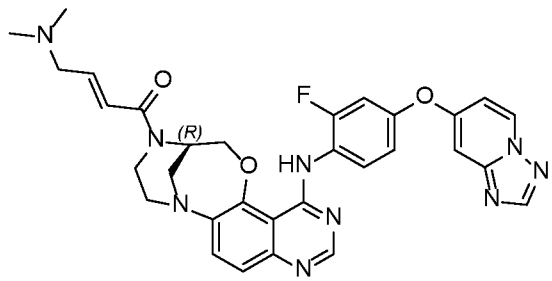
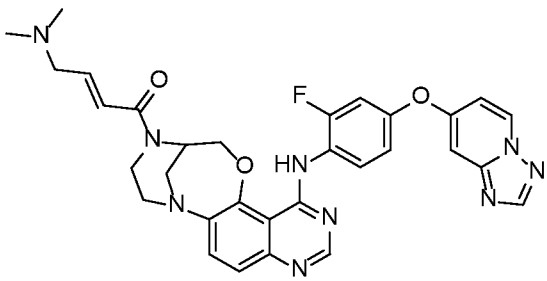
| **74** |  | 74-1 |  |
| **75** |  | 75-1 |  |
| **76** |  | 76-1 |  |
| **77** |  | 77-1 |  |
| **78** |  | 78-1 |  |

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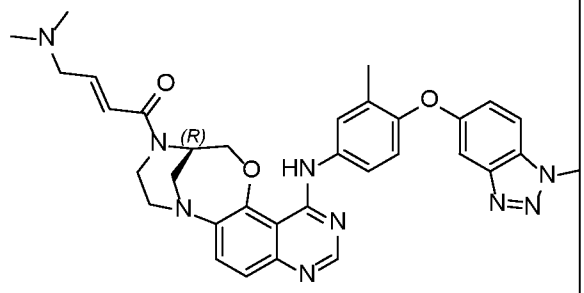
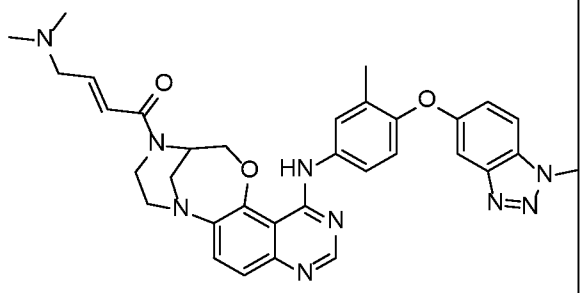
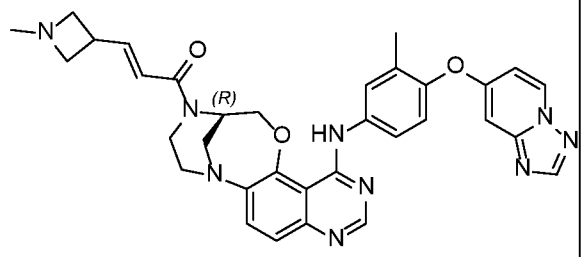
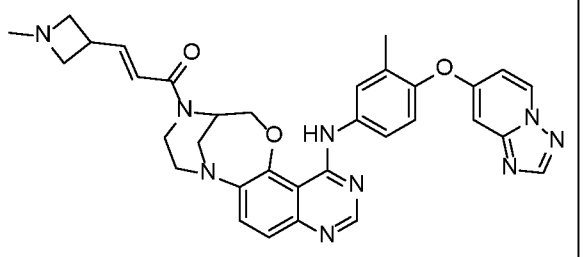
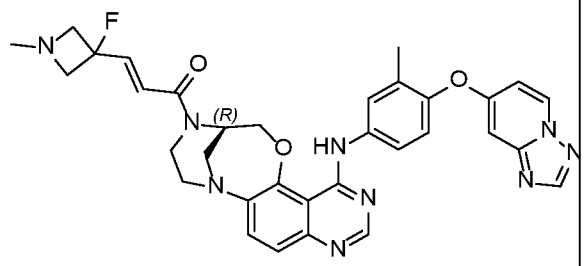
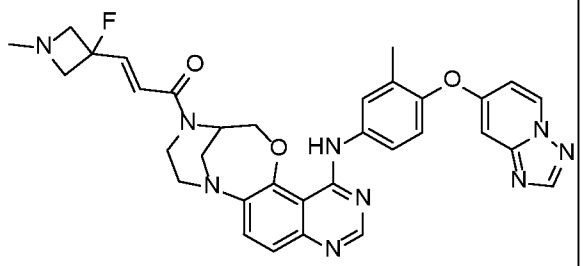
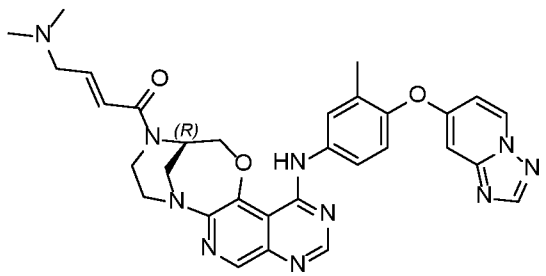
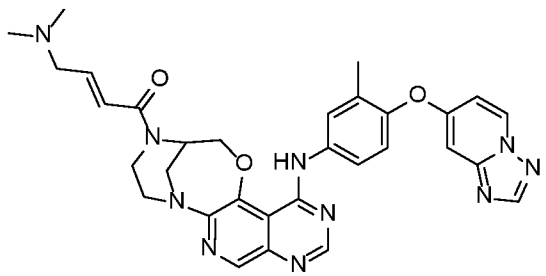
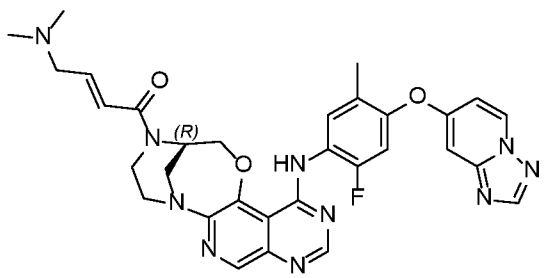
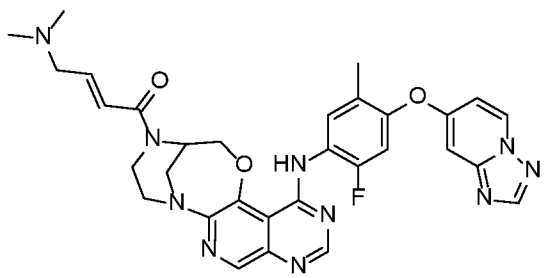
| **79** |  | 79-1 |  |
| **80** |  | 80-1 |  |
| **81** |  | 81-1 |  |
| **82** |  | 82-1 |  |
| **83** |  | 83-1 |  |

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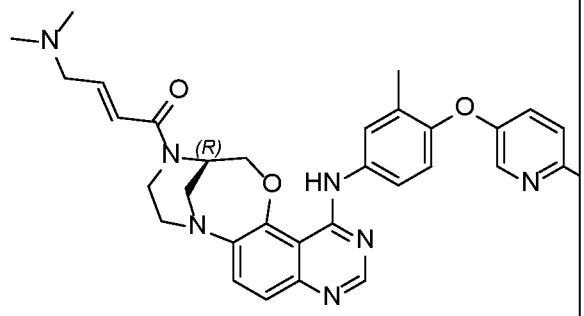
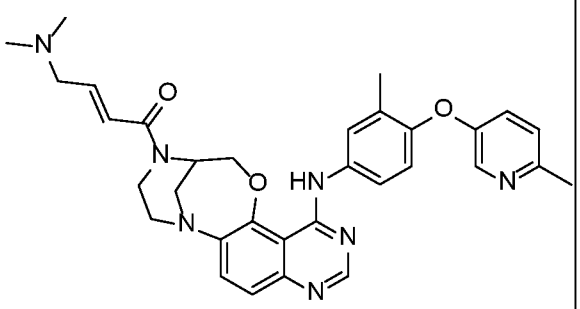
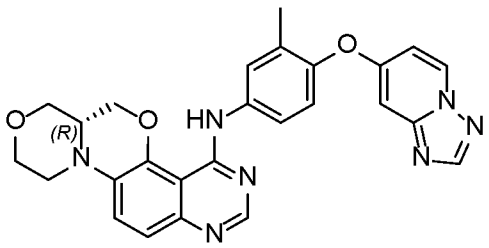
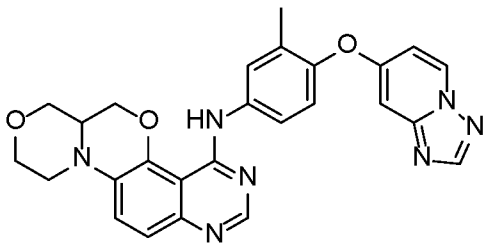
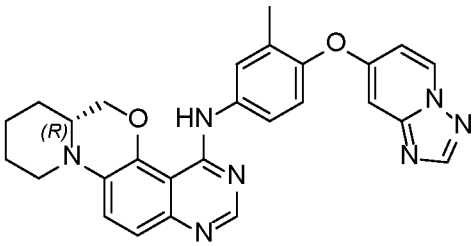
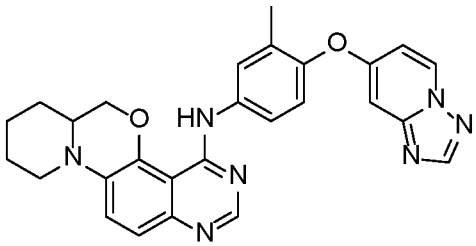
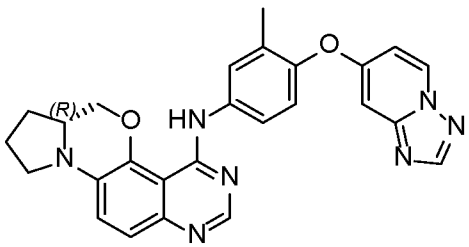
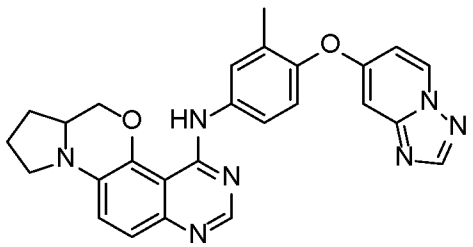
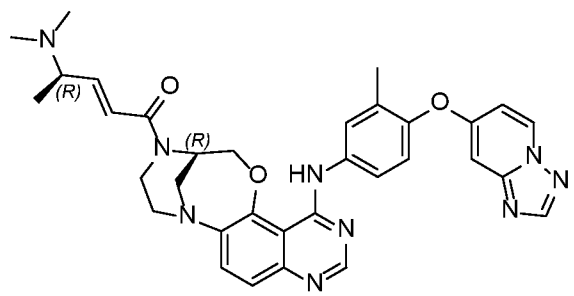
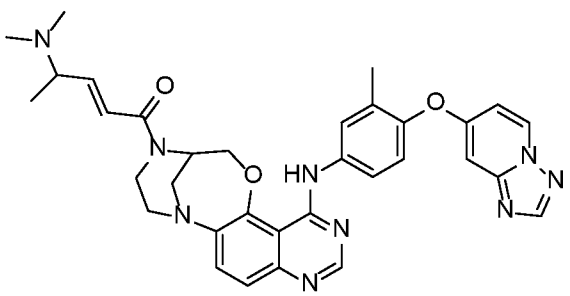
| **84** |  | 84-1 |  |
| **85** |  | 85-1 |  |
| **86** |  | 86-1 |  |
| **87** |  | 87-1 |  |
| **88** |  | 88-1 |  |

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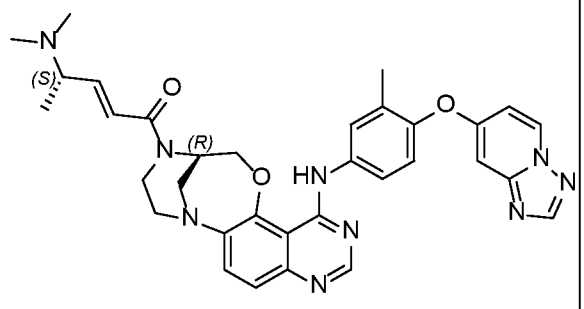
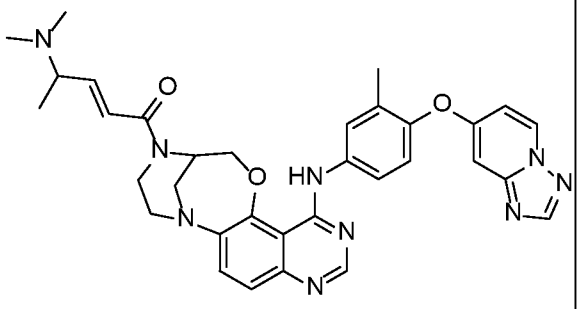
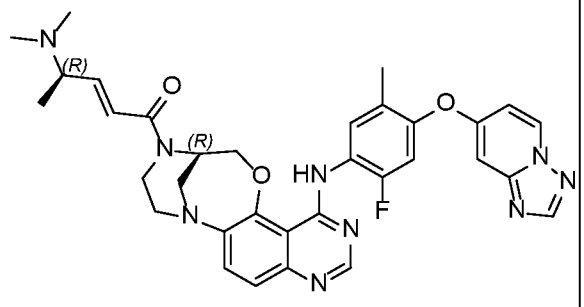
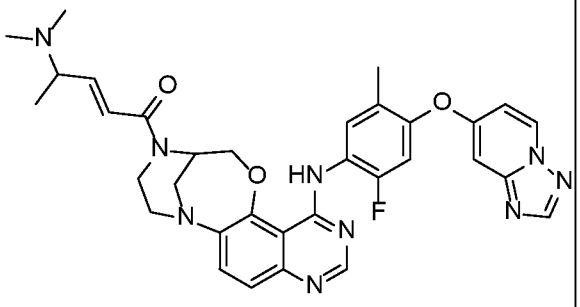
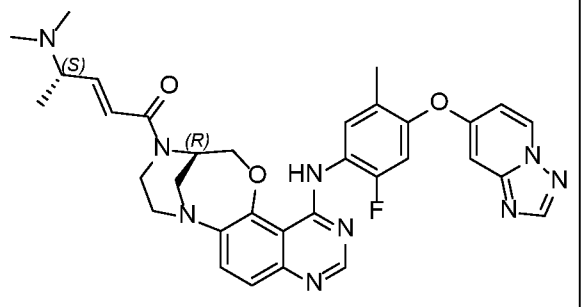
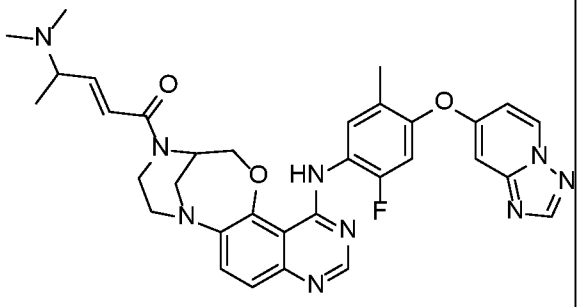
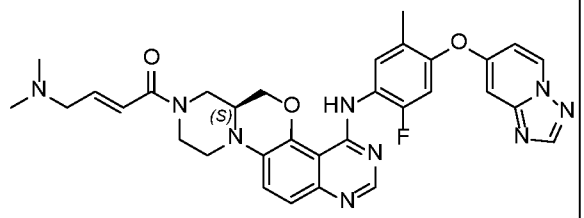
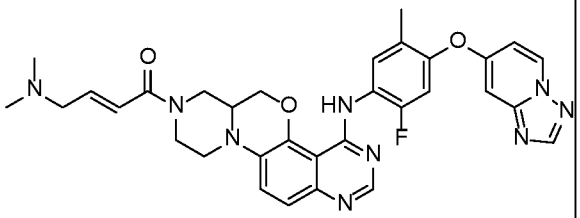
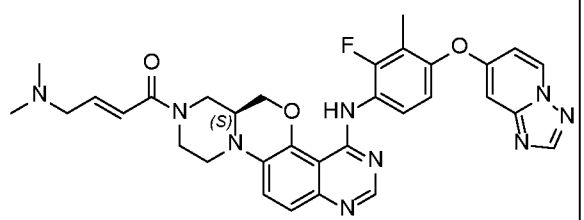
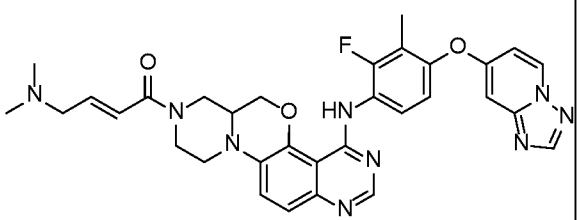
| **89** |  | 89-1 |  |
| **90** |  | 90-1 |  |
| **91** |  | 91-1 |  |
| **92** |  | 92-1 |  |
| **93** |  | 93-1 |  |

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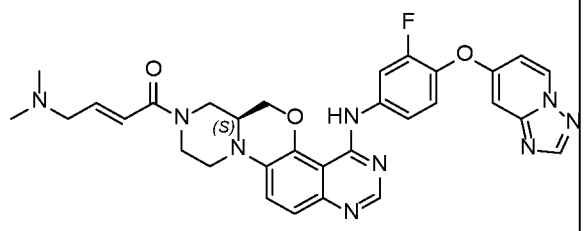
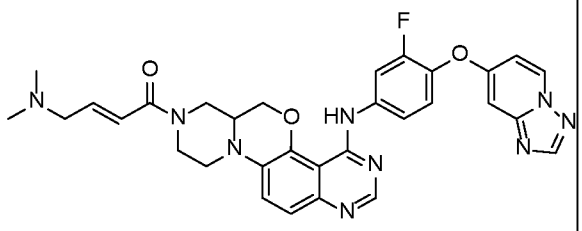
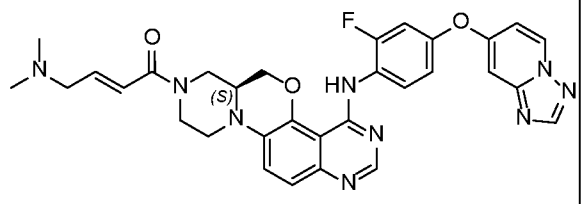
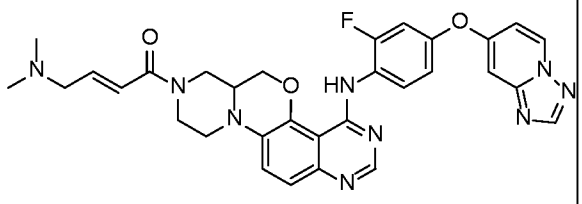
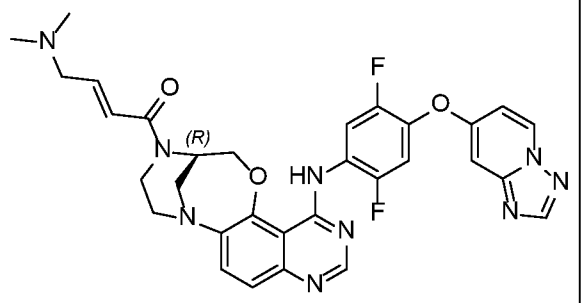
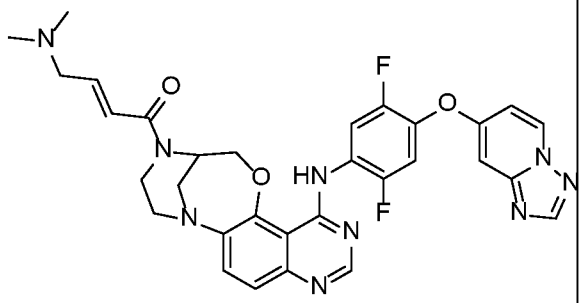
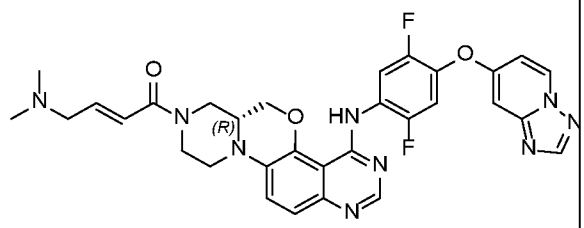
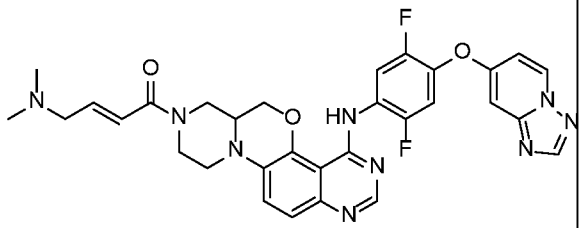
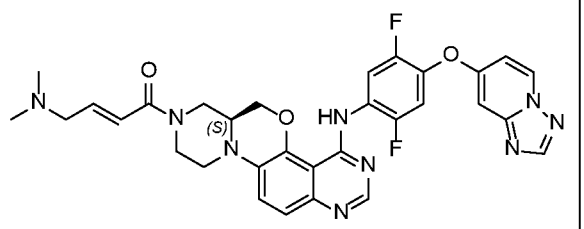
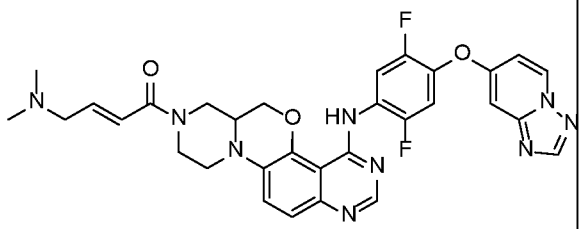
| **94** |  | 94-1 |  |
| **95** |  | 95-1 |  |
| **96** |  | 96-1 |  |
| **97** |  | 97-1 |  |
| **98** |  | 98-1 |  |

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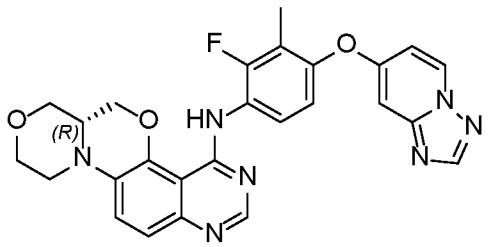
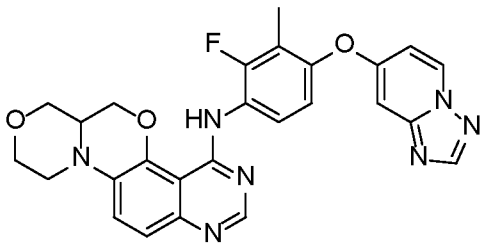
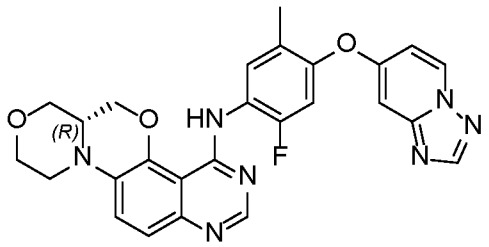
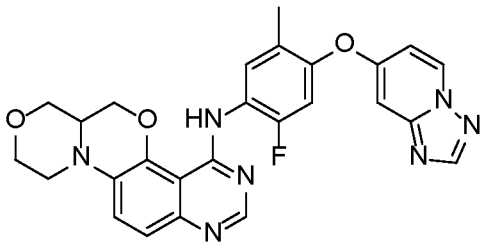
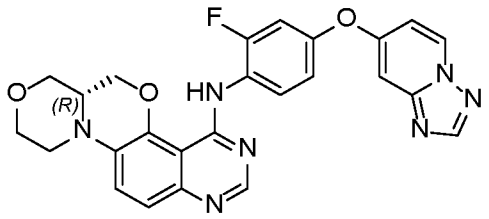
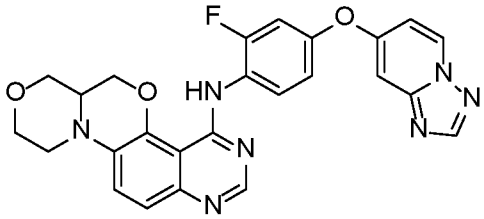
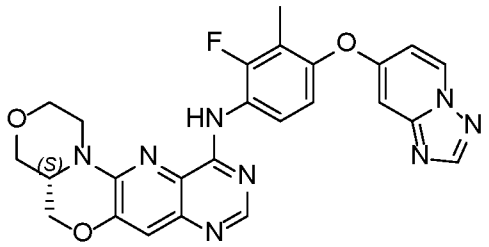
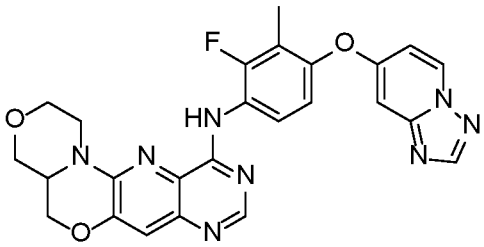
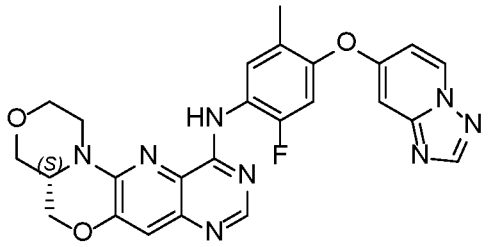
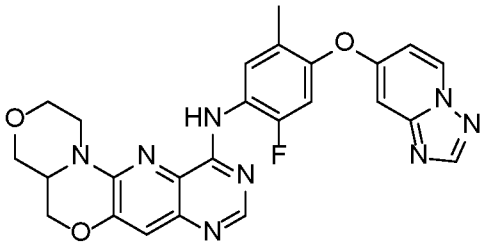
| **99** |  | 99-1 |  |
| **100** |  | 100-1 |  |
| **101** |  | 101-1 |  |
| **102** |  | 102-1 |  |
| **103** |  | 103-1 |  |

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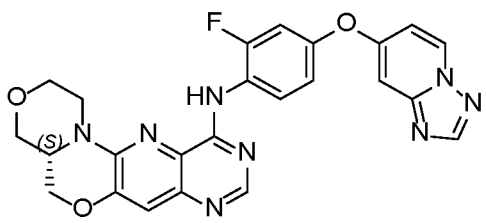
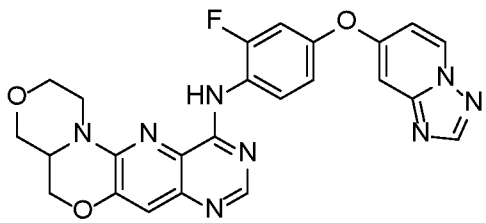
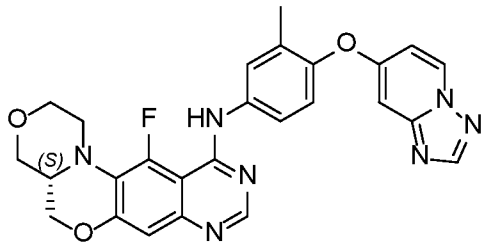
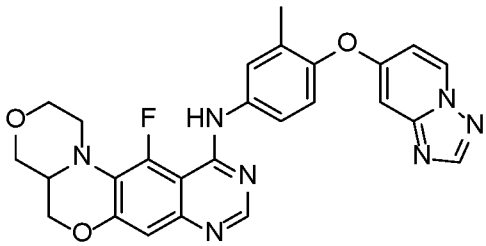
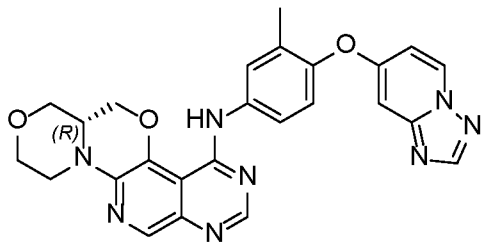
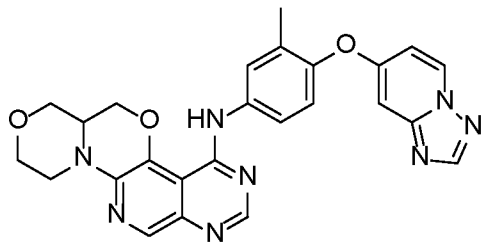
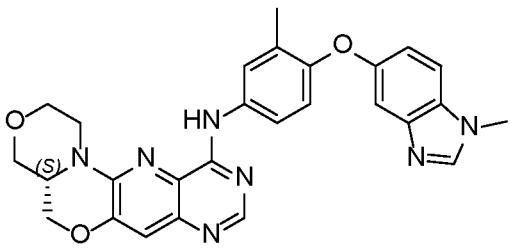
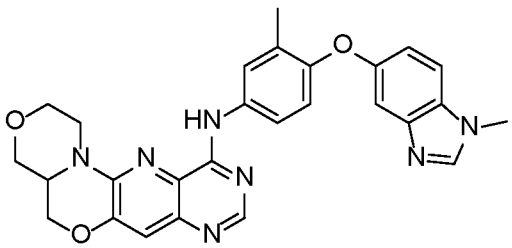
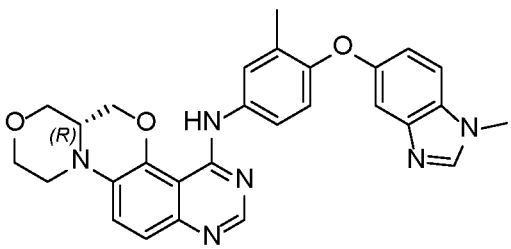
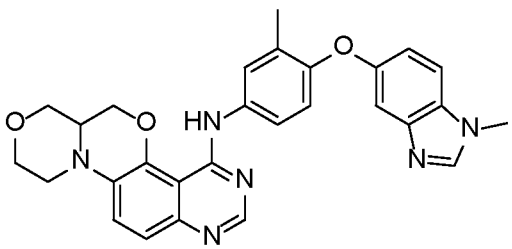
| **104** |  | 104-1 |  |
| **105** |  | 105-1 |  |
| **106** |  | 106-1 |  |
| **107** |  | 107-1 |  |
| **108** |  | 108-1 |  |

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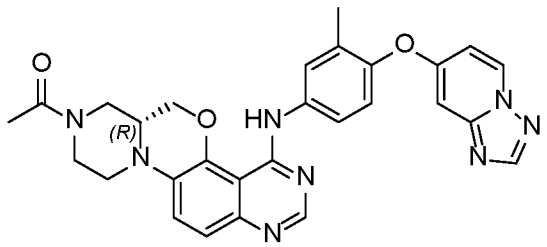
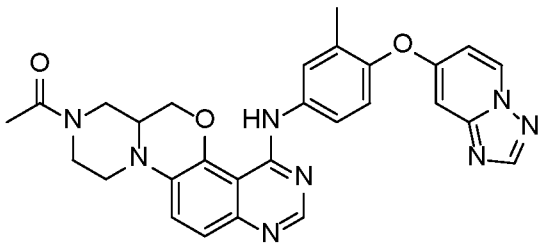
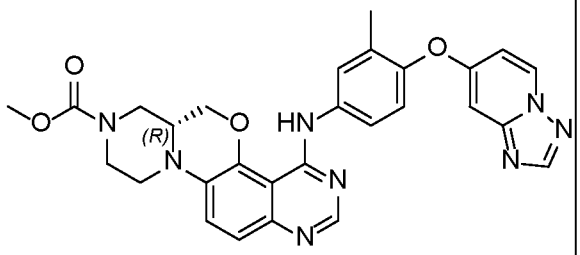
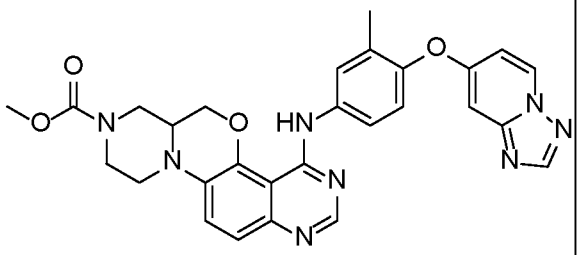
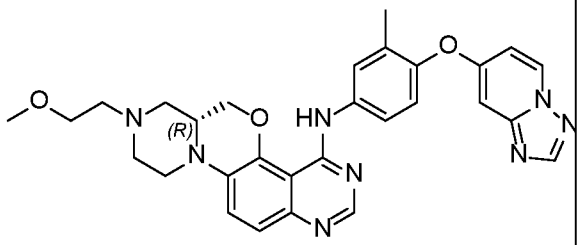
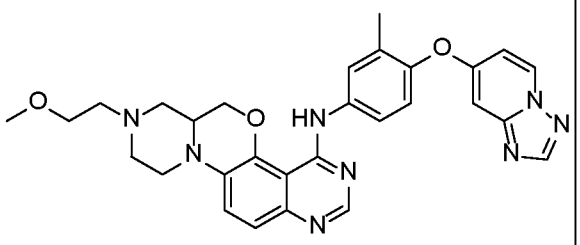
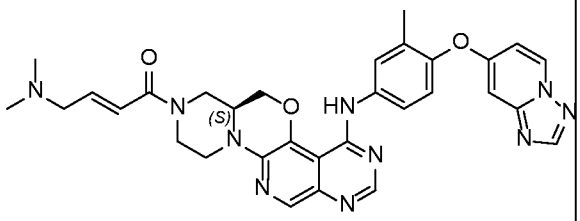
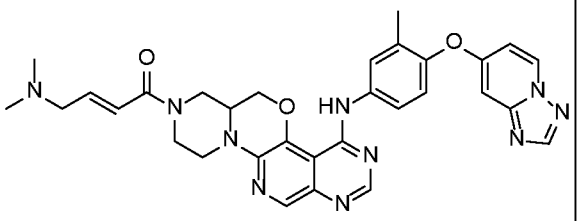
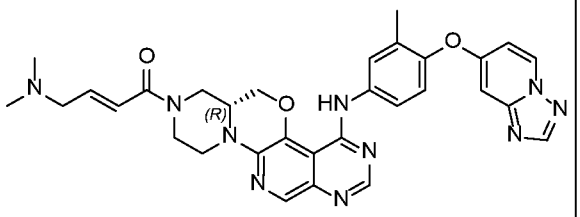
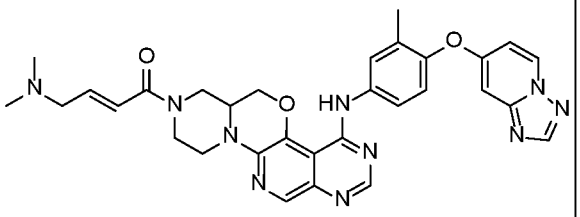
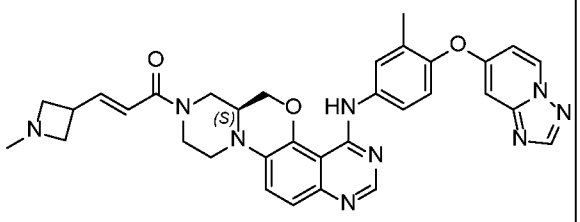
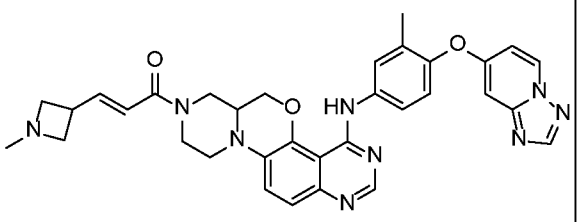
| **109** |  | 109-1 |  |
| **110** |  | 110-1 |  |
| **111** |  | 111-1 |  |
| **112** |  | 112-1 |  |
| **113** |  | 113-1 |  |
| **114** |  | 114-1 |  |

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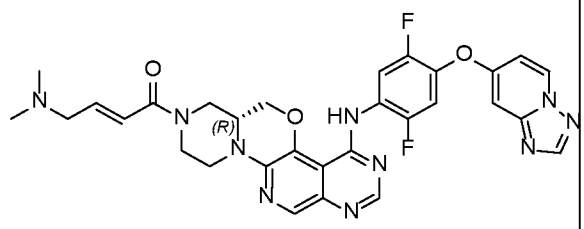
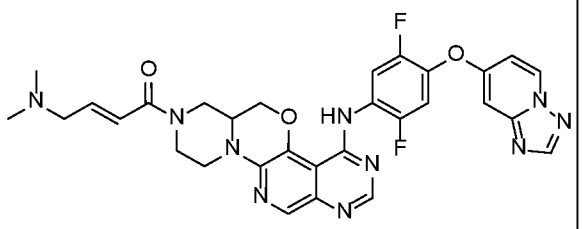
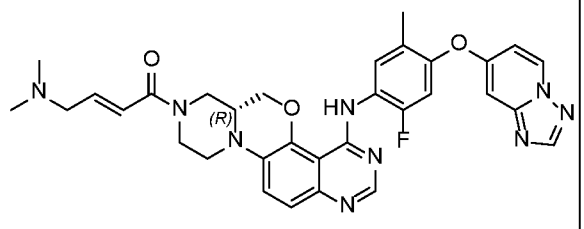
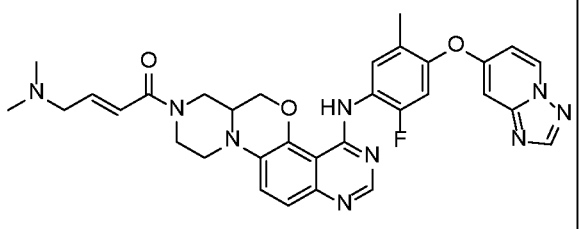
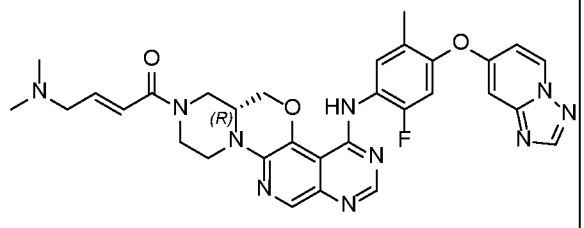
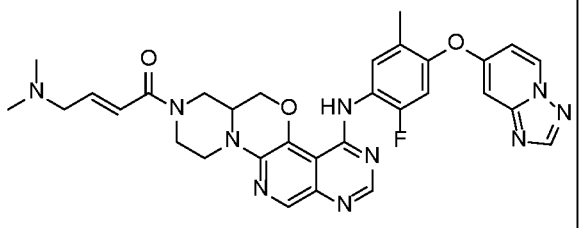
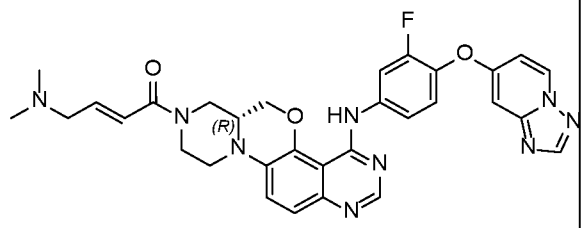
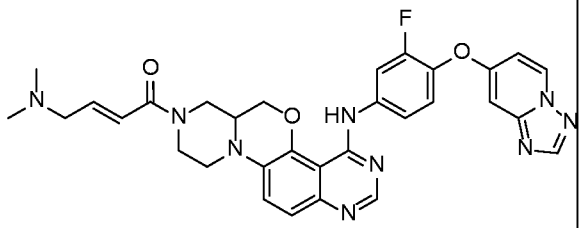
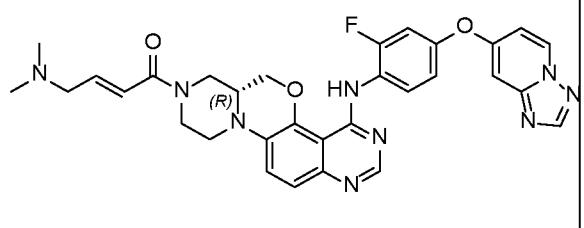
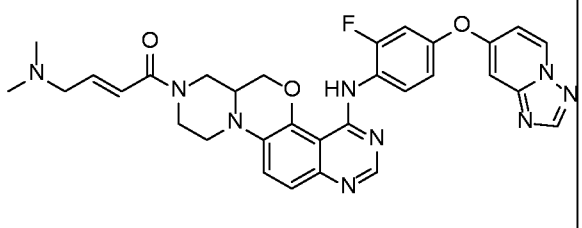
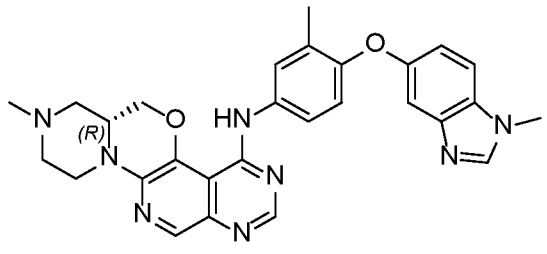
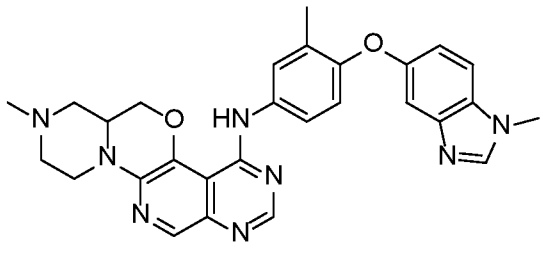
| **115** |  | 115-1 |  |
| **116** |  | 116-1 |  |
| **117** |  | 117-1 |  |
| **118** |  | 118-1 |  |
| **119** |  | 119-1 |  |
| **120** |  | 120-1 |  |

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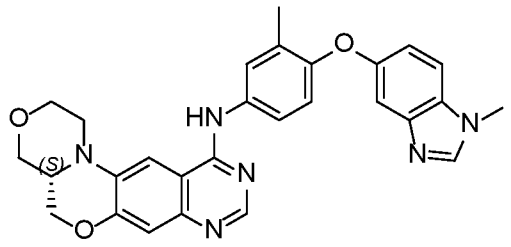
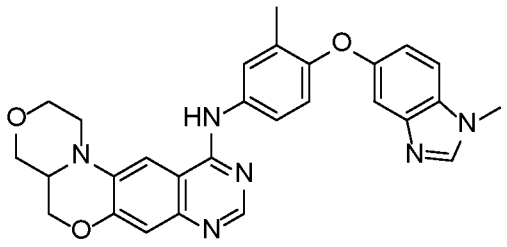
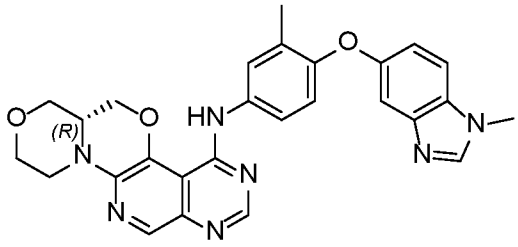
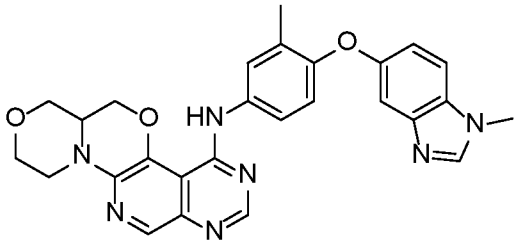
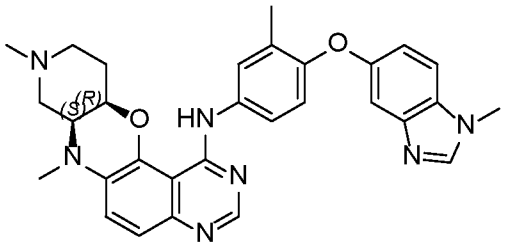
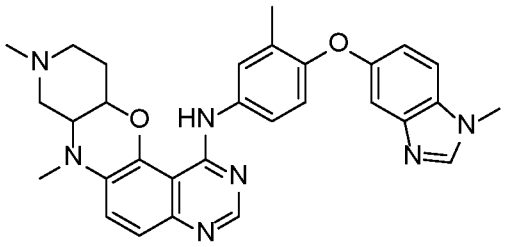
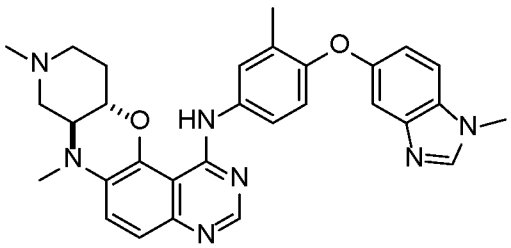
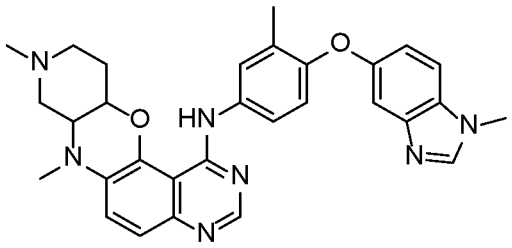
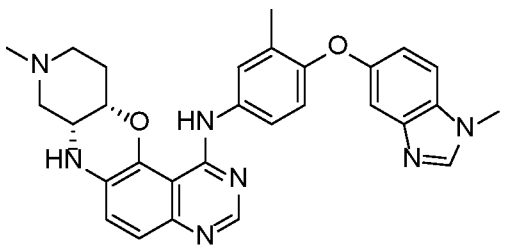
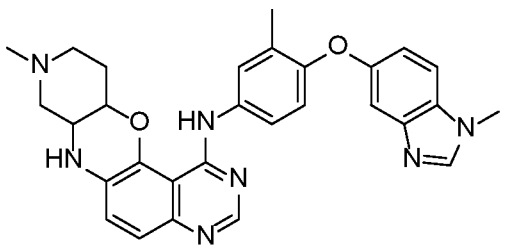
| **121** |  | 121-1 |  |
| **122** |  | 122-1 |  |
| **123** |  | 123-1 |  |
| **124** |  trans- | 124-1 |  |
| **125** |  | 125-1 |  |

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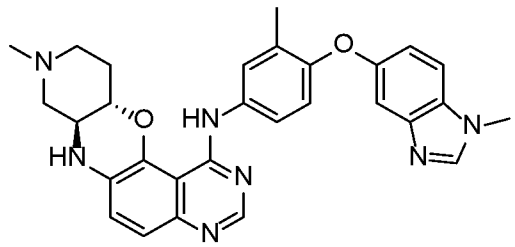
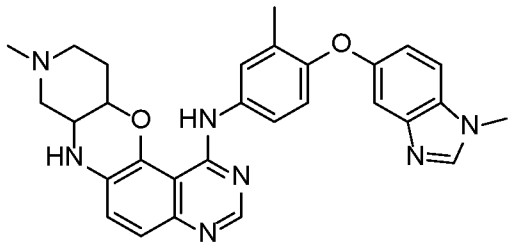
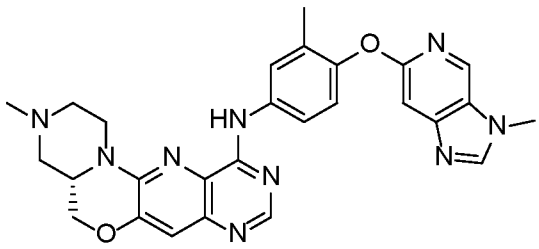
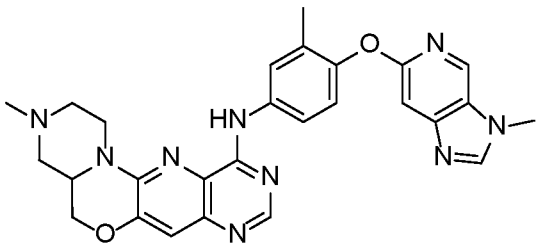
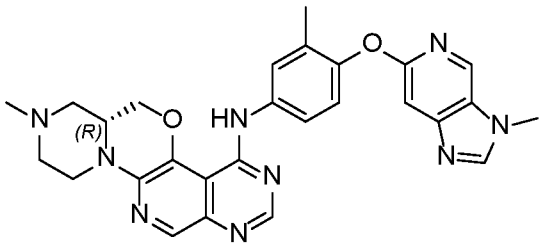
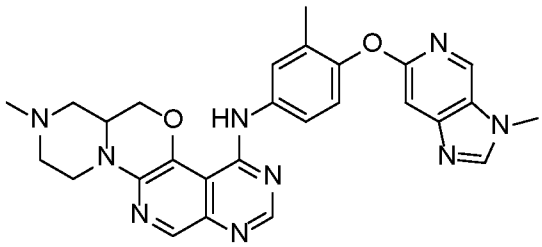
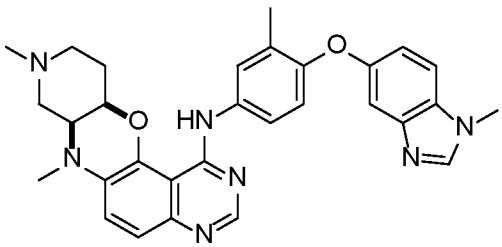
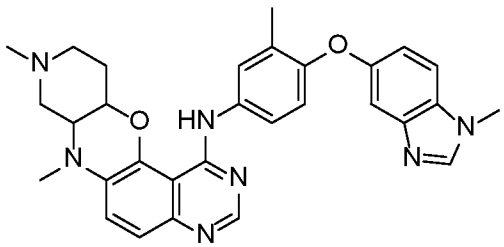
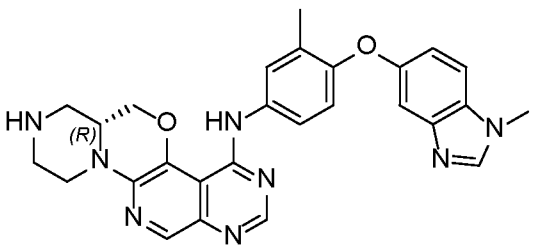
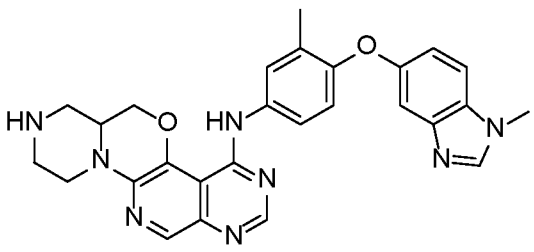
| **126** |  **trans-** | 126-1 |  |
| **127** |  | 127-1 |  |
| **128** |  | 128-1 |  |
| **129** |  | 129-1 |  |
| **130** |  | 130-1 |  |

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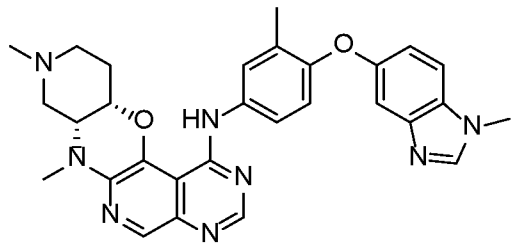
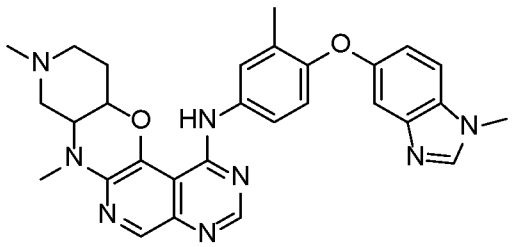
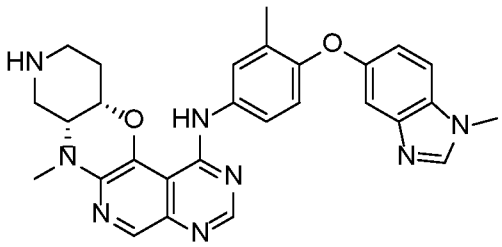
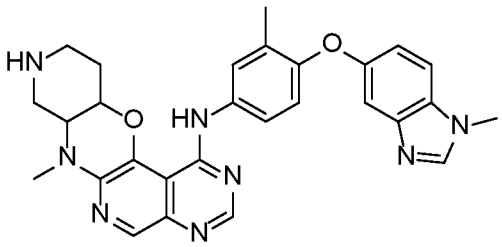
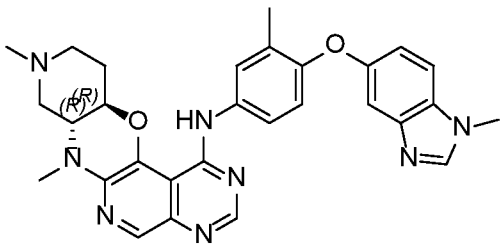
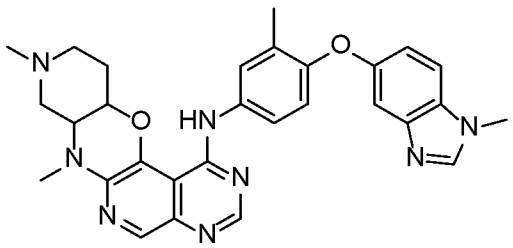
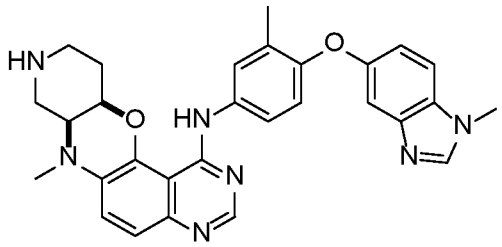
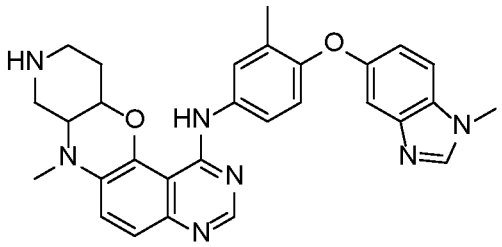
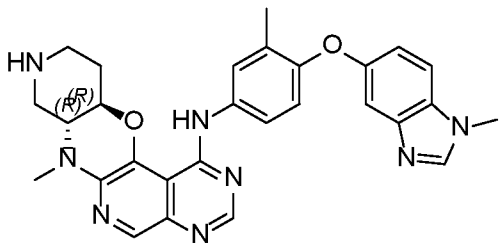
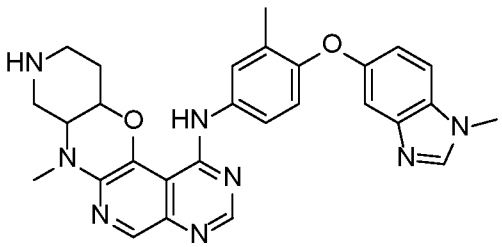
| **131** |  | 131-1 |  |
| **132** |  | 132-1 |  |
| **133** |  | 133-1 |  |
| **134** |  | 134-1 |  |
| **135** |  | 135-1 |  |

**[0110]** Although certain compounds described in Table 1 are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all non-

stereochemical forms and any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of Table 1 are herein described. In some embodiments, the compound described herein is selected from Compound Nos. 1-119. In some embodiments, the compound described herein is selected from Compound Nos. (1-1) to (119-1). In some embodiments, the compound described herein is selected from Compound Nos. 1-135. In some embodiments, the compound described herein is selected from Compound Nos. (1-1) to (135-1).

**[0111]** This disclosure also includes all salts, such as pharmaceutically acceptable salts, of compounds referred to herein. This disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms, such as N-oxides, solvates, hydrates, or isotopomers, of the compounds described. The present disclosure also includes co-crystals of the compounds described herein. Unless stereochemistry is explicitly indicated in a chemical structure or name, the structure or name is intended to embrace all possible stereoisomers of a compound depicted. In addition, where a specific stereochemical form is depicted, it is understood that other stereochemical forms are also embraced by the invention. All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form thereof. Compositions comprising a mixture of compounds of the invention in any ratio are also embraced by the invention, including mixtures of two or more stereochemical forms of a compound of the invention in any ratio, such that racemic, non-racemic, enantioenriched and scalemic mixtures of a compound are embraced.

**[0112]** Any variation or embodiment of A, $X_1$, $X_2$, L, E, M, n, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^{10}$, Y, Z, $R^{1a}$, or $R^{1b}$ provided herein can be combined with every other variation or embodiment of A, $X_1$, $X_2$, L, E, M, n, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^{10}$, Y, Z, $R^{1a}$, or $R^{1b}$, as if each combination had been individually and specifically described.

## III. PHARMACEUTICAL COMPOSITION AND FORMULATIONS

**[0113]** Any of the compounds described herein may be formulated as a pharmaceutically acceptable composition.

**[0114]** Pharmaceutical compositions of any of the compounds detailed herein are embraced by this disclosure. Thus, the present disclosure includes pharmaceutical compositions comprising a compound as detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

**[0115]** A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, as detailed herein are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, as detailed herein is in substantially pure form. In one variation, "substantially pure" intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. For example, a composition of a substantially pure compound selected from a compound of Table 1 intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound of Table 1. In one variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 25% impurity. In another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains or no more than 20% impurity. In still another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains or no more than 10% impurity. In a further variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 5% impurity. In another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is

provided wherein the composition contains no more than 3% impurity. In still another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 1% impurity. In a further variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 0.5% impurity. In yet other variations, a composition of substantially pure compound means that the composition contains no more than 15%, no more than 10%, no more than 5%, no more than 3%, or no more than 1% impurity, which impurity may be the compound in a different stereochemical form. For instance, and without limitation, a composition of substantially pure (S) compound means that the composition contains no more than 15% or no more than 10% or no more than 5% or no more than 3% or no more than 1% of the (R) form of the compound.

**[0116]** In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the present disclosure embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein. In some embodiments, the compounds and compositions as provided herein are sterile. Methods for sterilization known in the art may be suitable for any compounds or form thereof and compositions thereof as detailed herein.

**[0117]** A compound detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous

liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

**[0118]** A compound detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, with a pharmaceutically acceptable carrier. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

**[0119]** A compound detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, etc. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

**[0120]** Any of the compounds, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, described herein can be formulated in a tablet in any dosage form described, for example, a compound as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, can be formulated as a 10 mg tablet.

**[0121]** Compositions comprising a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, provided herein are

also described. In one variation, the composition comprises a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided. In some embodiments, the composition is for use as a human or veterinary medicament. In some embodiments, the composition is for use in a method described herein. In some embodiments, the composition is for use in the treatment of a disease or disorder described herein.

**[0122]** Compositions formulated for co-administration of a compound provided herein and one or more additional pharmaceutical agents are also described. The co-administration can be simultaneous or sequential in any order. A compound provided herein may be formulated for co-administration with the one or more additional pharmaceutical agents in the same dosage form (*e.g.*, single tablet or single i.v.) or separate dosage forms (*e.g.*, two separate tablets, two separate i.v., or one tablet and one i.v.). Furthermore, co-administration can be, for example, 1) concurrent delivery, through the same route of delivery (*e.g.*, tablet or i.v.), 2) sequential delivery on the same day, through the same route or different routes of delivery, or 3) delivery on different days, through the same route or different routes of delivery.

## IV. METHODS OF USE

**[0123]** Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof provided herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays.

**[0124]** In one aspect, provided herein is a method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2, comprising contacting the ErbB2 or the mutant form with a therapeutically effective amount of a compound or composition provided herein. In some embodiments, provided herein is a method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2 in a cell, comprising administering an effective amount of a compound or composition of the

disclosure to the cell. In some embodiments, provided herein is a method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2 in an individual in need thereof, comprising administering an effective amount of a compound or composition of the disclosure to the individual.

**[0125]** In some embodiments, the mutant form of human ErbB2 comprises a mutation in Exon 20 that introduces certain amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, V777_G778insGSP. In other embodiments, the mutant form of human ErbB2 comprises one or more mutations that introduce certain amino acid substitutions selected from the group consisting of: P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, and A1232fs. In still further embodiments of the present aspect, the mutant form of human ErbB2 comprises one or more point mutations in ErbB2 that introduce (a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or (b) a frameshift at A1232.

**[0126]** In some variations, the compounds provided herein are selective for inhibiting human receptor tyrosine kinase ErbB2. As such, in some embodiments, provided herein is a method of selectively inhibiting human receptor tyrosine kinase ErbB2, as compared to other receptor tyrosine kinases, including but not limited to ErbB1 (EGFR), ErbB3, or ErbB4.

**[0127]** The compounds and compositions described herein may be used in a method of treating a disease or disorder in an individual, wherein the individual has cells or cell tissue having increased ErbB2 kinase activity, for example, as compared to the ErbB2 kinase activity in a corresponding cell type or cell tissue from a healthy individual. In some embodiments, the compound or composition is administered according to a dosage described herein.

**[0128]** In some embodiments, provided herein is a method for treating a disease or disorder in an individual, wherein the individual has cells or cell tissue having increased ErbB2 kinase activity, comprising administering to an individual in need of treatment a therapeutically effective amount of a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically

acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a therapeutically effective amount of a composition as described herein. In some embodiments, the disease or disorder is cancer. In some embodiments, the disease or disorder is lung cancer, glioma, head and/or neck cancer, salivary gland cancer, breast cancer, esophageal cancer, liver cancer, stomach (gastric) cancer, uterine cancer, cervical cancer, biliary tract cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, prostate, or ovarian cancer. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the individual has received at least one, at least two or at least three prior therapies for the cancer. In certain embodiments, the one or more prior therapies are selected from the group consisting of lapatinib, neratinib, afatinib, pyrotinib, poziotinib, TAK-788 and tucatinib.

**[0129]** In some embodiments, the disease or disorder is refractory or resistant to first-line treatment, second-line treatment, and/or third-line treatment. In certain embodiments, the condition having increased activation of ErbB2 kinase activity is refractory or resistant to treatment with one or more tyrosine kinase inhibitors selected from the group consisting of lapatinib, neratinib, afatinib, pyrotinib, poziotinib, TAK-788, and tucatinib.

**[0130]** Resistant subtypes of tyrosine kinase-mediated diseases or disorders may be associated with any number of ErbB2 independent resistance mechanisms. In some embodiments wherein the disease or disorder in the individual having cells or cell tissue with increased ErbB2 kinase activity is refractory to treatment, the disease or disorder is characterized as being associated with one or more ErbB2 dependent resistance mechanisms. ErbB2-dependent resistance mechanisms include, but are not limited to, one or more mutations in Exon 20 of ErbB2 or other disease-associated point mutations. The one or more mutations of ErbB2 introduce certain amino acid deletions and/or insertions, for example, A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and/or V777_G778insGSP. In other variations, the mutations introduce certain amino acid substitutions, for example, P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, and/or A1232fs. In some variations, the mutations introduce certain (a) amino acid substitutions, for example, P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S, and/or (b) frameshifts, such as a frameshift at A1232.In some variations, the refractory

disease or disorder in an individual having increased activation of the ErbB2 kinase activity is associated with one or more mutations in Exon 20 of the ErbB2. In certain variations, the one or more mutations in Exon 20 of the ErbB2 that introduce certain amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In other variations, the refractory disease or disorder in an individual having increased activation of the ErbB2 kinase activity is associated with one or more disease-associated point mutations. In certain variations, the one or more point mutations introduce certain amino acid substitutions selected from the group consisting of: P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, and A1232fs. In other embodiments, the one or more point mutations introduce (a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or (b) a frameshift at A1232.

**[0131]** In some embodiments, provided is a method for treating cancer in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof as described herein, or a therapeutically effective amount of a composition as described herein. In some embodiments, the cancer comprises cells or cell tissue having increased ErbB2 kinase activity, for example, as compared to the ErbB2 kinase activity in a corresponding cell type or cell tissue from a healthy individual. In some embodiments, the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2. In certain embodiments, the one or more mutations in Exon 20 of the ErbB2 introduce certain amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In some embodiments, the cancer comprises cells or cell tissue comprising one or more disease-associated point mutations. In certain embodiments, the one or more point mutations introduce certain amino acid substitutions selected from the group consisting of: P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D,

E1021Q, F1030C, V1128I, N1219S, and A1232fs. In certain other embodiments, the cancer comprises cells or cell tissue having one or more point mutations that introduce (a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or (b) a frameshift at A1232. In some embodiments, the disease or disorder is lung cancer, glioma, head and/or neck cancer, salivary gland cancer, breast cancer, esophageal cancer, liver cancer, stomach (gastric) cancer, uterine cancer, cervical cancer, biliary tract cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, prostate, or ovarian cancer. In some embodiments, the cancer is non-small cell lung cancer.

**[0132]** In one aspect, provided herein is a method of treating cancer in an individual in need thereof, wherein modulation of ErbB2 kinase activity inhibits or ameliorates the pathology and/or symptomology of the cancer, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In one embodiment, provided herein is a method of treating cancer, wherein modulation of ErbB2 kinase activity inhibits the pathology and/or symptomology of the cancer, in an individual, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In one embodiment, provided herein is a method of treating a cancer, wherein modulation of ErbB2 kinase activity ameliorates the pathology and/or symptomology of the cancer, in an individual, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein.

**[0133]** In another aspect, provided herein is a method of preventing cancer, wherein modulation of ErbB2 kinase activity prevents the pathology and/or symptomology of the cancer, in an individual, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In another aspect, provided herein is a method of delaying the onset and/or development of a cancer in an individual (such as a human) who is at risk for developing the cancer, *e.g.*, an individual who has cells or cell tissue having increased ErbB2 kinase activity. It is appreciated that delayed development may encompass prevention in the event the individual does not develop the cancer.

**[0134]** In one aspect, provided herein is a method of delaying the onset and/or development of cancer in an individual having cells or cell tissue having increased ErbB2 kinase activity in need thereof, comprising administering to the individual a therapeutically effective amount of a

compound or composition provided herein. In some embodiments, the cancer is lung cancer, glioma, head and/or neck cancer, salivary gland cancer, breast cancer, esophageal cancer, liver cancer, stomach (gastric) cancer, uterine cancer, cervical cancer, biliary tract cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, prostate, or ovarian cancer. In some embodiments, the cancer is non-small cell lung cancer.

**[0135]** In one aspect, provided herein is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in therapy. In some embodiments, provided herein is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or pharmaceutical composition comprising such compound, for use in the treatment of cancer. In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of cancer. In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of cancer, wherein the cancer comprises cells or cell tissue having increased activation of ErbB2 kinase activity. In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of cancer, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2. In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of cancer, wherein the cancer cells comprise one or more genetic alterations in Exon 20 of the ErbB2 that introduce certain amino acid deletions and/or

insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of cancer, wherein the cancer comprises cells or cell tissue having one or more disease-associated point mutations in ErbB2. In certain embodiments, the cancer comprises cells or cell tissue having one or more point mutations that introduce certain amino acid substitutions selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, and A1232fs. In certain other embodiments, the cancer comprises cells or cell tissue having one or more point mutations that introduce (a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or (b) a frameshift at A1232. In some embodiments, provided is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of lung cancer, glioma, head and/or neck cancer, salivary gland cancer, breast cancer, esophageal cancer, liver cancer, stomach (gastric) cancer, uterine cancer, cervical cancer, biliary tract cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, prostate, or ovarian cancer. In some embodiments, the lung cancer is non-small cell lung cancer.

**[0136]** In another embodiment, provided herein is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in the manufacture of a medicament for the treatment of cancer. In another embodiment, provided herein is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in the manufacture of a medicament for the treatment of

cancer, wherein the cancer comprises cells or cell tissue having increased ErbB2 kinase activity. In another embodiment, provided herein is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in the manufacture of a medicament for the treatment of cancer, wherein the cancer cells or cancer cell tissue comprise one or more mutations in Exon 20 of the ErbB2. In some embodiments, the medicament is for the treatment of cancer, wherein the cancer cells comprise one or more genetic alterations in Exon 20 of the ErbB2 that introduce certain amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In another embodiment, provided herein is a compound of formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in the manufacture of a medicament for the treatment of cancer, wherein the cancer cells or cancer cell tissue comprise one or more disease-associated point mutations in ErbB2. In some embodiments, the medicament is for the treatment of cancer, wherein the cancer cells comprise one or more point mutations that introduce certain amino acid substitutions selected from the group consisting of:P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, and A1232fs. In some embodiments, the medicament is for the treatment of cancer, wherein the cancer cells comprise one or more point mutations that introduce (a) an amino acid substitution selected from the group consisting of: P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S, or (b) a frameshift at A1232. In some embodiments, the medicament is for the treatment of lung cancer, glioma, head and/or neck cancer, salivary gland cancer, breast cancer, esophageal cancer, liver cancer, stomach (gastric) cancer, uterine cancer, cervical cancer, biliary tract cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, prostate, or ovarian cancer. In some embodiments, the medicament is for the treatment of non-small cell lung cancer.

**[0137]** In some embodiments, the individual is a mammal. In some embodiments, the individual is a primate, dog, cat, rabbit, or rodent. In some embodiments, the individual is a

primate. In some embodiments, the individual is a human. In some embodiments, the human is at least about or is about any of 18, 21, 30, 50, 60, 65, 70, 75, 80, or 85 years old. In some embodiments, the human is a child. In some embodiments, the human is less than about or about any of 21, 18, 15, 10, 5, 4, 3, 2, or 1 years old.

**[0138]** In some embodiments, the method further comprises administering one or more additional pharmaceutical agents. In some embodments, the method further comprises administering one or more additional anti-cancer agents to the patient. In some embodiments, the method further comprises administering radiation. In some embodiments, the method further comprises administering one or more additional pharmaceutical agents and radiation.

## V. DOSING AND ADMINISTRATION

**[0139]** The dose of a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular cancer, such as type and stage of cancer, being treated. In some embodiments, the amount of the compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is a therapeutically effective amount.

**[0140]** The compounds provided herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be administered to an individual via various routes, including, *e.g.*, intravenous, intramuscular, subcutaneous, oral, and transdermal.

**[0141]** The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg. Effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease to be treated, the subject's health status, condition, and weight. An exemplary dose is in the range of about from about 0.7 mg to 7 g daily, or about 7 mg to 350 mg daily, or about 350 mg to 1.75 g daily, or about 1.75 to 7 g daily.

**[0142]** Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound

provided herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable excipient.

**[0143]** A compound or composition provided herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent, including a 'drug holiday' (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

## VI. ARTICLES OF MANUFACTURE AND KITS

**[0144]** The present disclosure further provides articles of manufacture comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, a composition described herein, or one or more unit dosages described herein in suitable packaging. In certain embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

**[0145]** The present disclosure further provides kits for carrying out the methods of the present disclosure, which comprises one or more compounds described herein or a composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of any disease or described herein, for example for the treatment of cancer, including lung, glioma, skin, head and neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal,

bladder, prostate, or ovarian cancer. In some embodiments, the kit may contain instructions for the treatment of non-small cell lung cancer.

**[0146]** In certain embodiments of the foregoing, the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2. In still further embodiments, the cancer cells or cancer cell tissue comprise one or more mutations in Exon 20 of the ErbB2 that introduce certain amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In certain other embodiments of the cancer comprises cells or cell tissue having one or more disease-associated point mutations in ErbB2. In still further embodiments, the cancer cells or cancer cell tissue comprise the one or more point mutations that introduce amino acid substitutions selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, and A1232fs. In other embodiments, the cancer comprises cells or cell tissue having one or more point mutations that introduce (a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or (b) a frameshift at A1232.

**[0147]** The kits optionally further comprise a container comprising one or more additional pharmaceutical agents and which kits further comprise instructions on or in the package insert for treating the subject with an effective amount of the one or more additional pharmaceutical agents.

**[0148]** Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

**[0149]** The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or an additional pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5

months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

**[0150]** The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to an individual.

## VII. GENERAL SYNTHETIC METHODS

**[0151]** The compounds of the present disclosure may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

**[0152]** The intermediates described in the following preparations may contain a number of nitrogen, hydroxy, and acid protecting groups such as esters. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are well known to the skilled artisan and are described in the literature. S*ee. e.g.*, Greene and Wuts, *Protective Groups in Organic Synthesis*, (T. Greene and P. Wuts, eds., 2d ed. 1991).

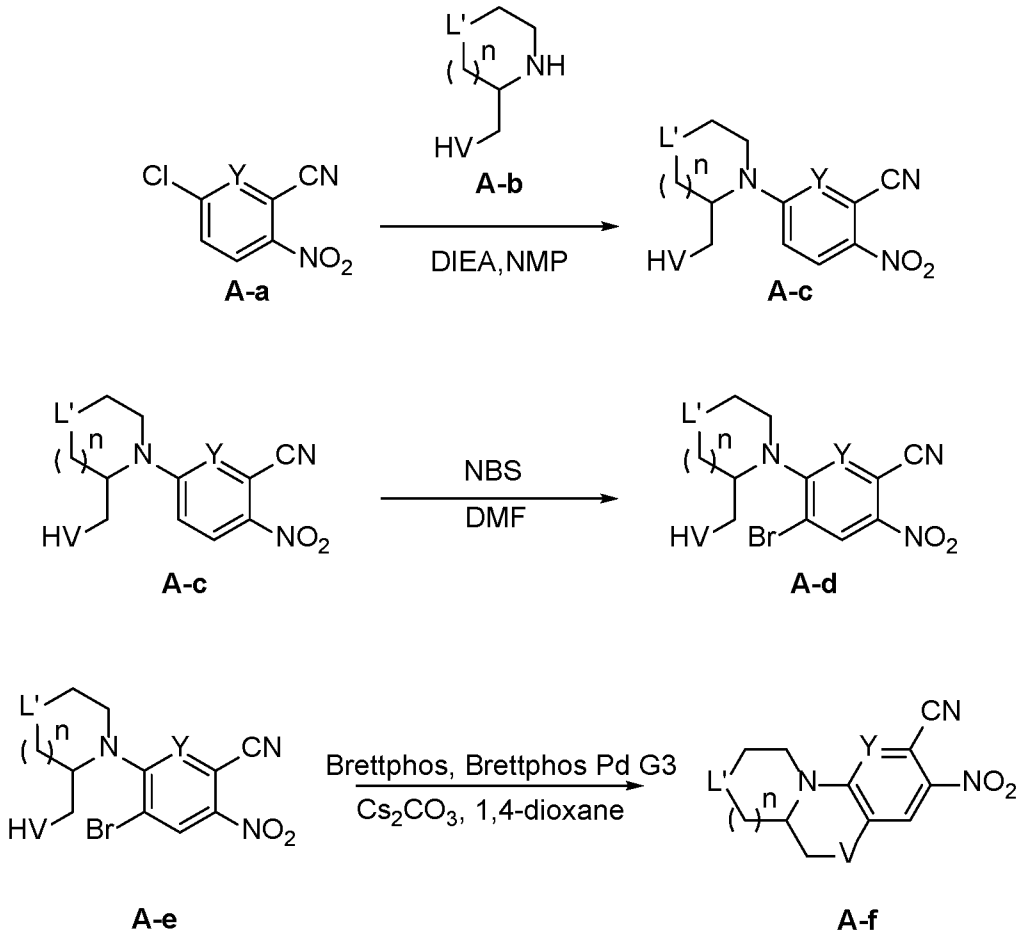
**[0153]** Certain stereochemical centers have been left unspecified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. Furthermore, individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," *Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994).

**[0154]** The compounds of the present invention, or salts thereof, may be prepared by a variety of procedures known in the art, some of which are illustrated in the Examples below. The specific synthetic steps for each of the routes described may be combined in different ways,

to prepare compounds of the invention, or salts thereof. The products of each step can be recovered by conventional methods well known in the art, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization. The reagents and starting materials are readily available to one of ordinary skill in the art. Others may be made by standard techniques of organic and heterocyclic chemistry which are analogous to the syntheses of known structurally-similar compounds and the procedures described in the Examples which follow including any novel procedures.

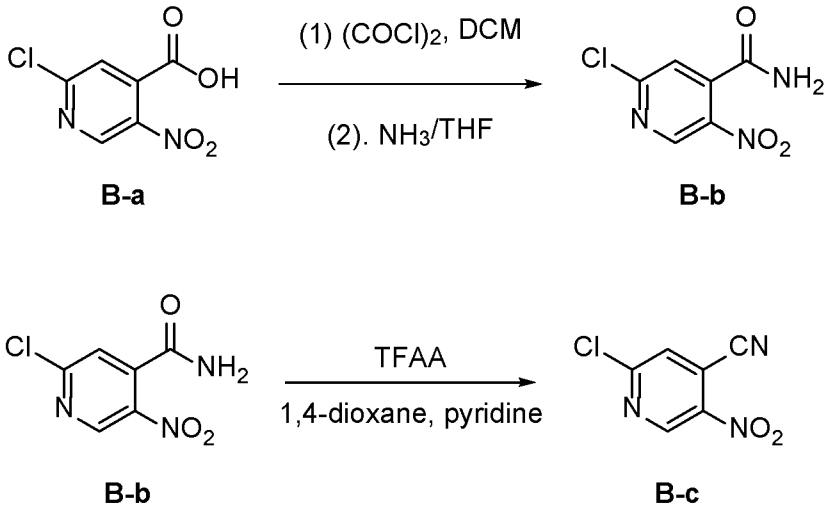
**[0155]** Compounds of formula (I), (I'), (I''), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-A-5), (I-A-6), (I-A-7), (I-A-8), (I-A-9), (I-A-10), (I-A-1a), (I-A-2a), (I-A-2b), (I-A-3a), (I-A-5a), (I-A-7a), (I-A-9a), (I-B), (I-B'), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-B-5), (I-B-6), (I-B-7), (I-B-8), (I-B-1a), (I-B-5a), (I-C), (I-C'), (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-5), (I-C-6), (I-C-1a), (I-C-2a), (I-C-5a), (I-D), (I-D-1), or (I-D-2) can be prepared according to Scheme A, Scheme B, Scheme C, Scheme D, Scheme E, Scheme F, Scheme G, Scheme H, Scheme I, Scheme J, Scheme K, Scheme L, Scheme M, Scheme N, Scheme O, Scheme P, Scheme Q, Scheme R, and Scheme S, wherein A, L, M, n, E, G, V, $X_1$, $X_2$, Y, $Y^1$, $Y^2$, Z, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, and $R^{10}$ are as defined for formula (I), formula (I'), formula (I''), formula (I-A), formula (I-B'), formula (I-C'), or formula (I-D), or any applicable variation thereof as detailed herein.

**Scheme A.**



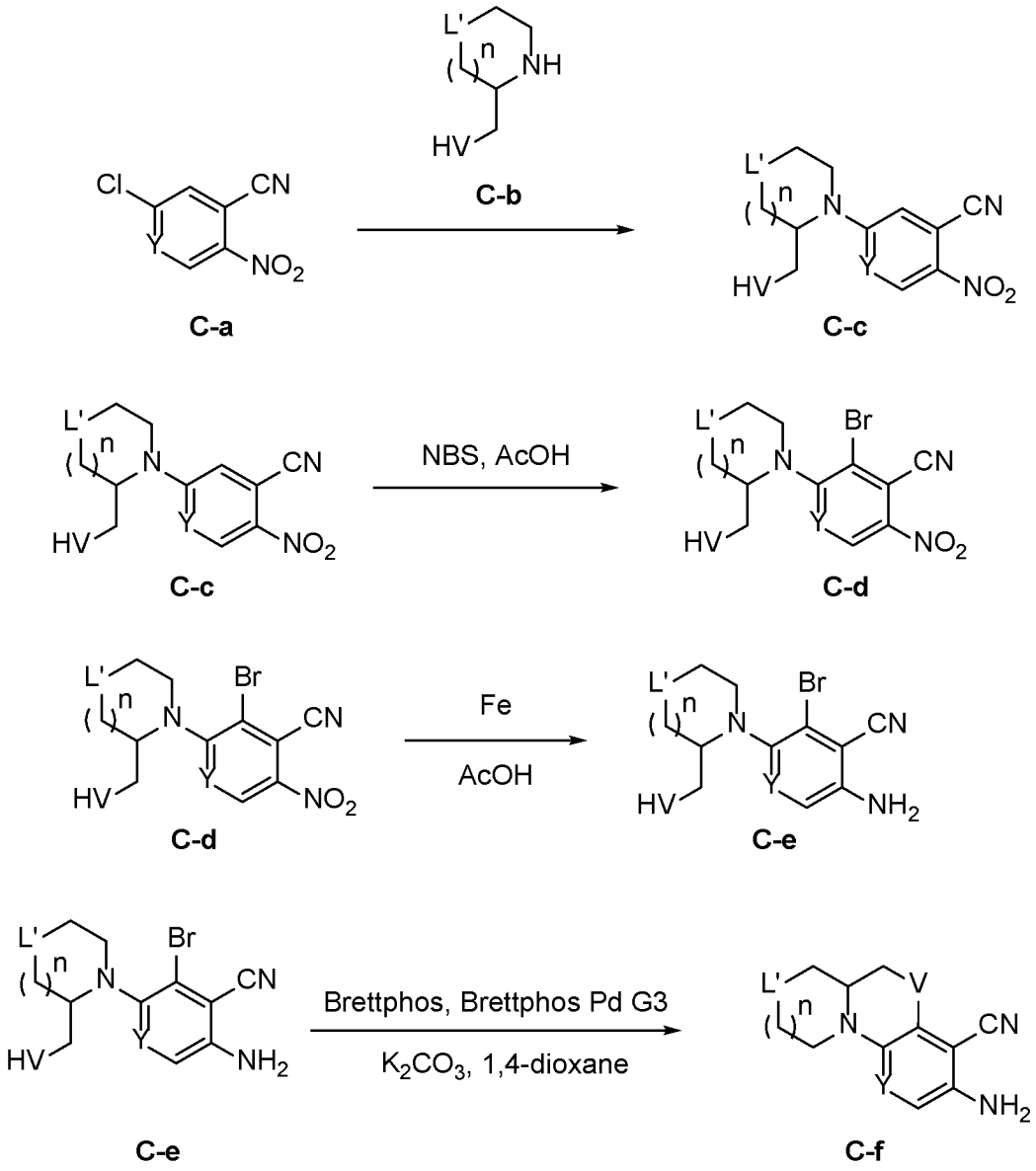

**[0156]** As shown in Scheme A, compounds of general formula **A-a** are reacted with compounds of general formula **A-b**, for example in the presence of DIEA and NMP, to provide compounds of general formula **A-c**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **A-c** are further brominated, for example in the presence of NBS and DMF, to provide compounds of general formula **A-d**. Compounds of general formula **A-d** are further cyclized, for example in the presence of Brettphos, Brettphos Pd G3, $Cs_2CO_3$, and 1,4-dioxane, to provide compounds of formula **A-e.**

**Scheme B.**



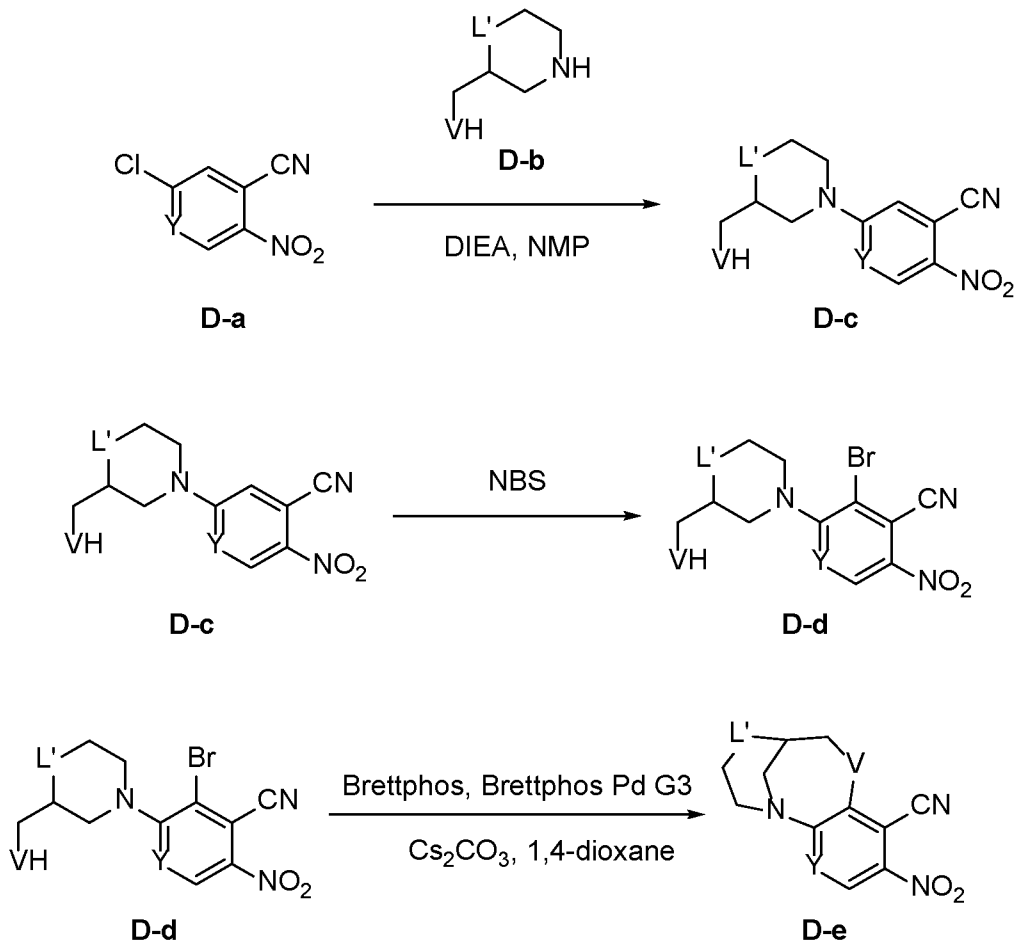

**[0157]** As shown in Scheme B, compounds of formula **B-a** are reacted, for example first in the presence of $(COCl)_2$ and DCM and then in the presence of $NH_3$ and THF, to provide compounds of formula **B-b**. Compounds of formula **B-b** are further reacted, for example in the presence of TFAA, 1,4-dioxane and pyridine, to provide compounds of general formula **B-c**.

**Scheme C.**



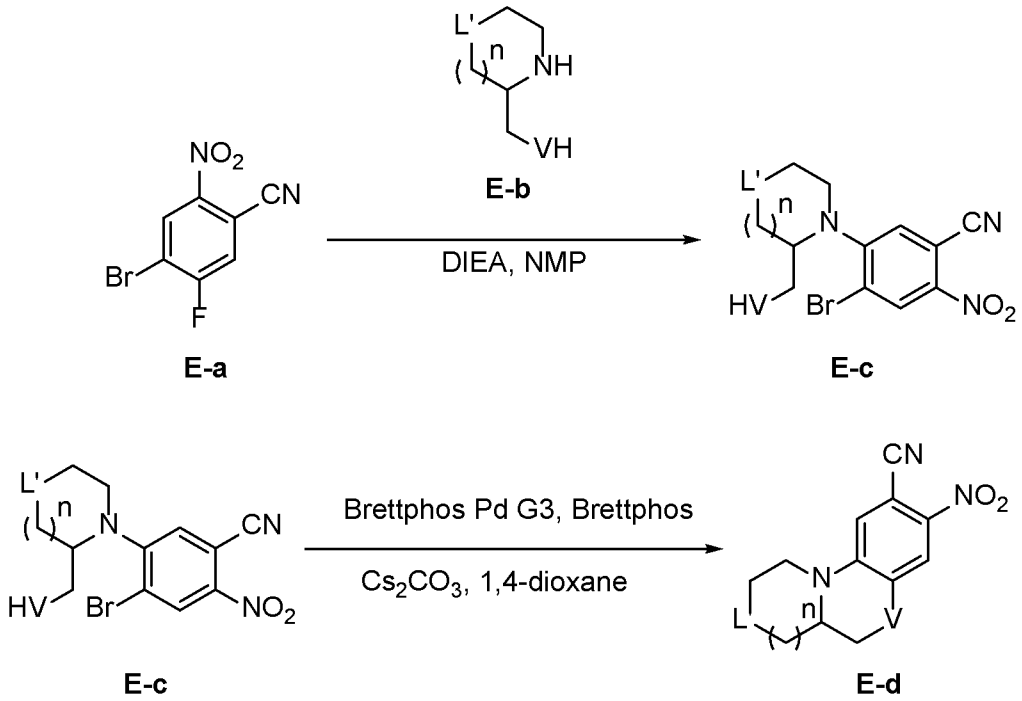

**[0158]** As shown in Scheme C, compounds of general formula **C-a** are reacted with compounds of general formula **C-b**, for example in the presence of X, to provide compounds of general formula **C-c**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **C-c** are further brominated, for example in the presence of NBS and AcOH, to provide compounds of general formula **C-d**. Compounds of general formula **C-d** are further reduced, for example in the presence of Fe and AcOH, to provide compounds of general formula **C-e**. Compounds of general formula **C-e** are further cyclized, for example in the presence of Brettphos, Brettphos Pd G3, $K_2CO_3$, and 1,4-dioxane, to provide compounds of general formula **C-f**.

**Scheme D.**



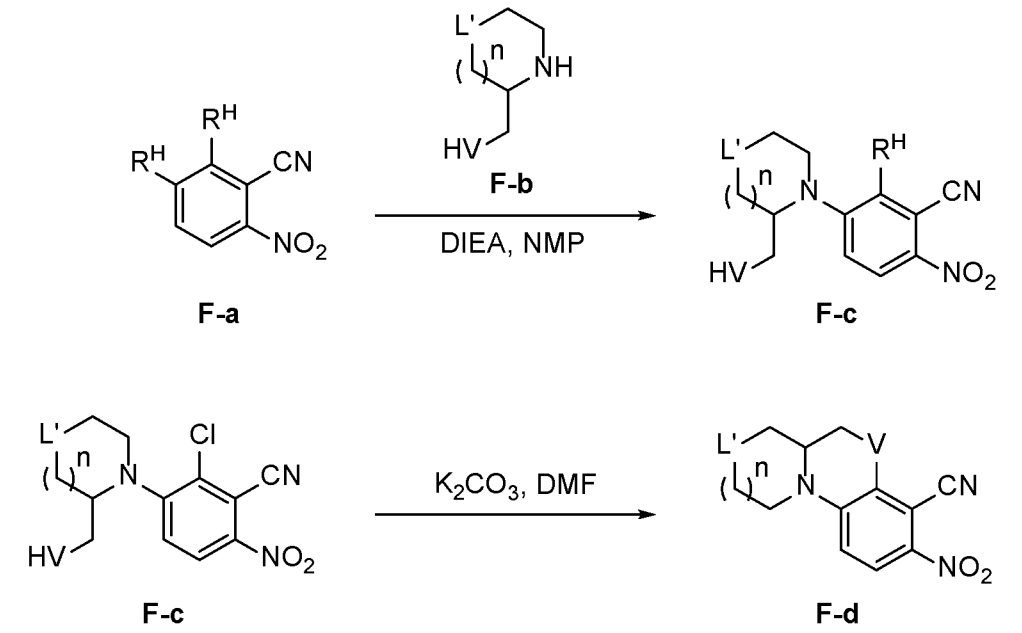

**[0159]** As shown in Scheme D, compounds of general formula **D-a** are reacted with compounds of general formula **D-b**, for example in the presence of DIEA and NMP, to provide compounds of general formula **D-c**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **D-c** are further brominated, for example in the presence of NBS, to provide compounds of general formula **D-d**. Compounds of general formula **D-d** are further cyclized, for example in the presence of Brettphos, Brettphos Pd G3, $Cs_2CO_3$, and 1,4-dioxane, to provide compounds of general formula **D-e**.

**Scheme E.**



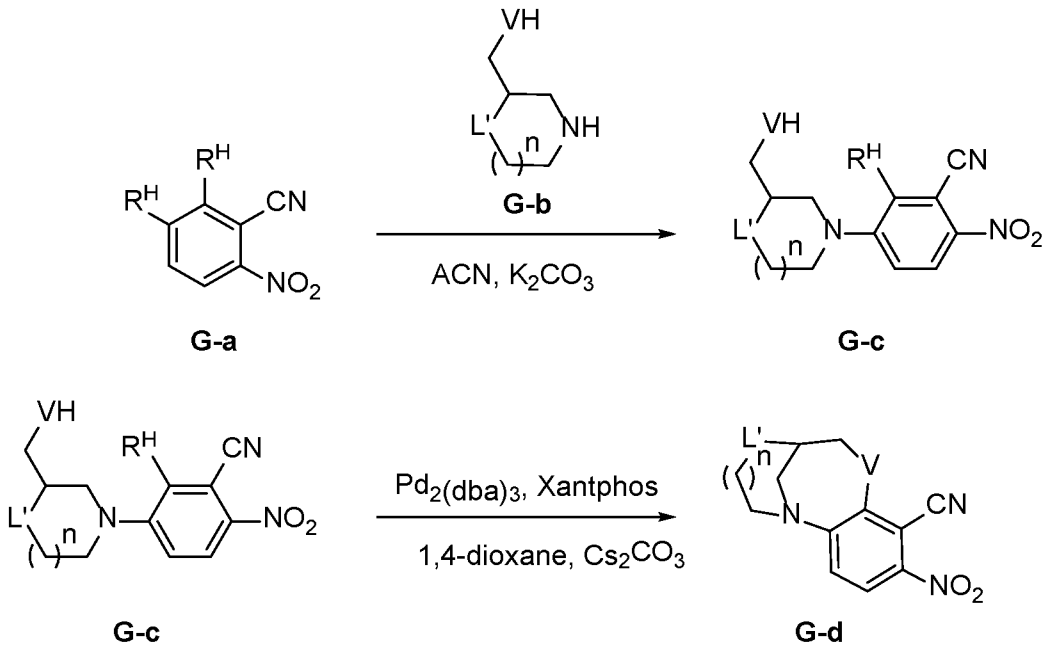

**[0160]** As shown in Scheme E, compounds of general formula **E-a** are reacted with compounds of general formula **E-b**, for example in the presence of DIEA and NMP, to provide compounds of general formula **E-c**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **E-c** are further cyclized, for example in the presence of Brettphos, Brettphos Pd G3, $Cs_2CO_3$, and 1,4-dioxane, to provide compounds of general formula **E-d**.

**Scheme F.**



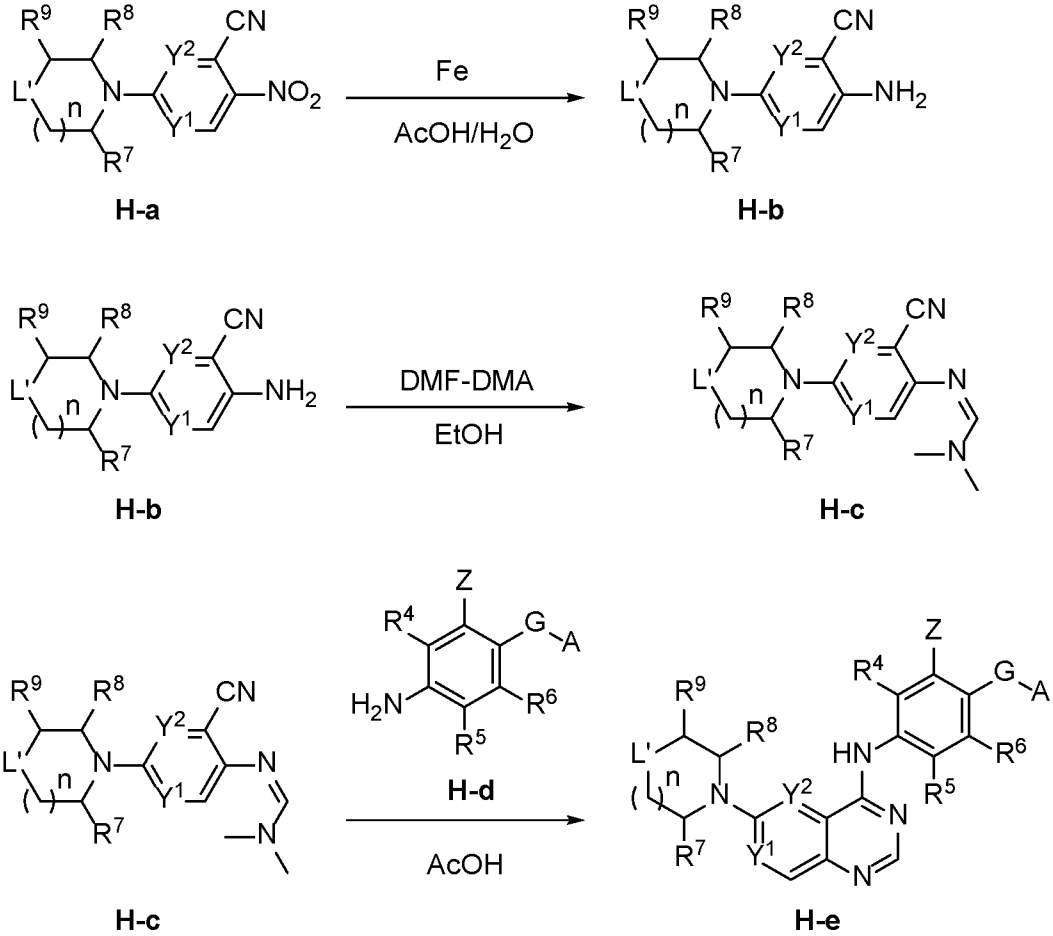
**[0161]** As shown in Scheme F, compounds of general formula **F-a** are reacted with compounds of general formula **F-b**, for example in the presence of DIEA and NMP, to provide compounds of general formula **F-c**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **F-c** are further cyclized, for example in the presence of $K_2CO_3$, and DMF, to provide compounds of general formula **F-d**.

**Scheme G.**




**[0162]** As shown in Scheme G, compounds of general formula **G-a** are reacted with compounds of general formula **G-b**, for example in the presence of ACN $K_2CO_3$, to provide compounds of general formula **G-c**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **G-c** are further cyclized, for example in the presence of $Pd(dba)_3$, Xantphos, 1,4-dioxane, and $Cs_2CO_3$, to provide compounds of general formula **G-d**.

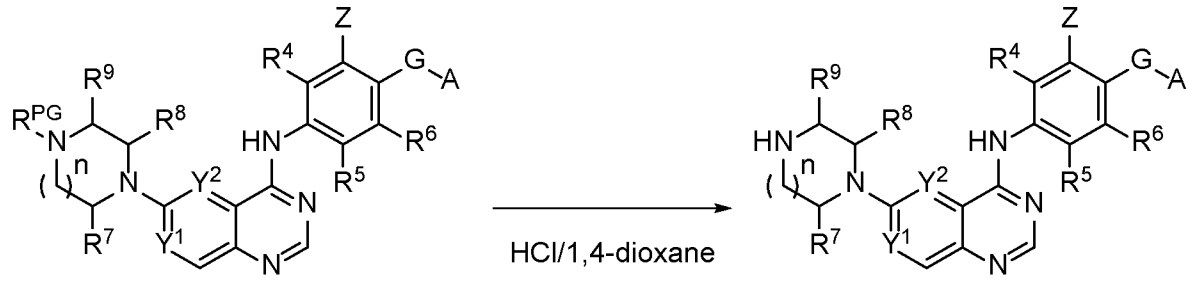
**Scheme H.**




H-a H-b H-b H-c H-c H-d H-e

**[0163]** As shown in Scheme H, compounds of general formula **H-a** are reduced, for example in the presence of Fe, AcOH, and $H_2O$, to provide compounds of general formula **H-b**, wherein L' is N-$R^{PG}$, $CH_2$, O, or a bond, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **H-b** are further reacted, for example in the presence of DMF-DMA and EtOH, to provide compounds of general formula **H-c**. Compounds of general formula **H-c** are further reacted with compounds of general formula **H-d**, for example in the presence of AcOH, to provide compounds of general formula **H-e**.

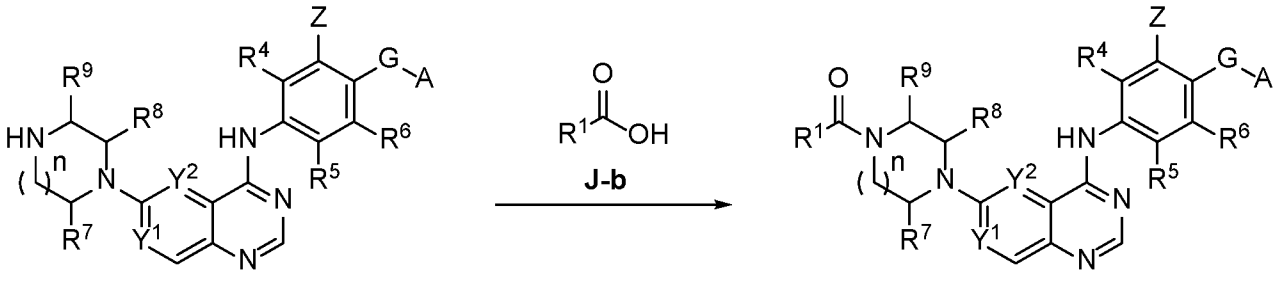
**Scheme I.**




**I-a** **I-b**

**[0164]** As shown in Scheme I, compounds of general formula **I-a** are deprotected, for example in the presence of HCl and 1,4-dioxane, to provide compounds of general formula **I-b**, wherein $R^{PG}$ is a protecting group, for example a -Boc group.

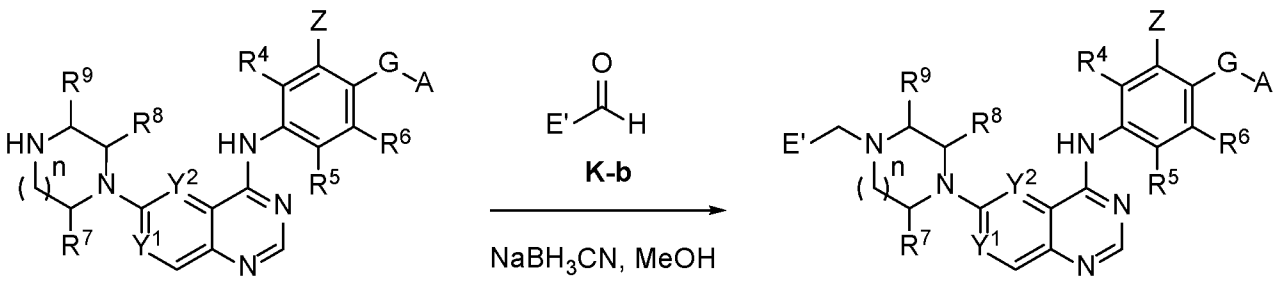
**Scheme J.**



**J-a** **J-b** **J-c**

**[0165]** As shown in Scheme J, compounds of general formula **J-a** are reacted with compounds of general formula **J-b**, for example in the presence of HATU, DIEA, and DMF, to provide compounds of general formula **J-c**. In some variations of Scheme J, compounds of general formula **J-a** are reacted with compounds of general formula **J-b** in the presence of EDCI and Pyridine to provide compounds of general formula **J-c**.

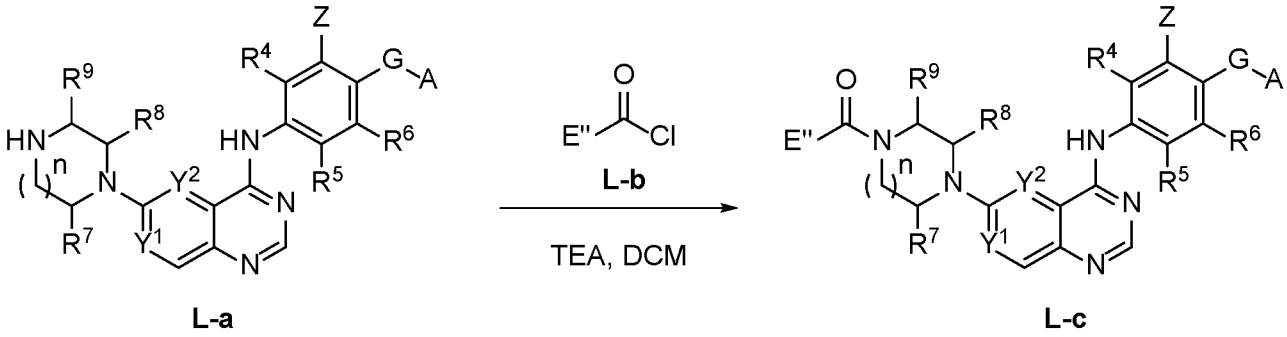
**Scheme K.**




**K-a** **K-b** **K-c**

**[0166]** As shown in Scheme K, compounds of general formula **K-a** are reacted with compounds of general formula **K-b**, for example in the presence of $NaBH_3CN$ and MeOH, to provide compounds of general formula **K-c**, wherein E' is $C_1$-$C_5$ alkyl.

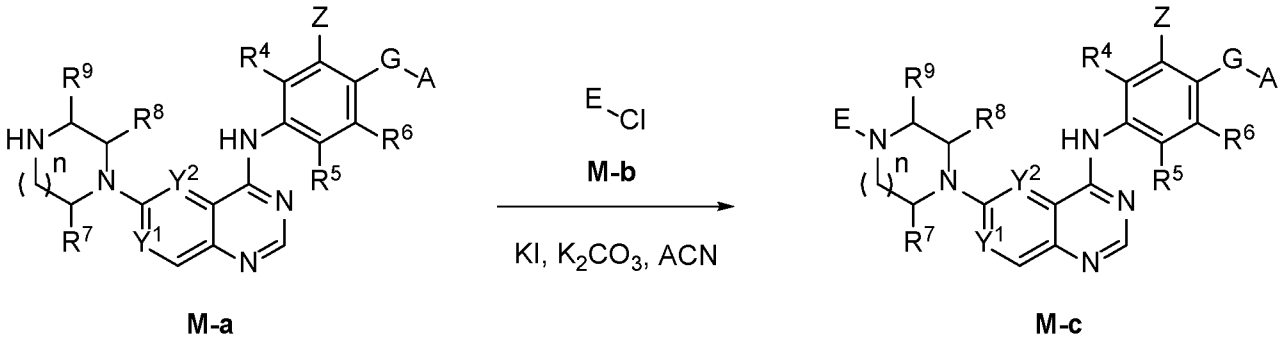
**Scheme L.**




**L-a** **L-c**

**[0167]** As shown in Scheme L, compounds of general formula **L-a** are reacted with compounds of general formula **L-b**, for example in the presence of TEA and DMC, to provide compounds of general formula **L-c**, wherein E'' is $R^1$ or -O-( $C_1$-$C_6$ alkyl).

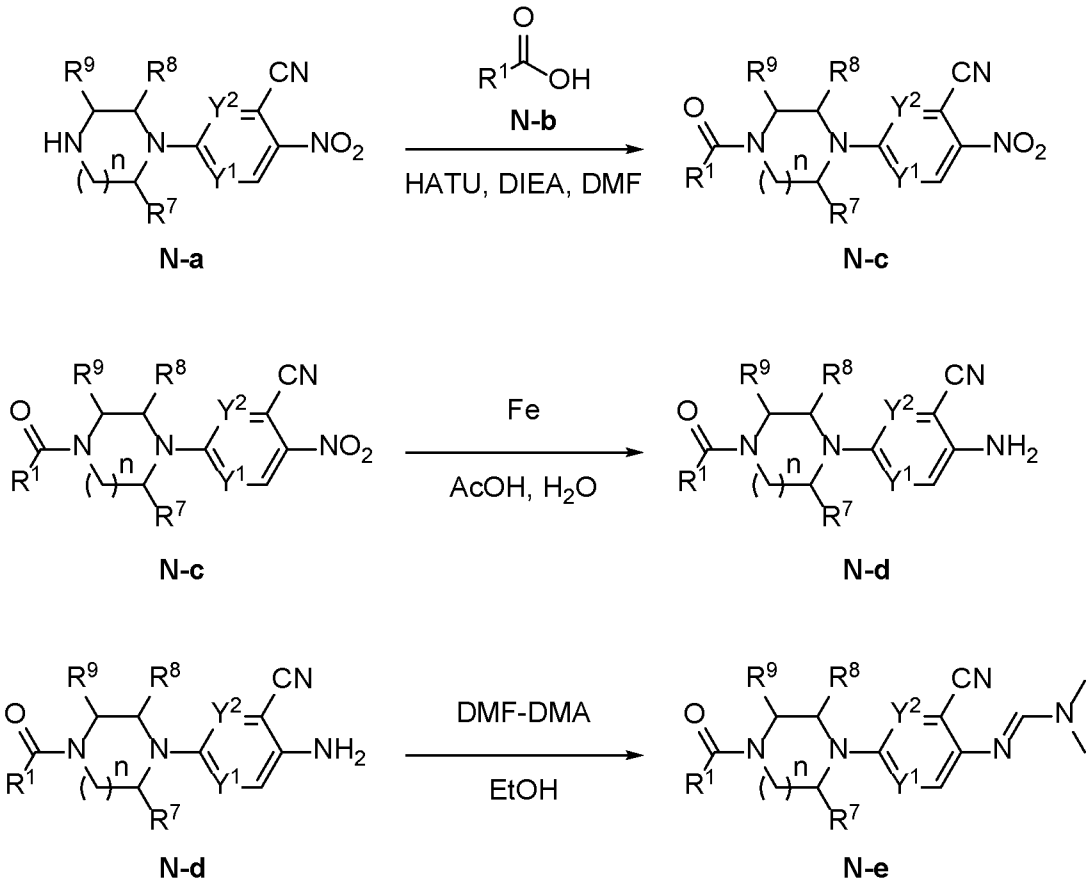
**Scheme M.**




**M-a** **M-c**

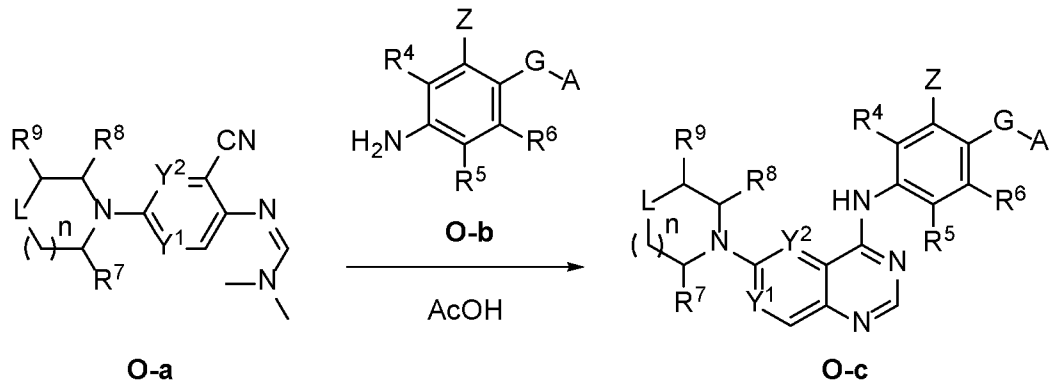
**[0168]** As shown in Scheme M, compounds of general formula **M-a** are reacted with compounds of general formula **M-b**, for example in the presence of KI, $K_2CO_3$, and ACN, to provide compounds of general formula **M-c**.

**Scheme N.**



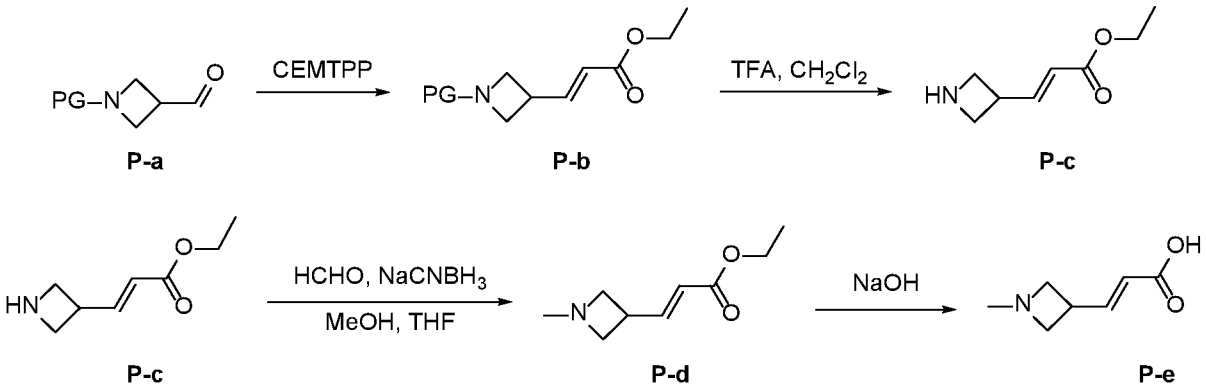

**[0169]** As shown in Scheme N, compounds of general formula **N-a** are reacted with compounds of general formula **N-b**, for example in the presence of HATU, DIEA, and DMF, to provide compounds of general formula **N-c**. Compounds of general formula **N-c** are further reduced, for example in the presence of Fe, AcOH, and $H_2O$, to provide compounds of general formula **N-d**. Compounds of general formula **N-d** are further reacted, for example in the presence of DMF-DMA and EtOH, to provide compounds of general formula **N-e**.

**Scheme O.**



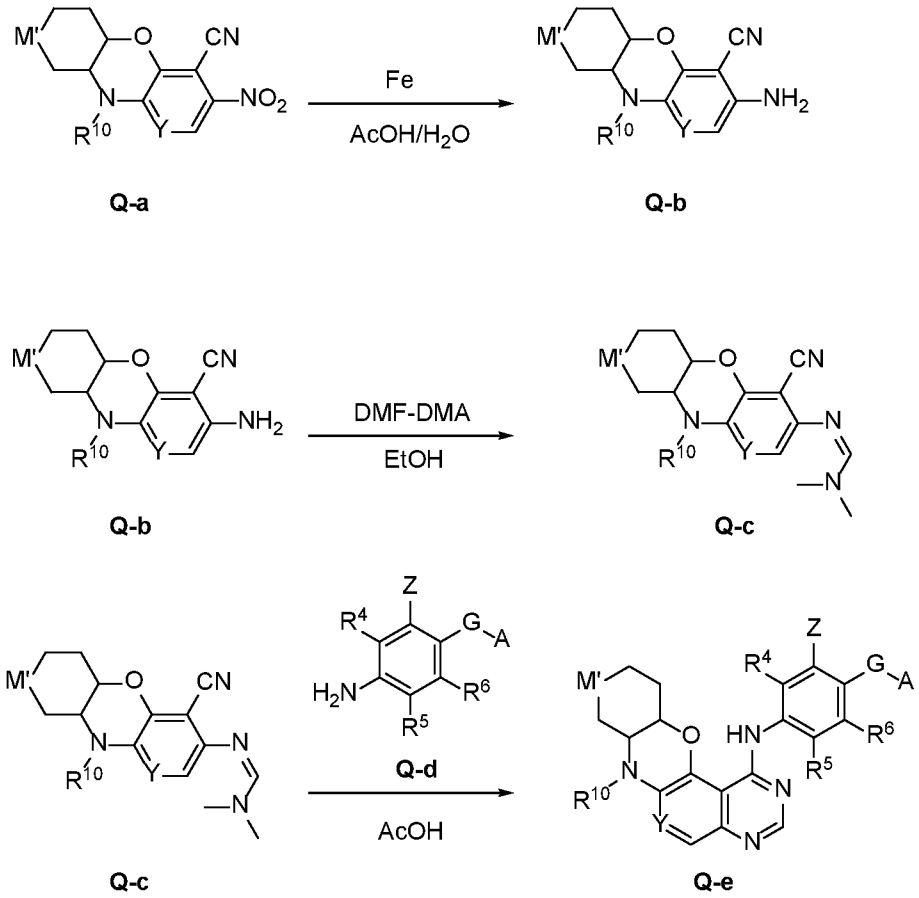
**[0170]** As shown in Scheme O, compounds of general formula **O-a** are reacted with compounds of general formula **O-b**, for example in the presence of AcOH, to provide compounds of general formula **O-c**.

**Scheme P.**



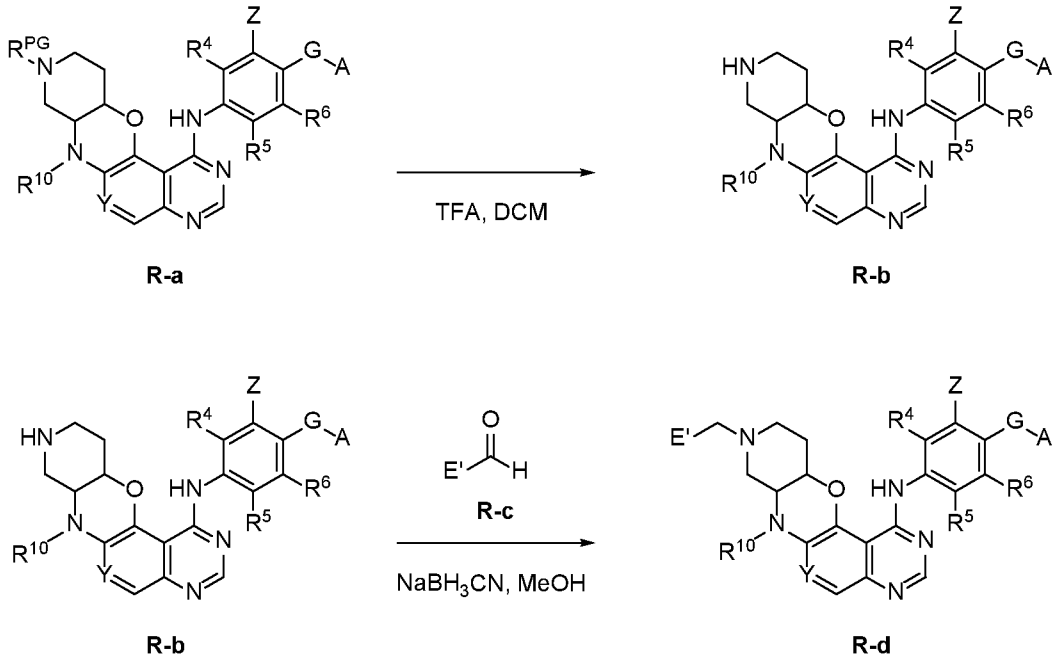

**[0171]** As shown in Scheme P, compounds of general formula **P-a** are reacted, for example in the presence of CEMTPP, to provide compounds of general formula **P-b**, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **P-b** are further deprotected, for example in the presence of TFA and $CH_2Cl_2$, to provide compounds of general formula **P-c**. Compounds of general formula **P-c** are further reacted, for example in the presence of HCHO, $NaCNBH_3$, MeOH, and THF, to provide compounds of general formula **P-d**. Compounds of general formula **P-d** are further reacted, for example in the presence of NaOH, to provide compounds of general formula **P-e**.

**Scheme Q.**




**[0172]** As shown in Scheme Q, compounds of general formula **Q-a** are reduced, for example in the presence of Fe, AcOH, and $H_2O$, to provide compounds of general formula **Q-b**, wherein M' is N-$R^{PG}$ or $CH_2$, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **Q-b** are further reacted, for example in the presence of DMF-DMA and EtOH, to provide compounds of general formula **Q-c**. Compounds of general formula **Q-c** are further reacted with compounds of general formula **Q-d**, for example in the presence of AcOH, to provide compounds of general formula **Q-e**.

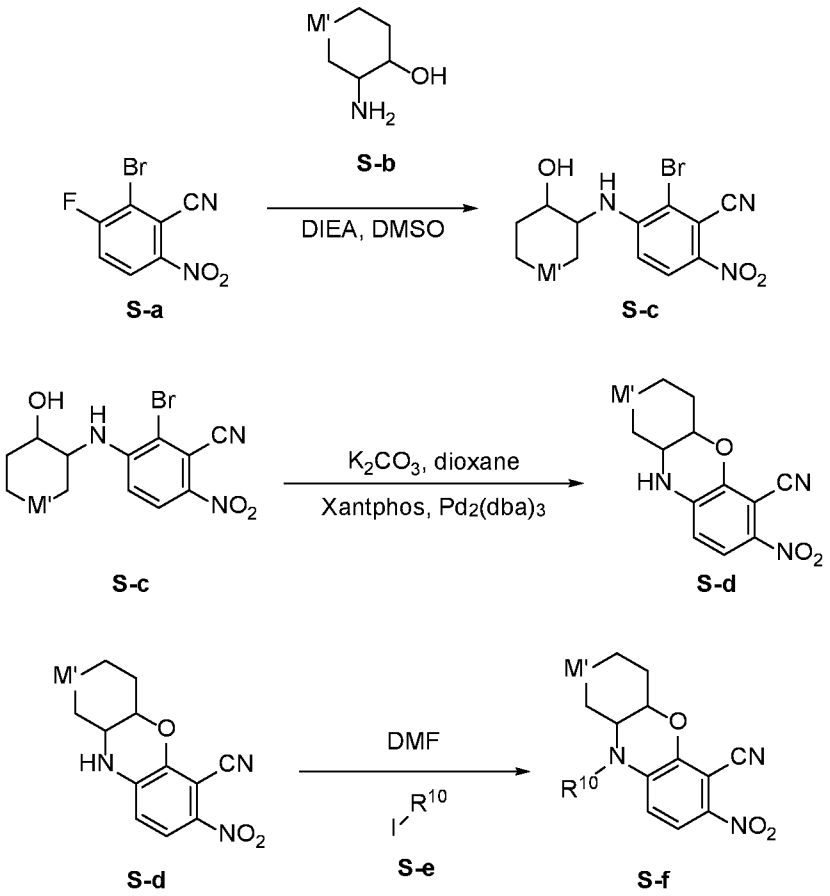
**Scheme R.**




**R-a** **R-b** **R-c** **R-b** **R-d**

**[0173]** As shown in Scheme R, compounds of general formula **R-a** are deprotected, for example in the presence of TFA and DCM, to provide compounds of general formula **R-b**, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **R-b** are reacted with compounds of general formula **R-c**, for example in the presence of $NaBH_3CN$ and MeOH, to provide compounds of general formula **R-d**, wherein E' is H or $C_1$-$C_5$ alkyl.

**Scheme S.**

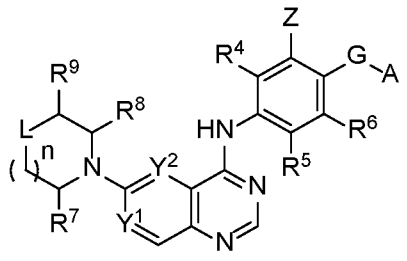



**[0174]** As shown in Scheme S, compounds of formula **S-a** are reacted with compounds of general formula **S-b**, for example in the presence of DIEA and DMSO, to provide compounds of general formula **S-c**, wherein M' is N-$R^{PG}$ or $CH_2$, wherein $R^{PG}$ is a protecting group, for example a -Boc group. Compounds of general formula **S-c** are reacted, for example in the presence of $K_2CO_3$, dioxane, Xantphos, and $Pd_2(dba)_3$, to provide compounds of general formula **S-d**. Compounds of general formula **S-d** are reacted with compounds of general formula **S-e**, for example in the presence of DMF, to provide compounds of general formula **S-f**.

ENUMERATED EMBODIMENTS

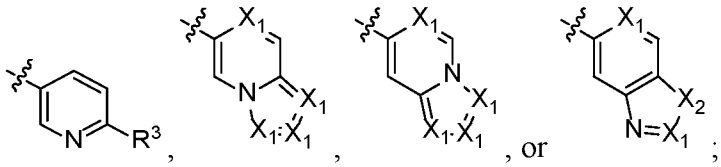
**[0175]** The following enumerated embodiments are representative of some aspects of the invention.

Embodiment 1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

either $Y^1$ is C-$R^{Y1}$, $Y^2$ is Y, $R^8$ is -H, $R^9$ is -H, and $R^{Y1}$ is taken together with $R^7$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^1$,

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$, or

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^8$ is -H, and $R^{Y2}$ is taken together with $R^9$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$;

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -S(O)$_2$-, or $CH_2$;

V is O, S, or $NR^2$;

$X_1$ is N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

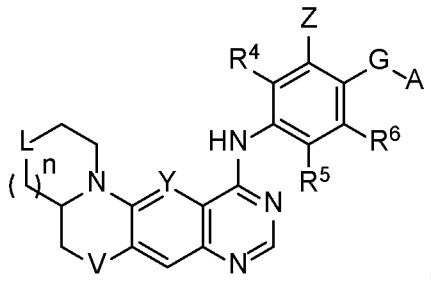
$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is independently optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, -$CD_3$, or $C_3$-$C_6$ cycloalkyl; and

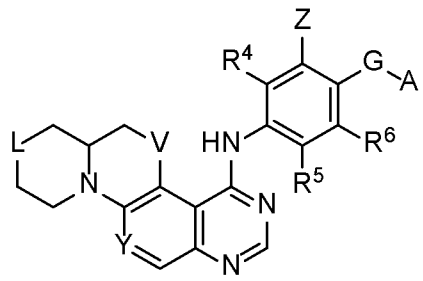
$R^4$, $R^5$, and $R^6$ are each independently -H or halogen.

Embodiment 2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-A)



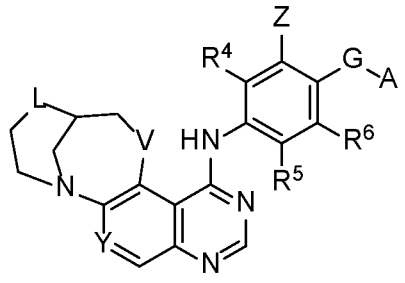
(I-A).

Embodiment 3. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-B)

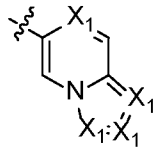
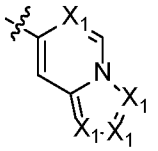
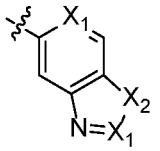


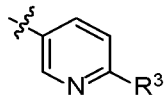
(I-B).

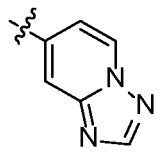
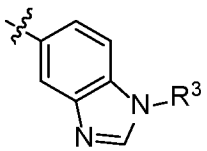
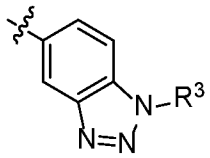
Embodiment 4. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-C)



(I-C).

Embodiment 5. The compound of any one of embodiments 1 to 4, or a pharmaceutically acceptable salt thereof, wherein A is  ,  , or  .

Embodiment 6. The compound of any one of embodiments 1 to 4, or a pharmaceutically acceptable salt thereof, wherein A is  .

Embodiment 7. The compound of any one of embodiments 1 to 5, or a pharmaceutically acceptable salt thereof, wherein A is  ,  , or  .

Embodiment 8. The compound of any one of embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein $R^3$ is -H or -$CH_3$.

Embodiment 9. The compound of any one of embodiments 1 to 8, or a pharmaceutically acceptable salt thereof, wherein L is N-E.

Embodiment 10. The compound of any one of embodiments 1 to 9, or a pharmaceutically acceptable salt thereof, wherein E is -C(O)-$R^1$.

Embodiment 11. The compound of any one of embodiments 1 to 10, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 4 membered heterocycle or -$N(CH_3)_2$, wherein the 4 membered heterocycle is optionally substituted by -F or -$CH_3$.

Embodiment 12. The compound of any one of embodiments 1 to 11, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $C_1$ alkyl, $C_2$-$C_4$ alkenyl, or $C_2$-$C_3$ alkynyl, each of which is independently optionally substituted by 4 membered heterocycle or $-N(CH_3)_2$, wherein the 4 membered heterocycle is optionally substituted by -F or $-CH_3$.

Embodiment 13. The compound of any one of embodiments 1 to 9, or a pharmaceutically acceptable salt thereof, wherein E is -H, $-C(O)O-(C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro.

Embodiment 14. The compound of any one of embodiments 1 to 9 and 13, or a pharmaceutically acceptable salt thereof, wherein E is -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_3OCH_3$, or $-C(O)O-CH_3$.

Embodiment 15. The compound of any one of embodiments 1 to 14, or a pharmaceutically acceptable salt thereof, wherein G is -O-.

Embodiment 16. The compound of any one of embodiments 1 to 14, or a pharmaceutically acceptable salt thereof, wherein G is -C(=O)-.

Embodiment 17. The compound of any one of embodiments 1 to 14, or a pharmaceutically acceptable salt thereof, wherein G is -S-, -S(O)-, or $-S(O)_2$-.

Embodiment 18. The compound of any one of embodiments 1 to 14, or a pharmaceutically acceptable salt thereof, wherein G is $-CH_2$-.

Embodiment 19. The compound of any one of embodiments 1 to 18, or a pharmaceutically acceptable salt thereof, wherein V is O.

Embodiment 20. The compound of any one of embodiments 1 to 18, or a pharmaceutically acceptable salt thereof, wherein V is S.

Embodiment 21. The compound of any one of embodiments 1 to 18, or a pharmaceutically acceptable salt thereof, wherein V is $NR^2$

Embodiment 22. The compound of any one of embodiments 1 to 21, wherein Y is N.

Embodiment 23. The compound of any one of embodiments 1 to 21, wherein Y is C-$R^y$.

Embodiment 24. The compound of any one of embodiments 1 to 21 and 23, or a pharmaceutically acceptable salt thereof, wherein Y is C-$R^y$, and $R^y$ is -H.

Embodiment 25. The compound of any one of embodiments 1 to 21 and 23, or a pharmaceutically acceptable salt thereof, wherein Y is C-$R^y$, and $R^y$ is -F.

Embodiment 26. The compound of any one of embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein Z is -H, halogen, -C≡CH, -$OCH_3$, or -$CH_3$.

Embodiment 27. The compound of any one of embodiments 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Z is -H, -F, or -$CH_3$.

Embodiment 28. The compound of any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is -H.

Embodiment 29. The compound of any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is -F.

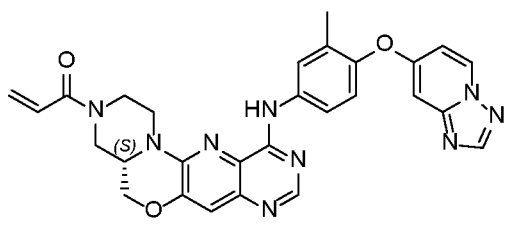
Embodiment 30. The compound of any one of embodiments 1 to 29, or a pharmaceutically acceptable salt thereof, wherein $R^5$ is -H.

Embodiment 31. The compound of any one of embodiments 1 to 29, or a pharmaceutically acceptable salt thereof, wherein $R^5$ is -F.

Embodiment 32. The compound of any one of embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is -H.

Embodiment 33. The compound of any one of embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is -F.

Embodiment 34. A compound selected from the group consisting of:

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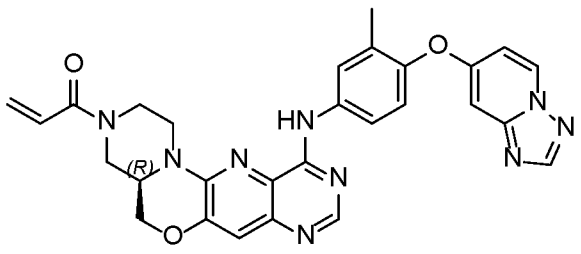


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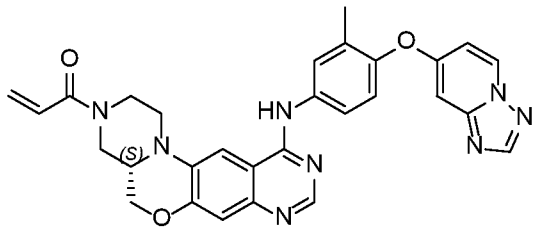
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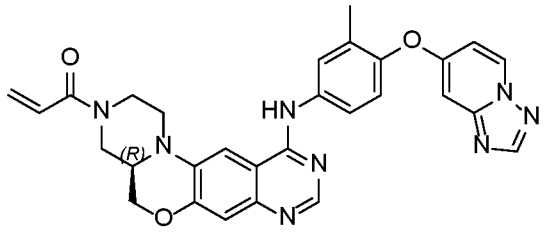
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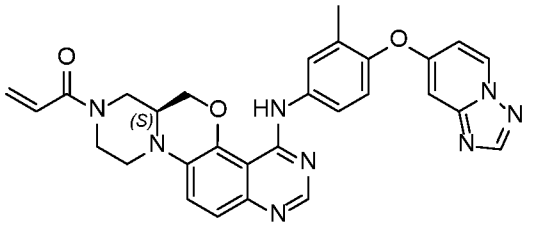
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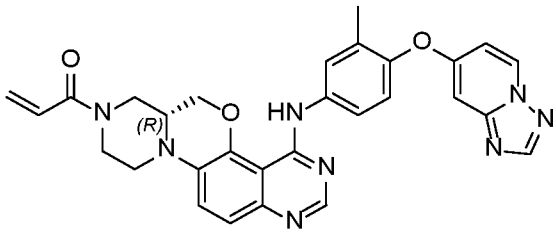
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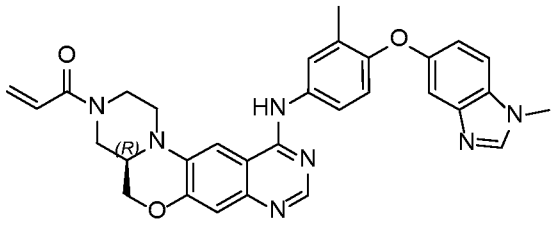
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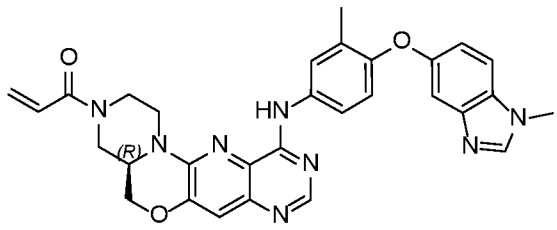
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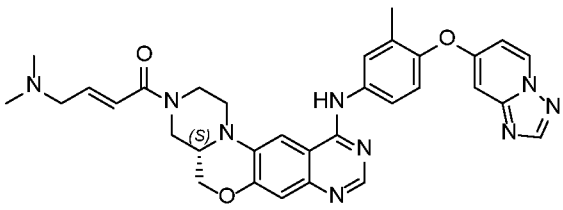
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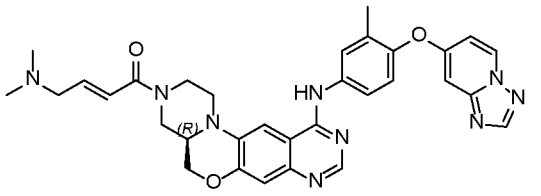
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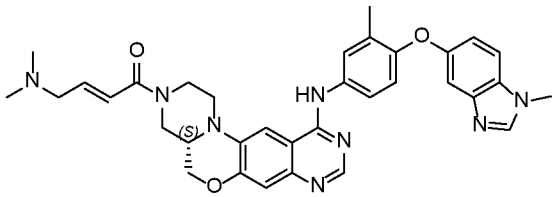
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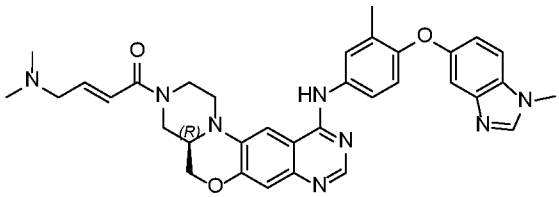
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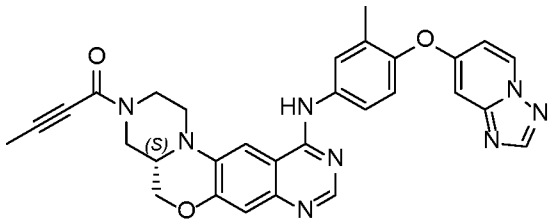
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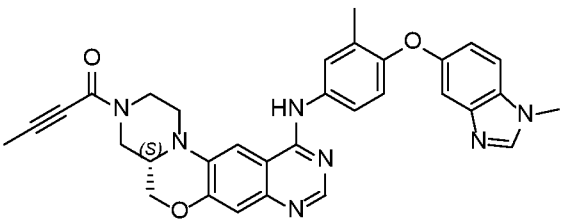
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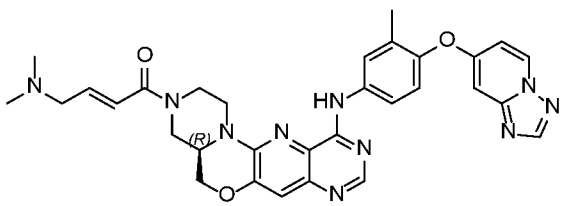
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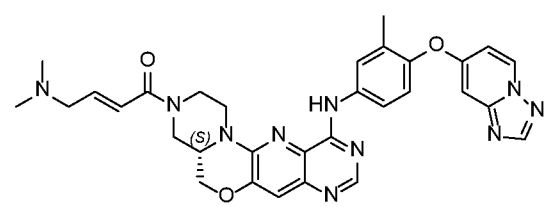
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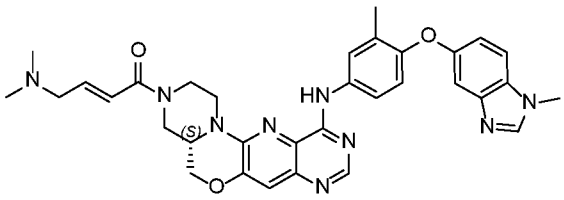
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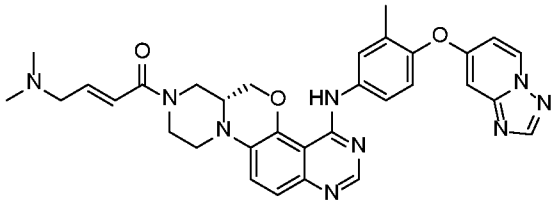
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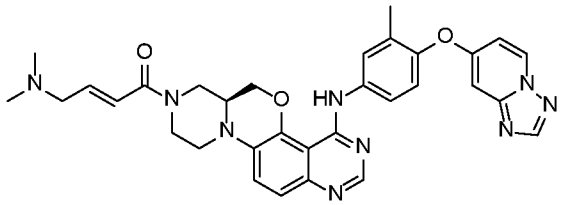
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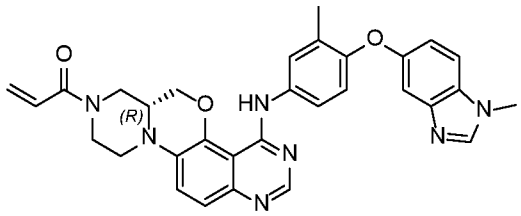
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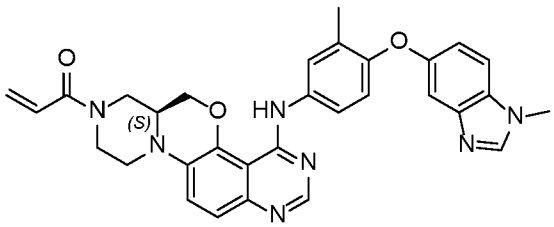
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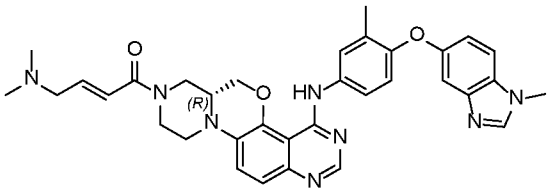
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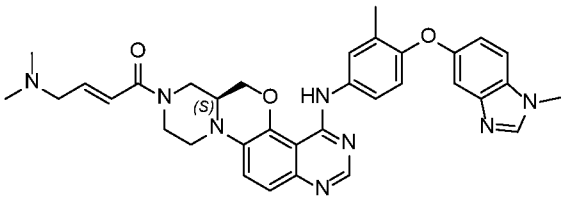
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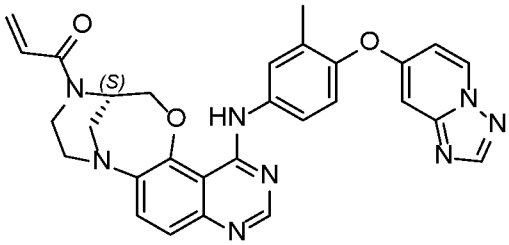
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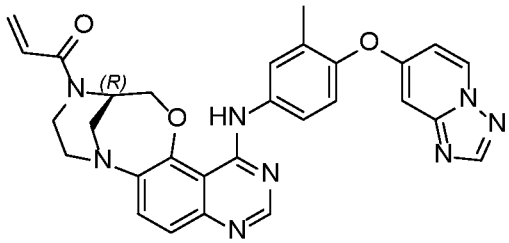
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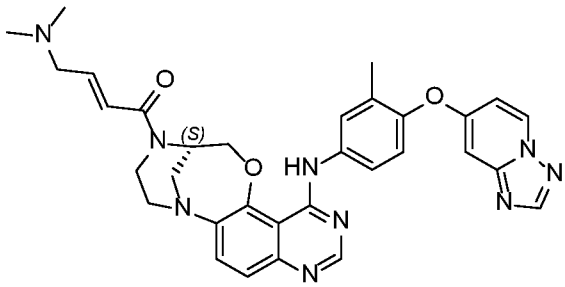
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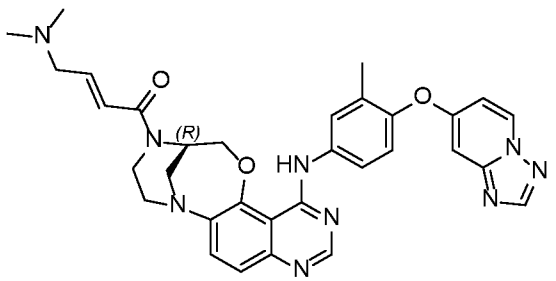
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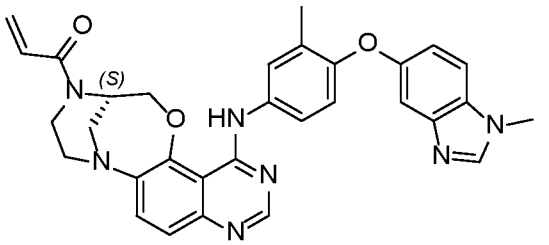
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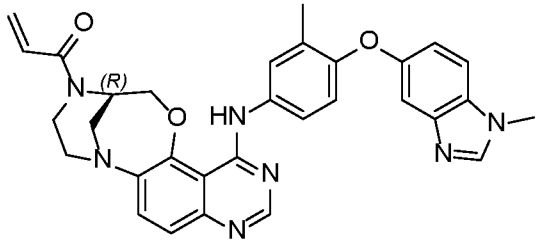
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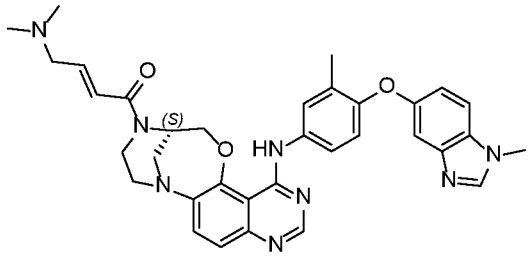
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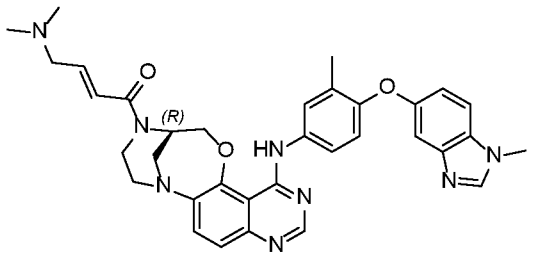
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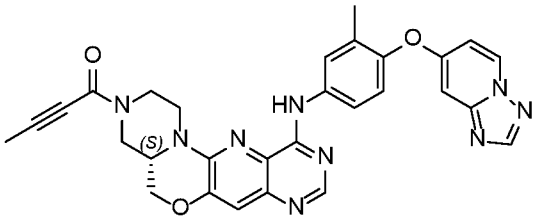
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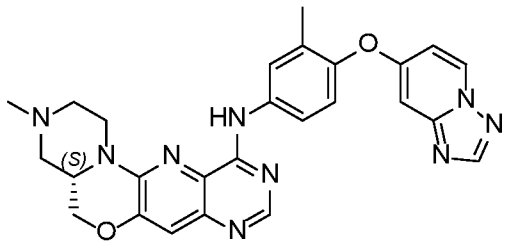
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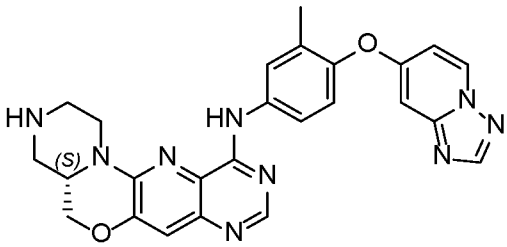
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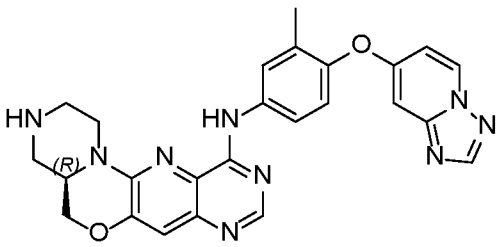
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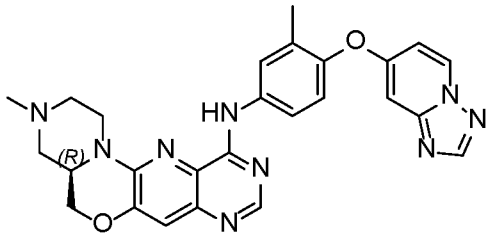
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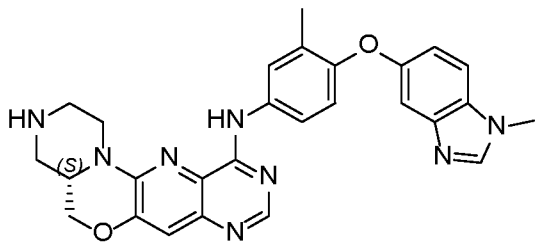
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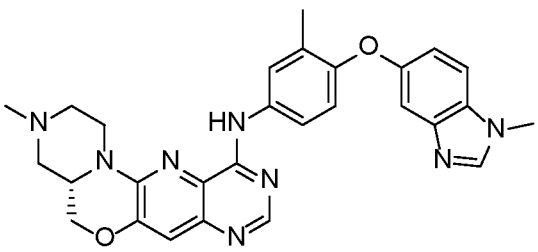
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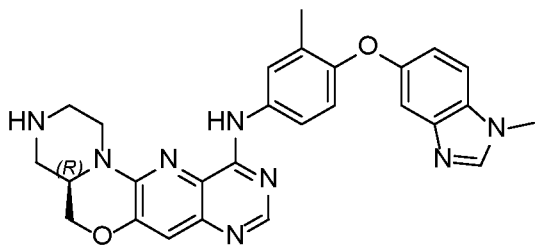
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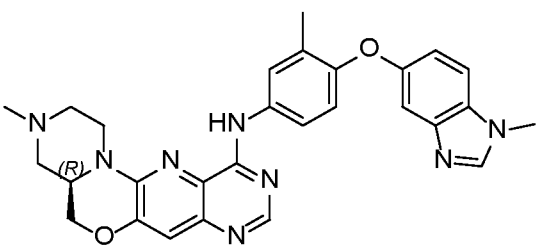
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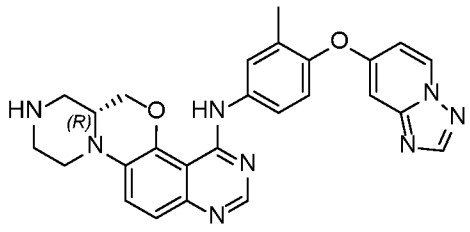
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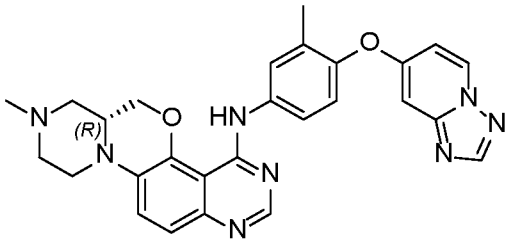
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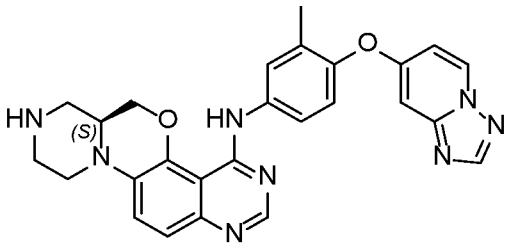
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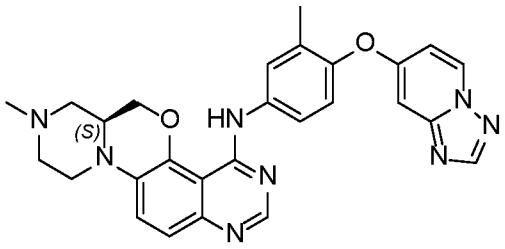
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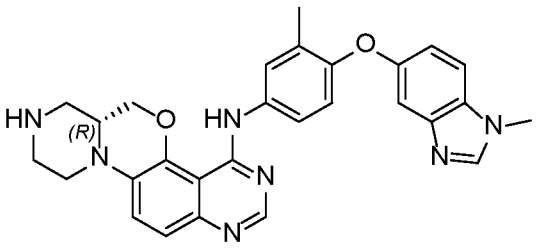
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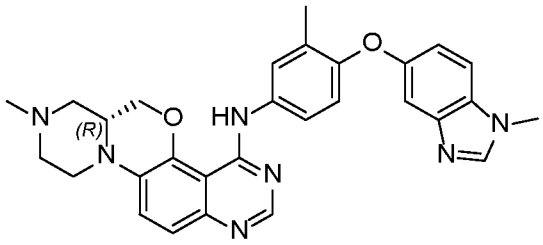
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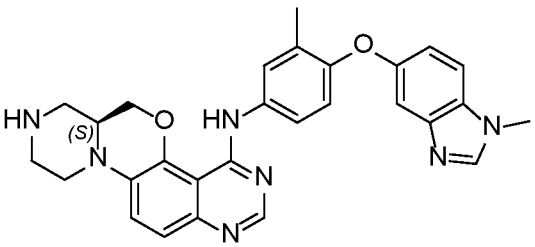
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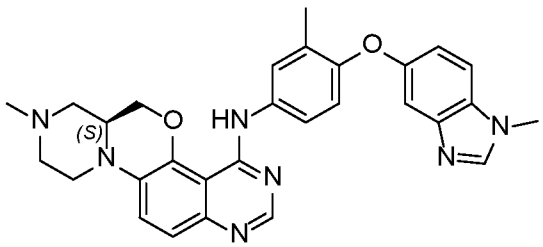
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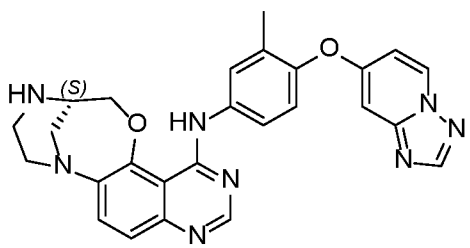
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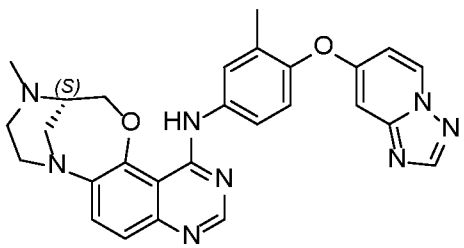
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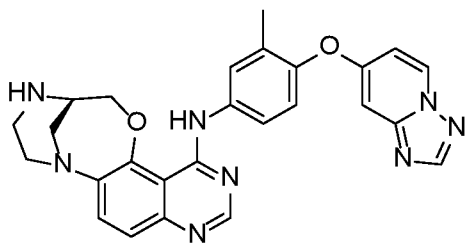
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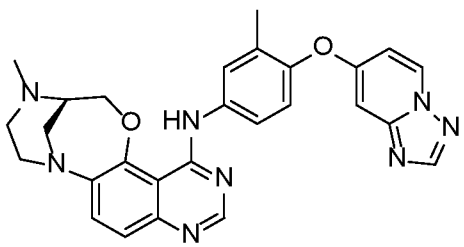
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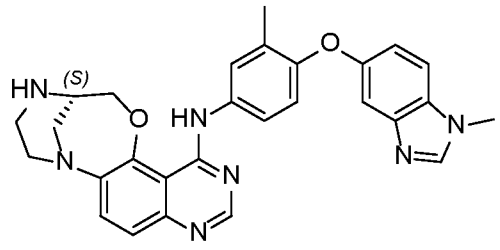
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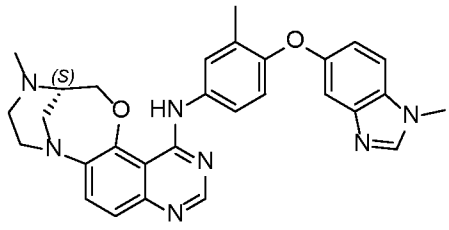
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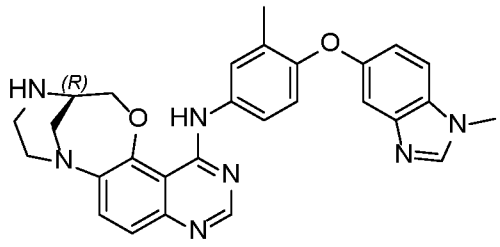
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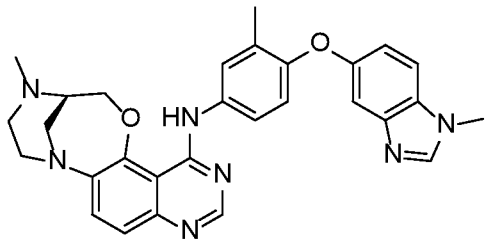
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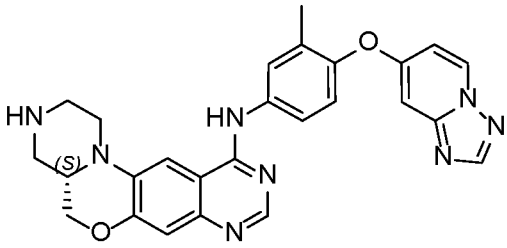
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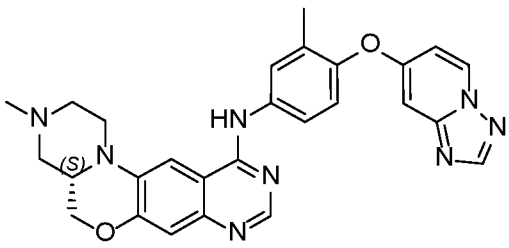
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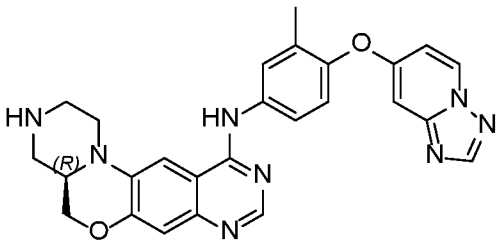
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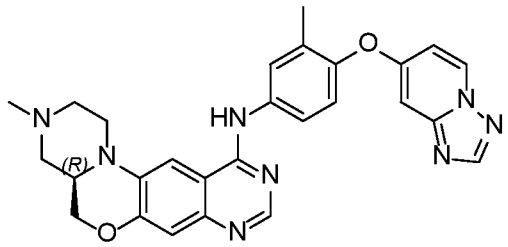
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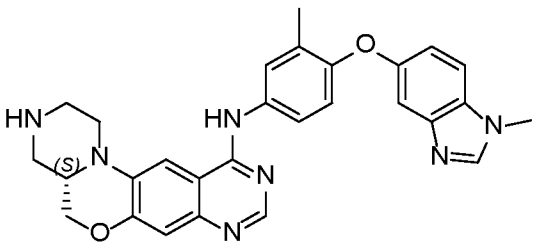
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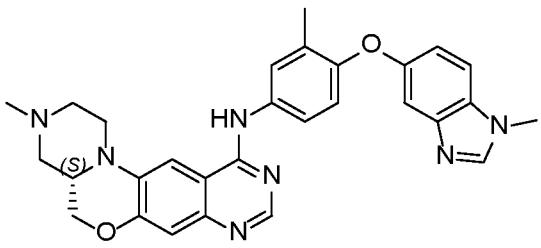
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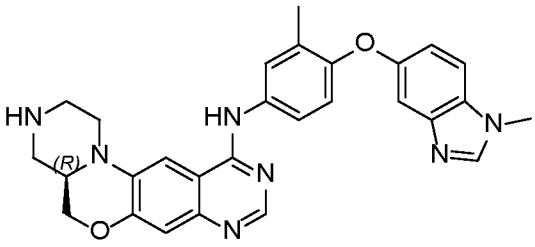
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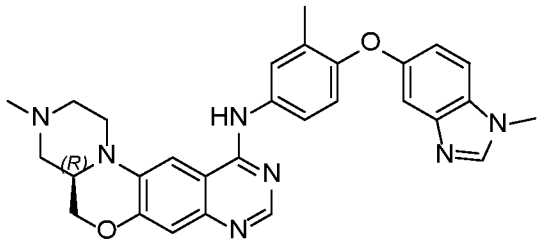
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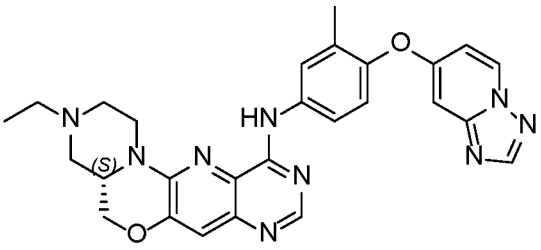
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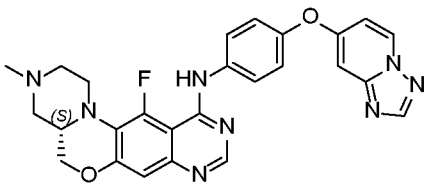
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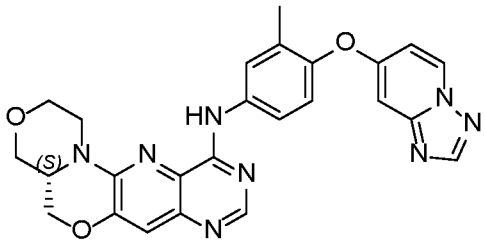
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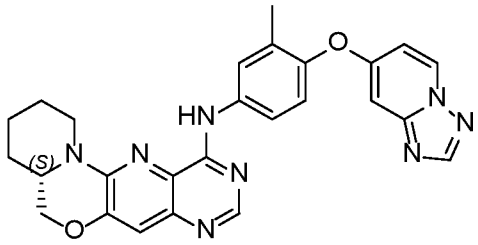
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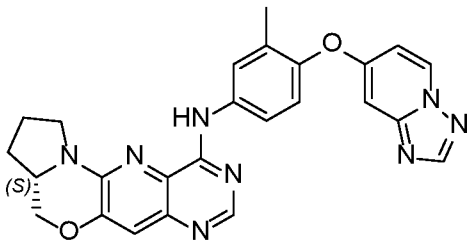
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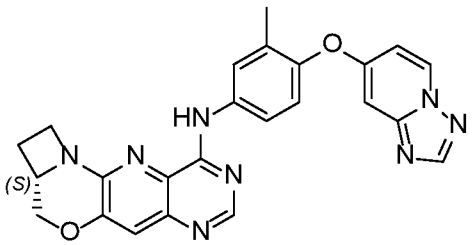
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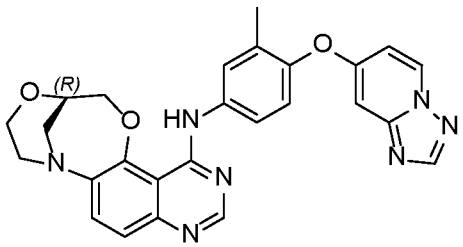
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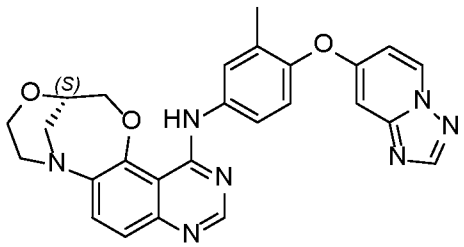
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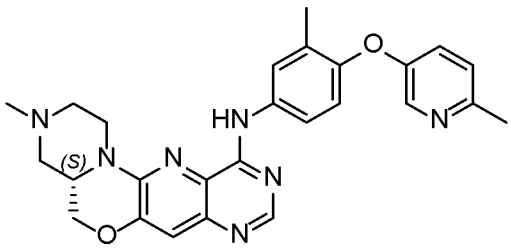
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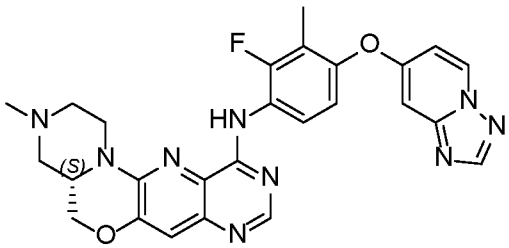
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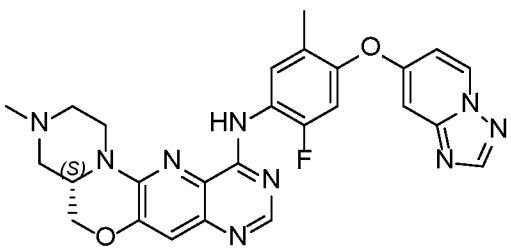
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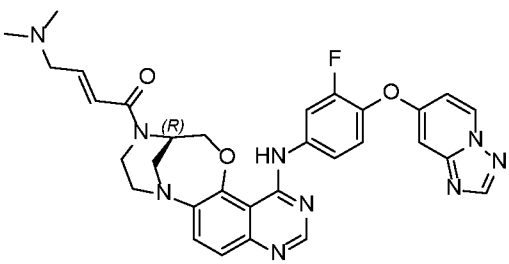
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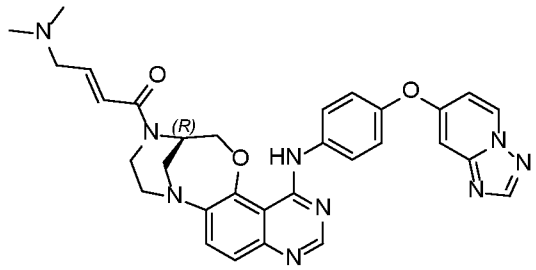
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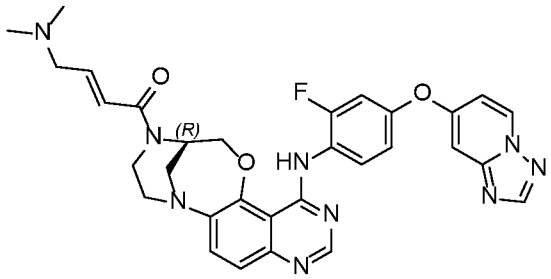
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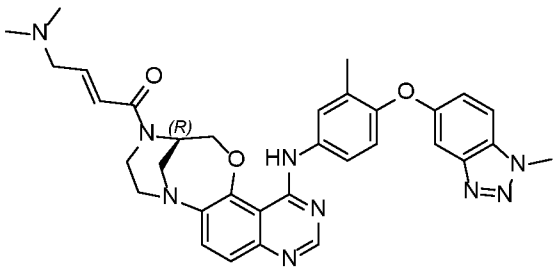
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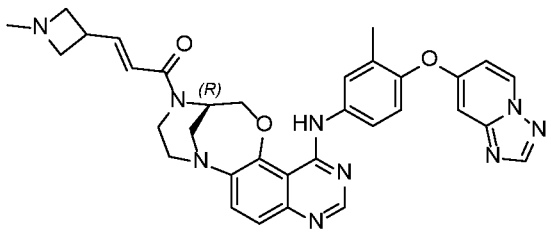
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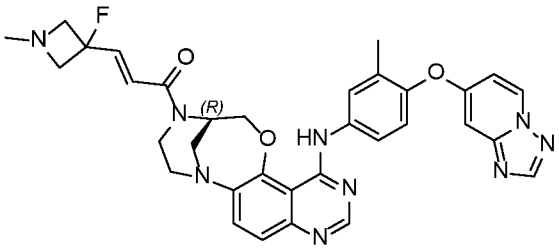
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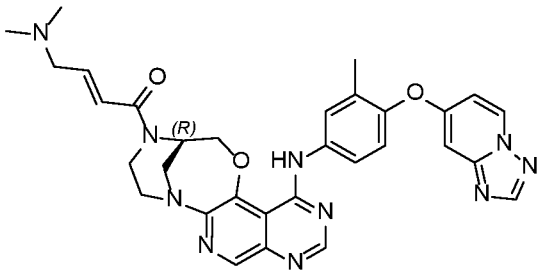
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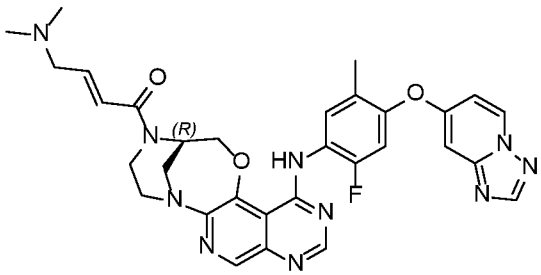
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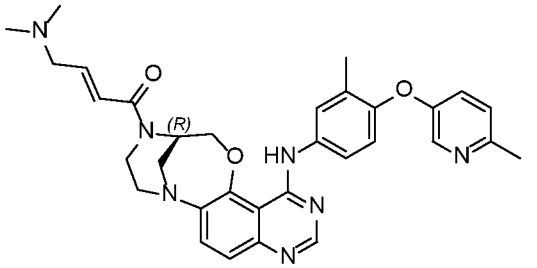
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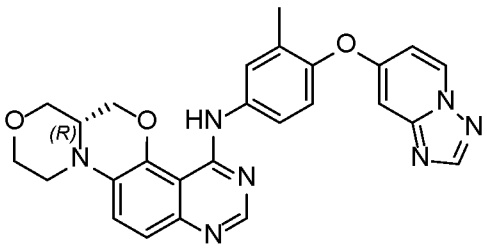
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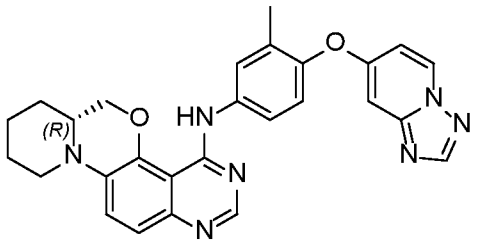
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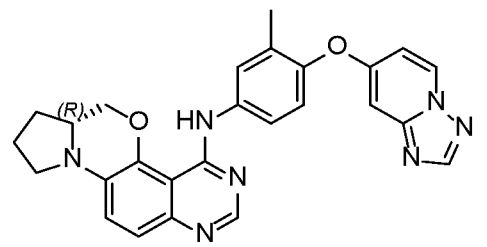
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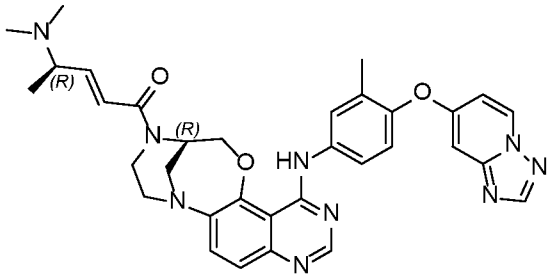
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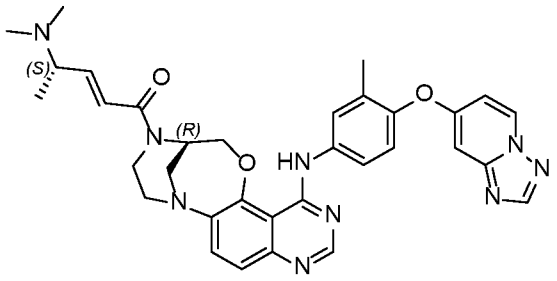
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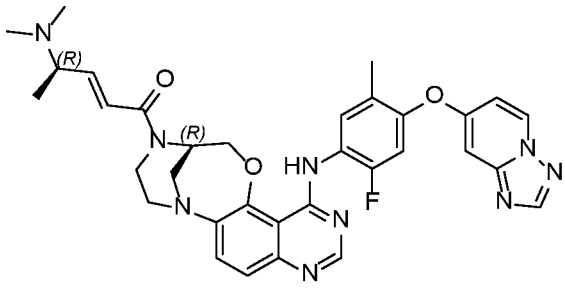
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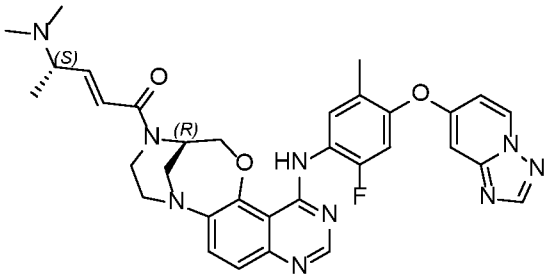
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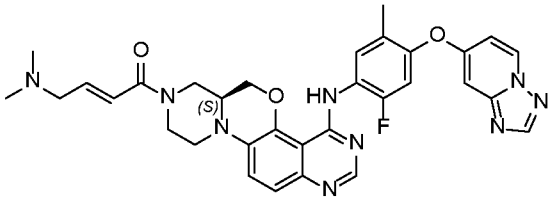
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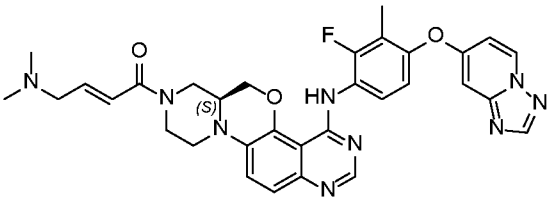
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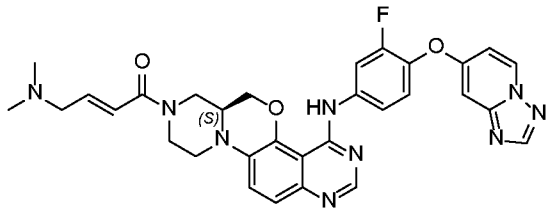
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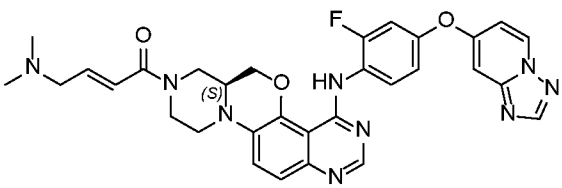
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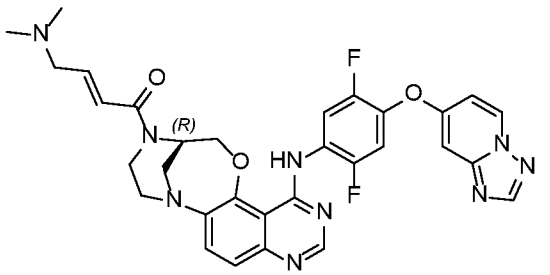
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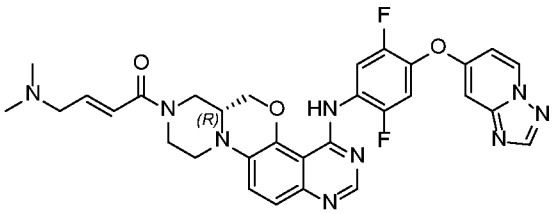
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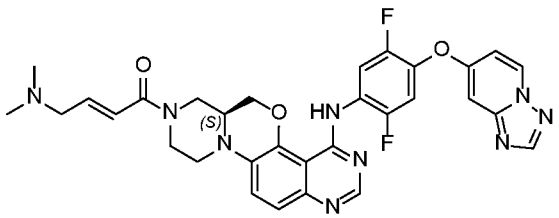
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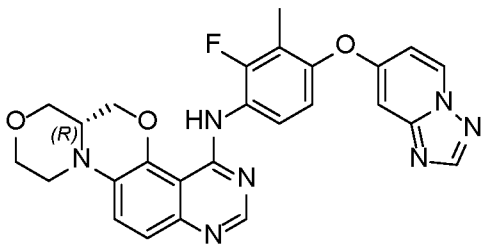
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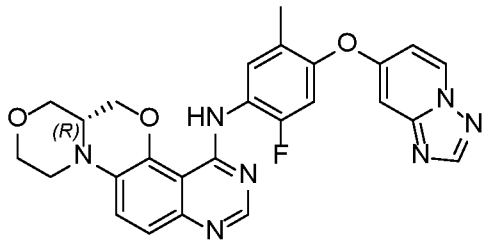
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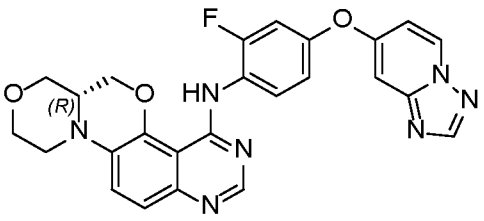
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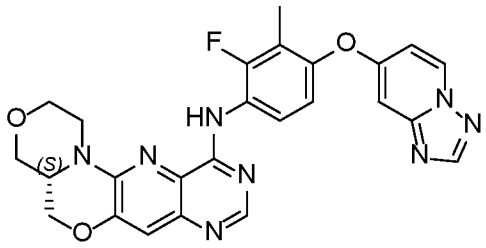
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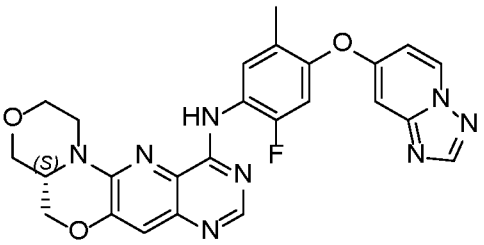
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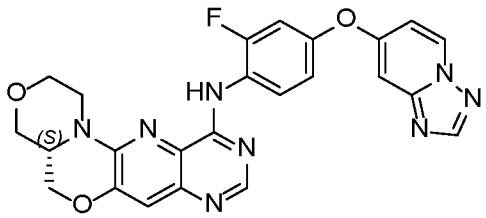
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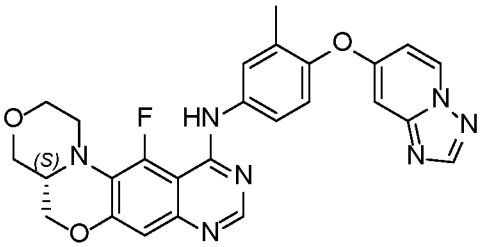
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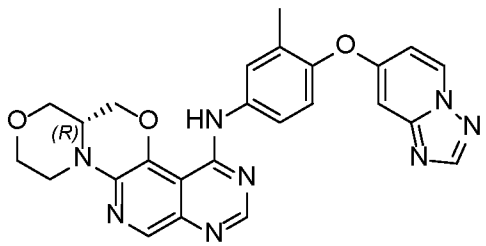
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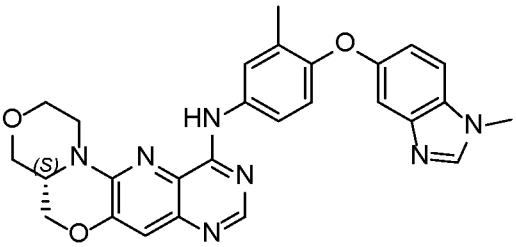
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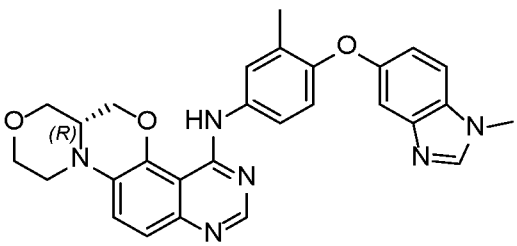
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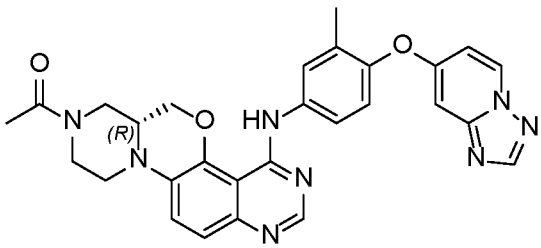
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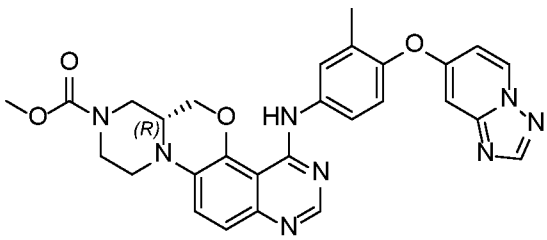
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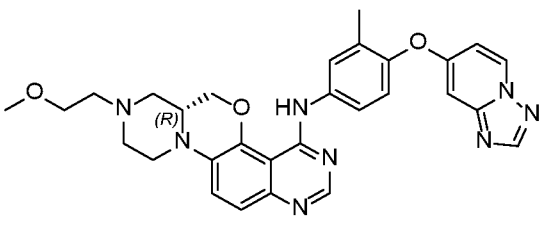
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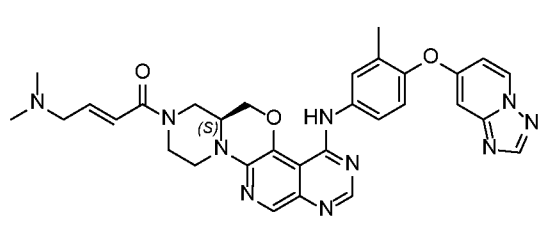
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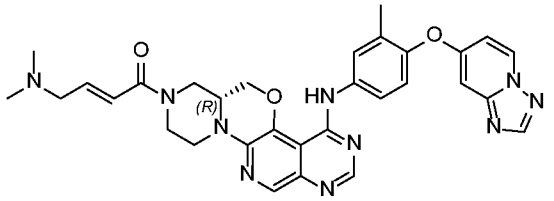
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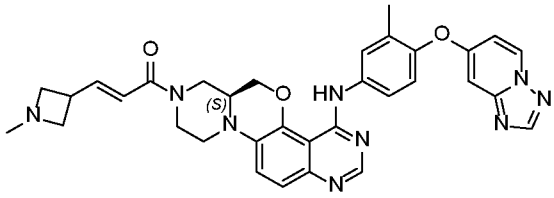
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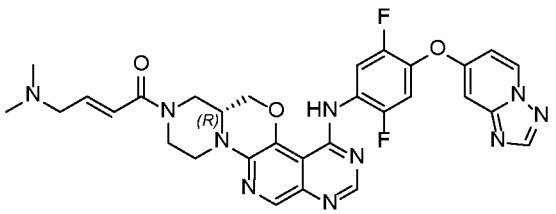
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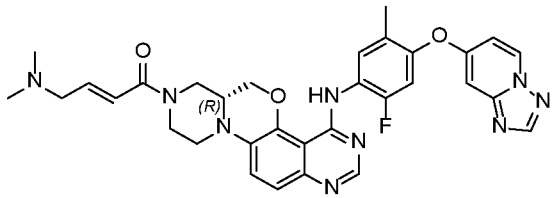
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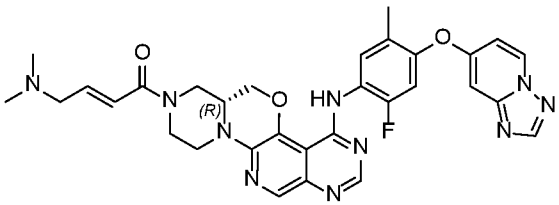
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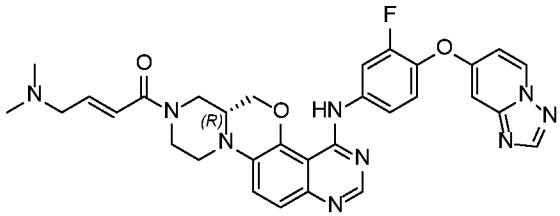
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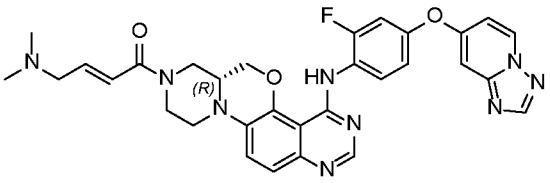
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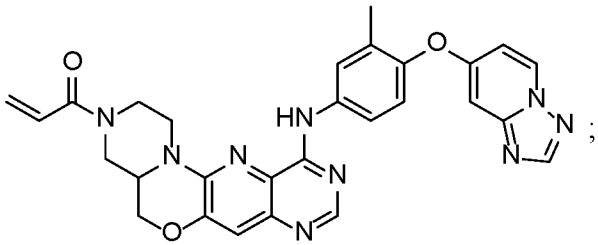
and

or a pharmaceutically acceptable salt thereof.

Embodiment 35. A compound selected from the group consisting of: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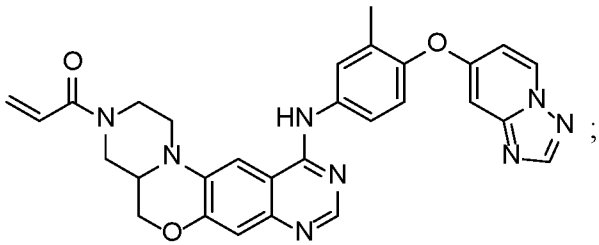
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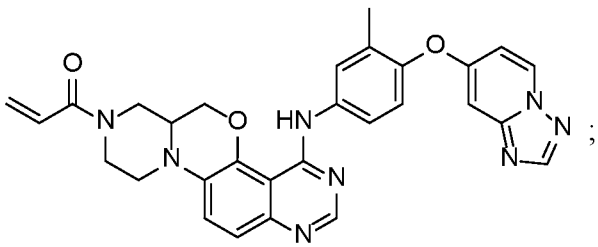
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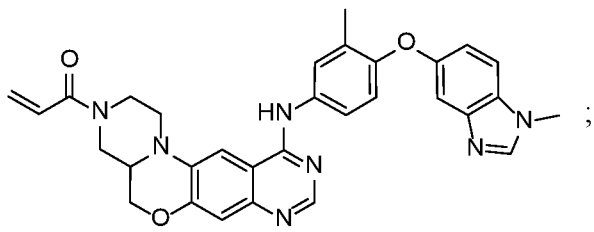
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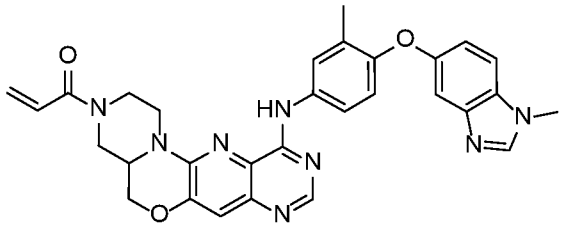
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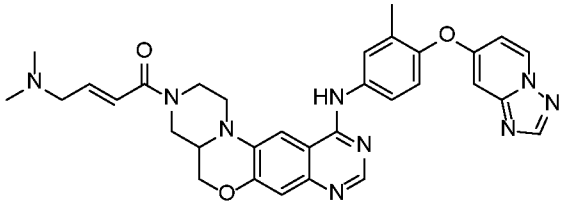
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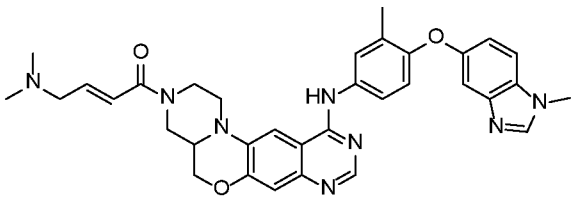
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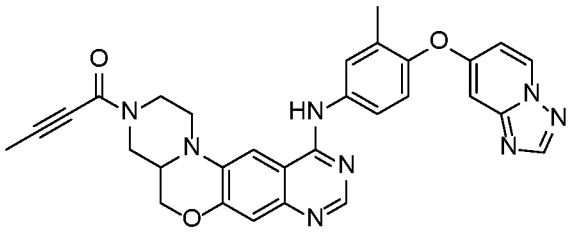
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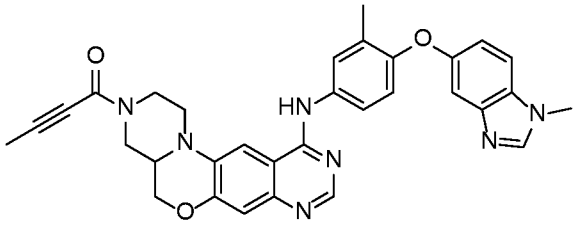
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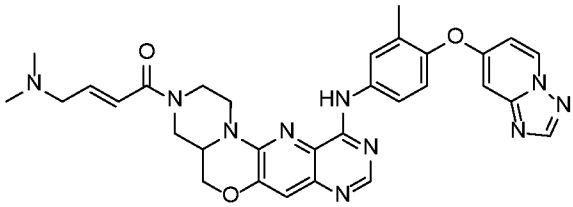
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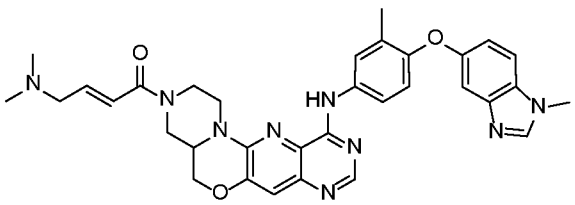
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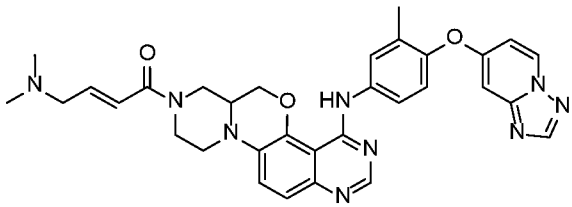
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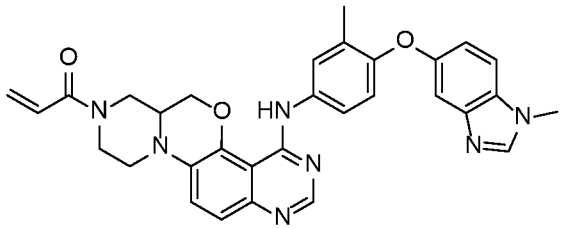
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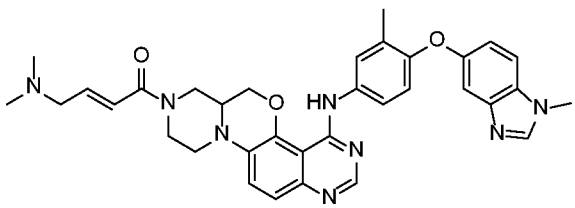
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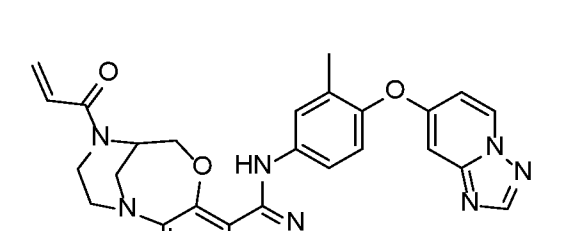
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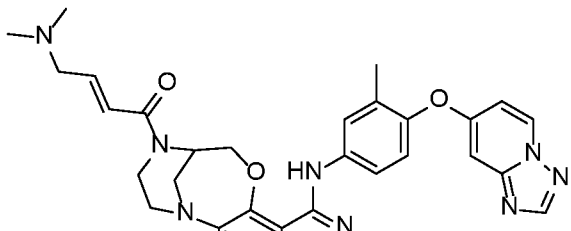
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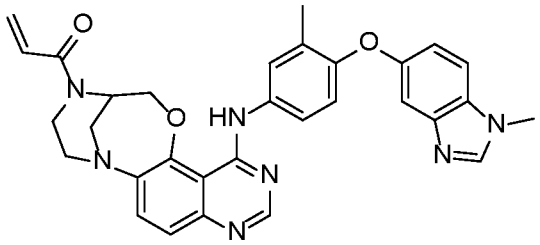
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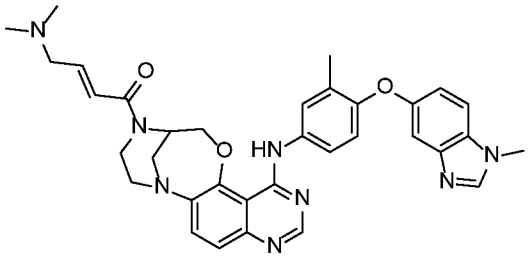
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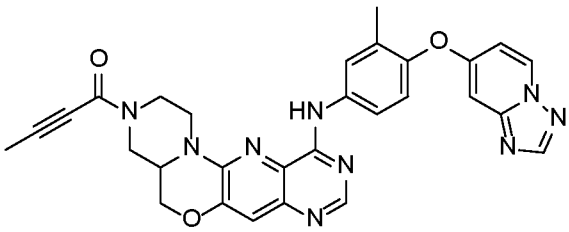
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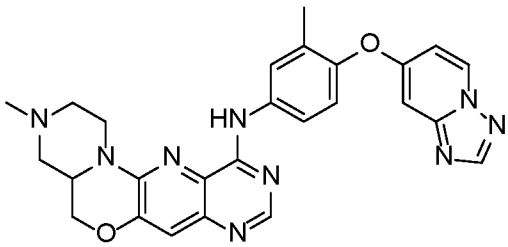
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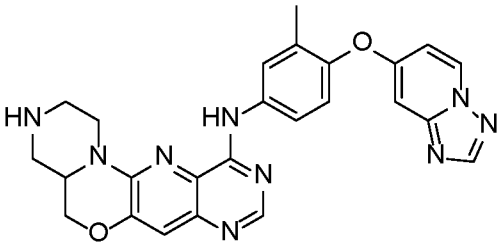
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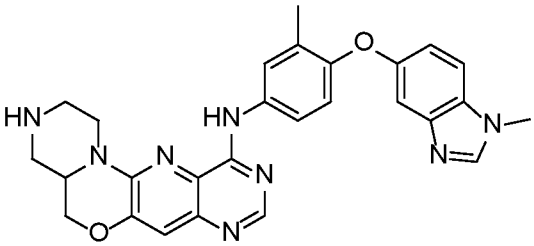
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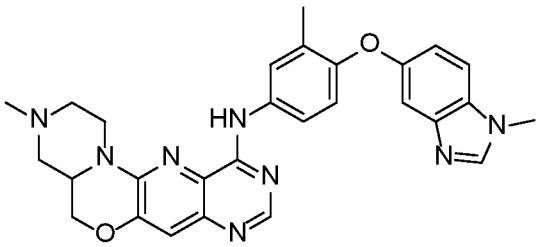
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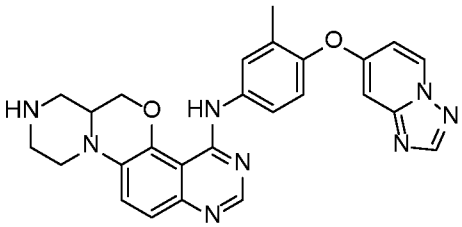
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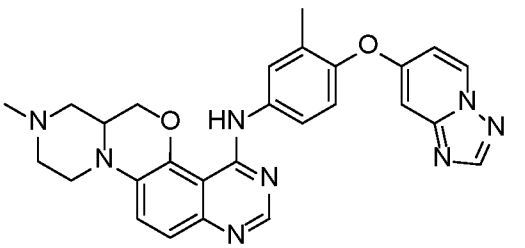
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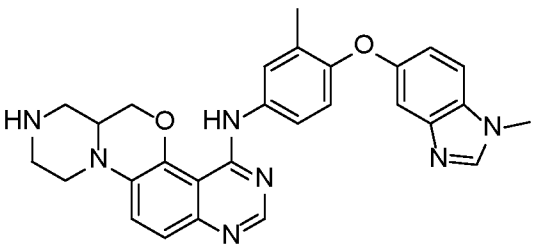
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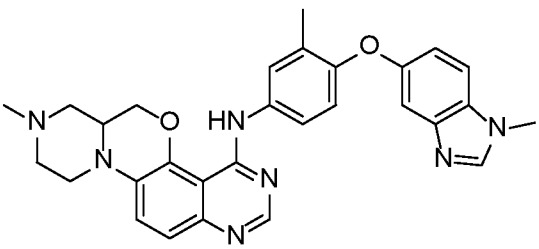
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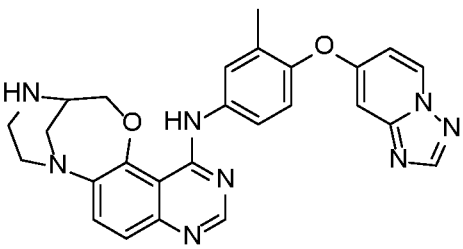
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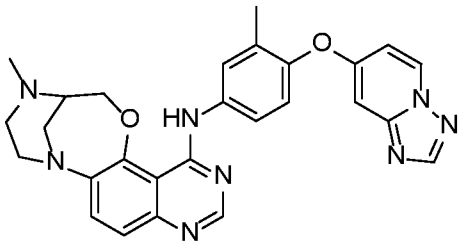
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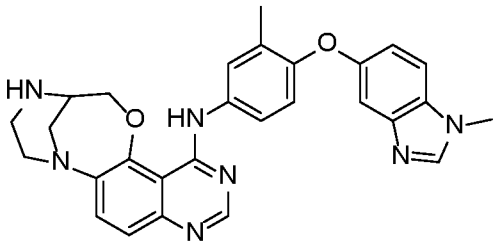
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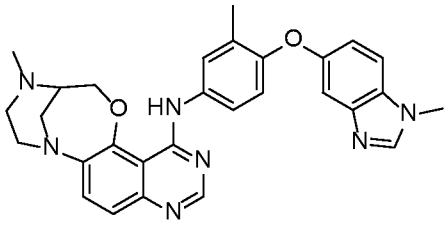
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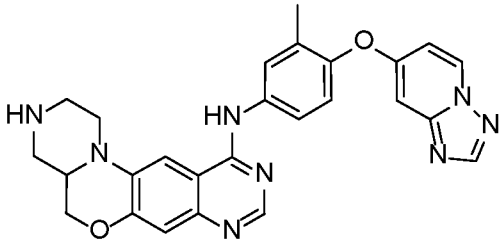
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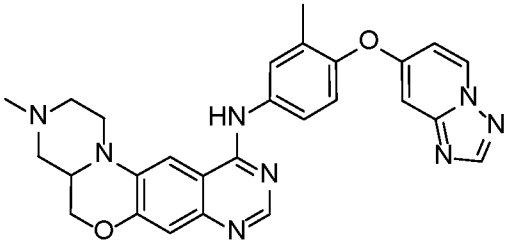
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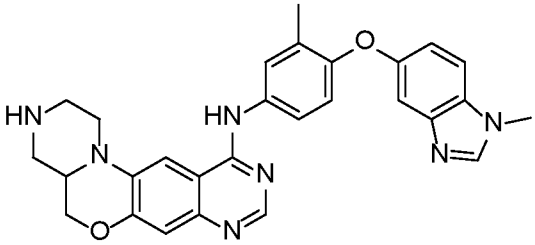
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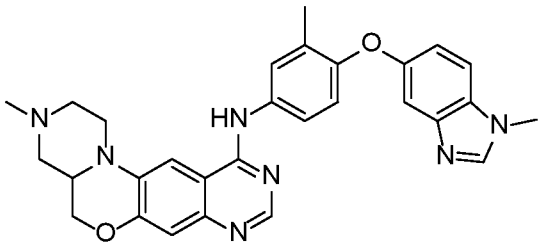
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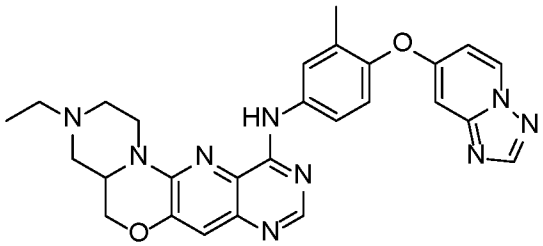
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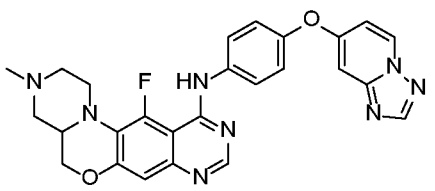
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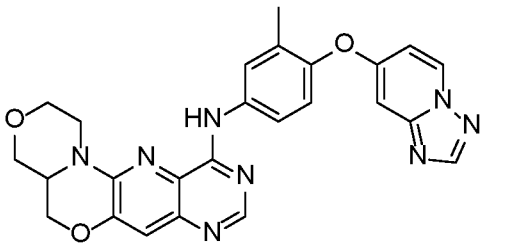
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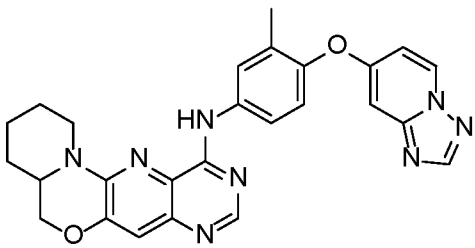
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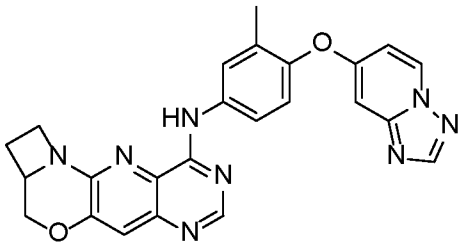
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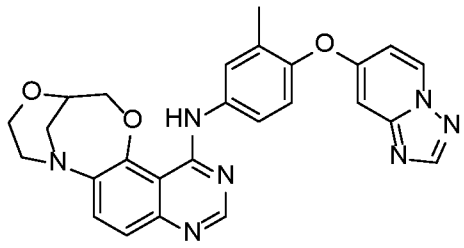
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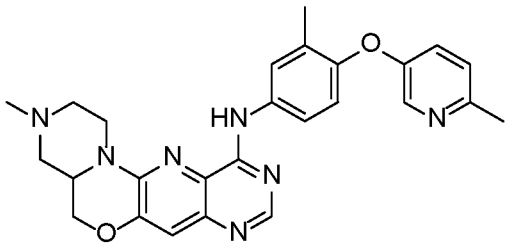
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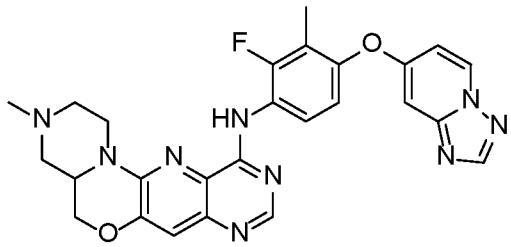
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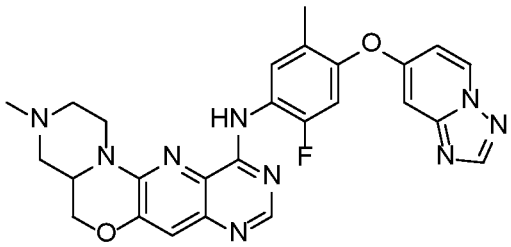
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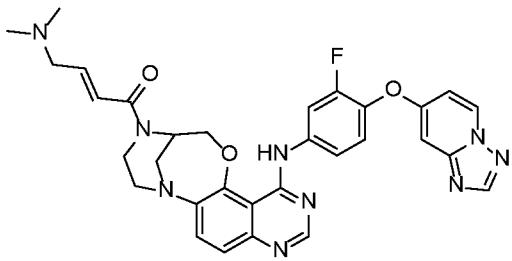
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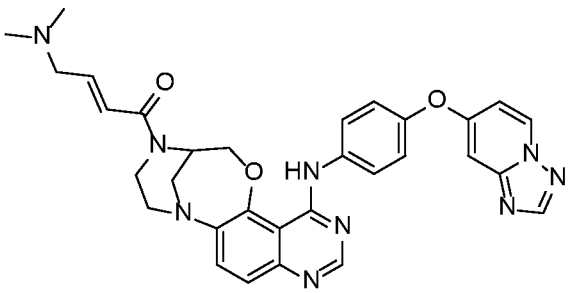
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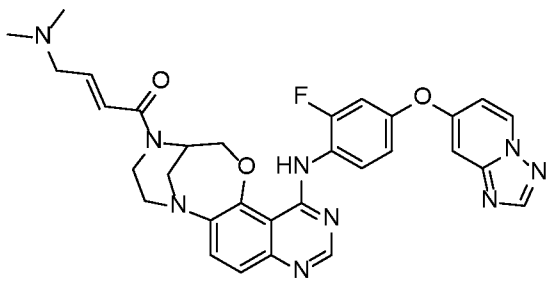
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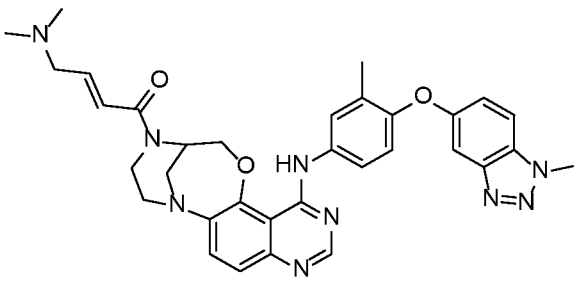
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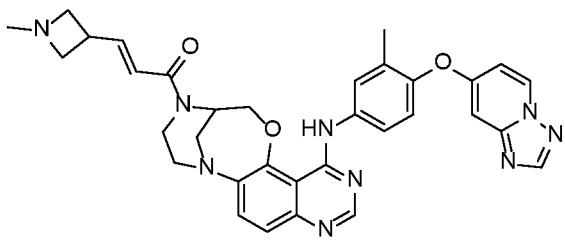
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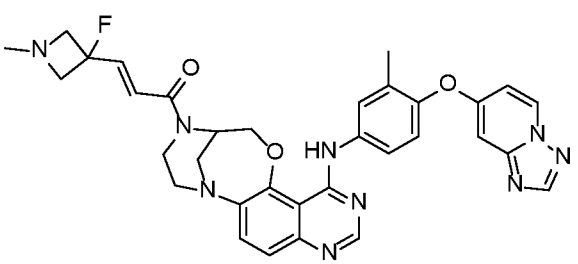
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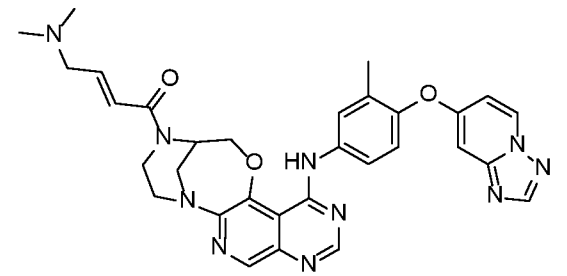
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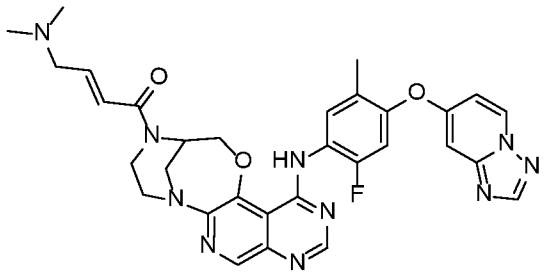
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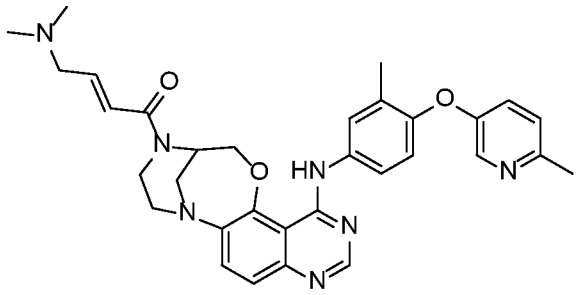
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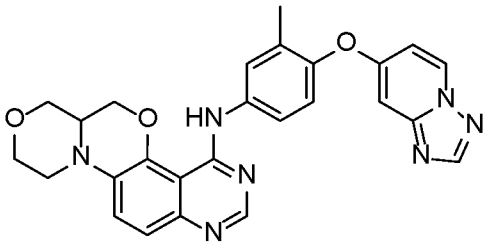
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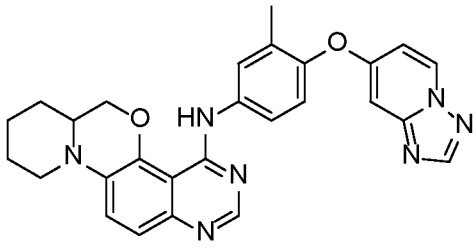
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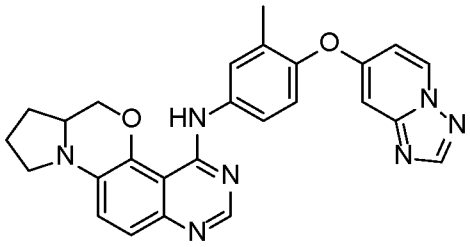
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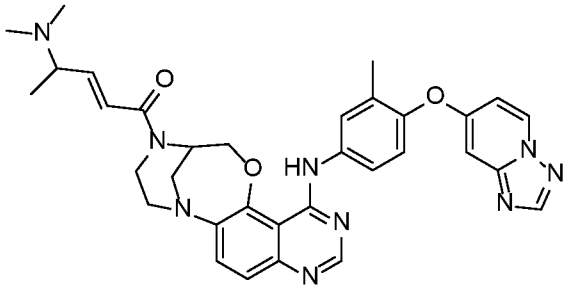
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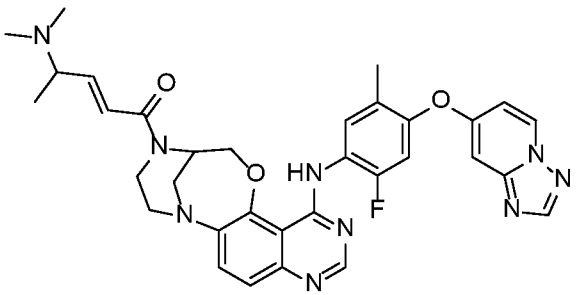
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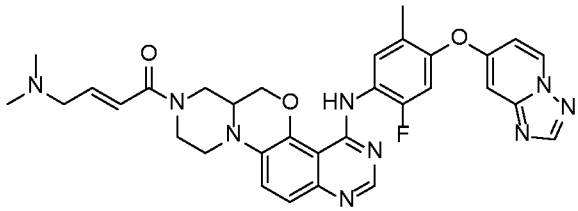
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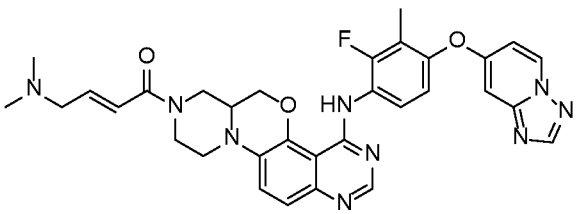
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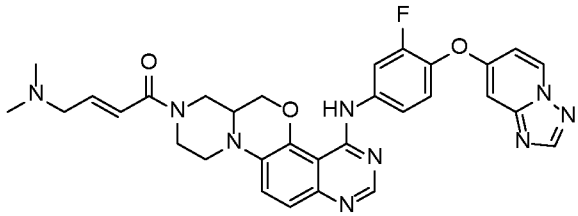
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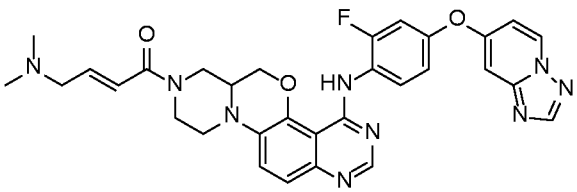
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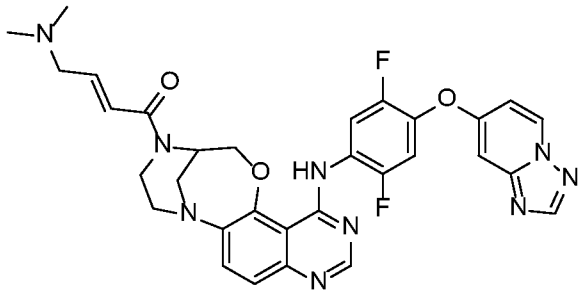
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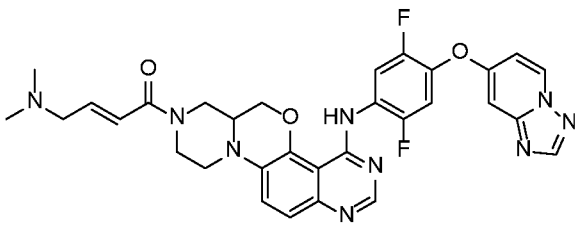
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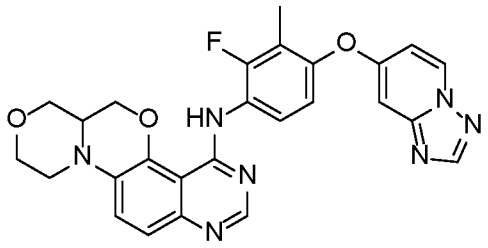
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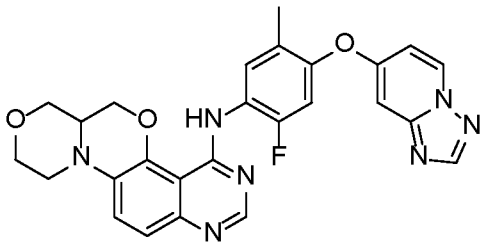
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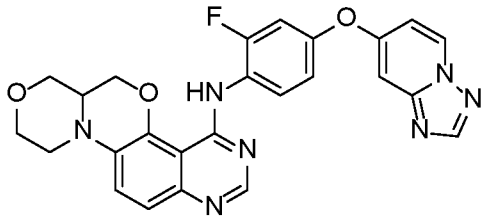
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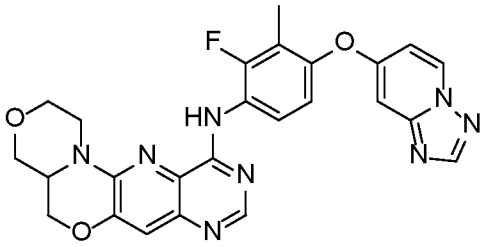
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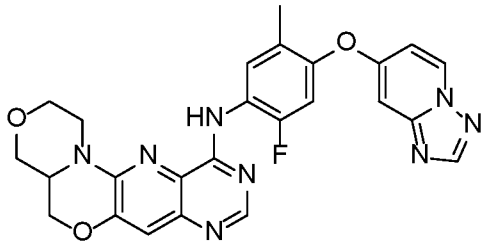
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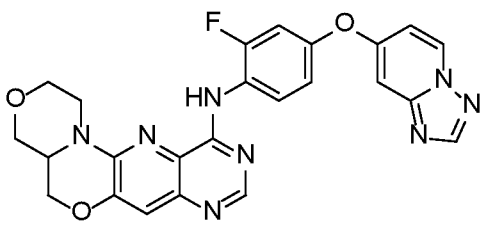
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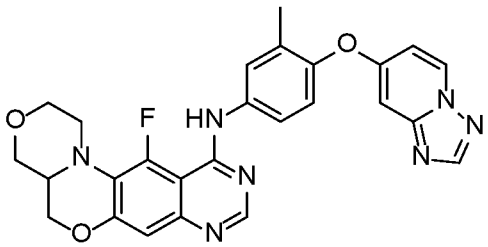
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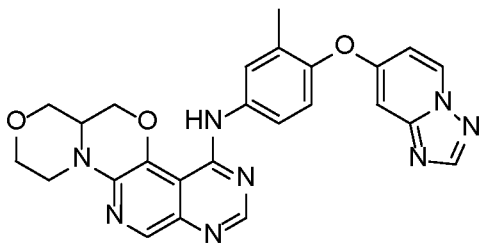
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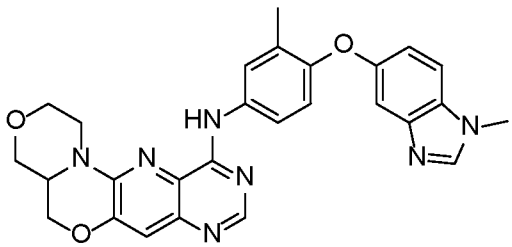
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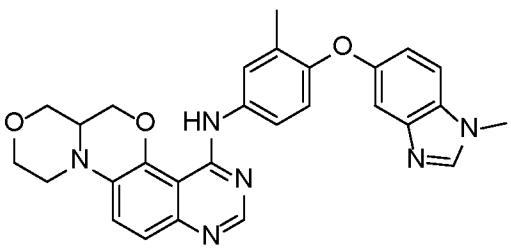
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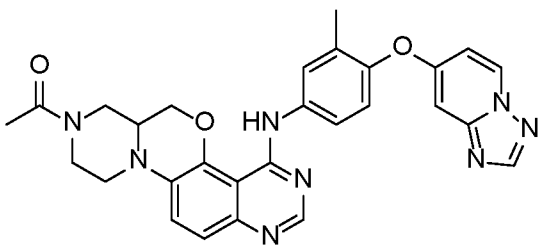
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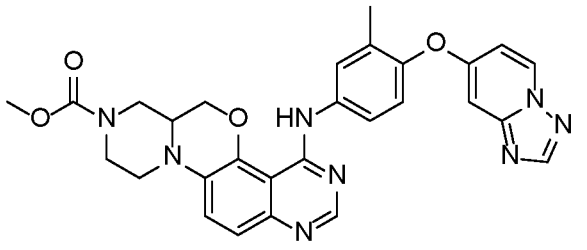
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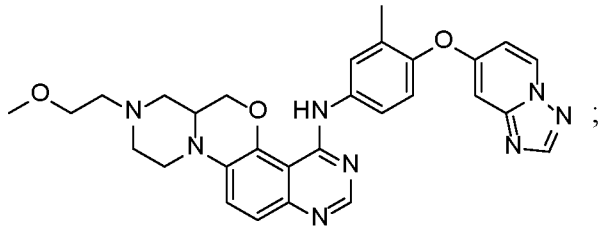
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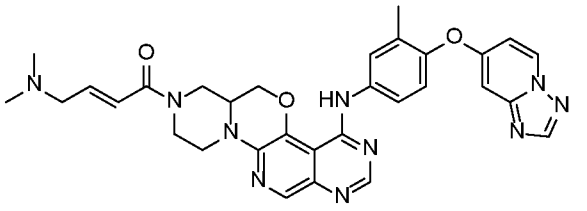
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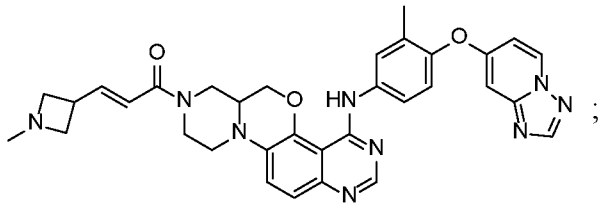
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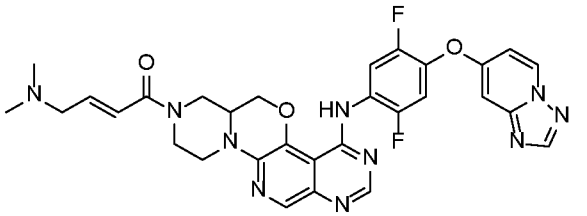
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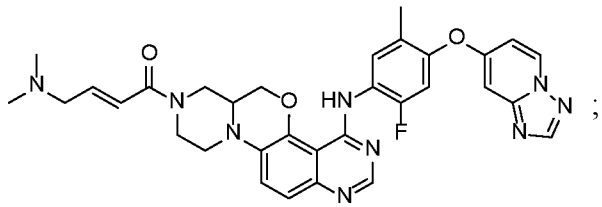
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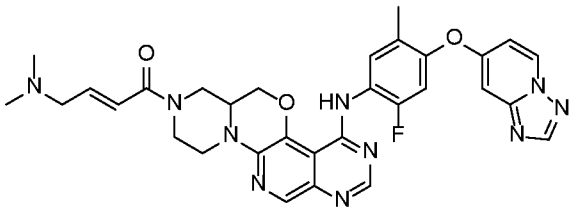
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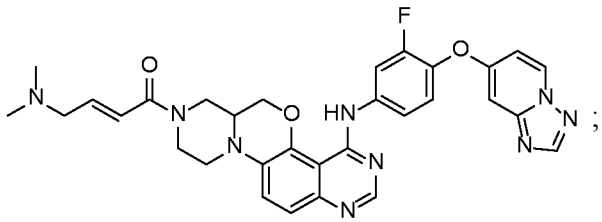
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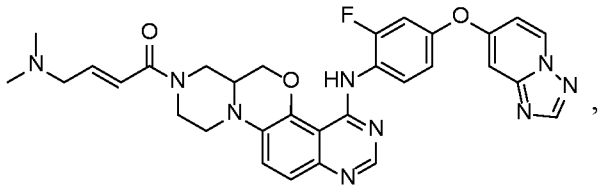
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and

or a pharmaceutically acceptable salt thereof.

Embodiment 36. A pharmaceutical composition comprising the compound of any one of embodiments 1 to 35, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Embodiment 37. A method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2 comprising contacting the ErbB2 or the mutant form with a therapeutically effective amount of the compound of any one of embodiments 1 to 35, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of embodiment 36.

Embodiment 38. The method of embodiment 37, wherein the mutant form of human ErbB2 comprises a mutation in Exon 20.

Embodiment 39. The method of embodiment 37 or embodiment 38, wherein the mutant form of human ErbB2 comprises one or more mutations that introduce amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP.

Embodiment 40. The method of embodiment 37, wherein the mutant form of human ErbB2 comprises a disease-associated point mutation in ErbB2.

Embodiment 41. The method of embodiment 37 or 40, wherein the mutant form of human ErbB2 comprises one or more point mutations in ErbB2 that introduce:

(a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or

(b) a frameshift at A1232.

Embodiment 42. A method of treating a patient having a cancer, comprising administering to the patient a therapeutically effective amount of the compound of any one of embodiments 1 to 35, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of embodiment 36.

Embodiment 43. The method of embodiment 42, wherein the cancer comprises cells or cell tissue having increased ErbB2 kinase activity as compared to a control.

Embodiment 44. The method of embodiment 42 or embodiment 43, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2.

Embodiment 45. The method of any one of embodiments 42 to 44, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2 that introduce amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP,

M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP.

Embodiment 46. The method of embodiment 42 or embodiment 43, wherein the cancer comprises cells or cell tissue having one or more disease-associated point mutations in ErbB2.

Embodiment 47. The method of any one of embodiments 42 to 43 and 46, wherein the cancer comprises cells or cell tissue having one or more point mutations that introduce:

(a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or

(b) a frameshift at A1232.

Embodiment 48. The method of any one of embodiments 42 to 47, wherein the cancer is lung, glioma, skin, head and neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal, bladder, prostate, or ovarian cancer.

Embodiment 49. The method of any one of embodiments 42 to 48, wherein the cancer is non-small cell lung cancer.

Embodiment 50. The method of any one of embodiments 42 to 49, wherein the patient has received at least one, at least two, or at least three prior therapies for the cancer.

Embodiment 51. The method of embodiment 50, wherein one or more of the prior therapies selected from the group consisting of lapatinib, neratinib, afatinib, pyrotinib, poziotinib, TAK-788, and tucatinib.

Embodiment 52. The method of any one of embodiments 42 to 51, wherein the method further comprises administering one or more additional anti-cancer agents.

## EXAMPLES

**[0176]** It is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the spirit and scope of present disclosure.

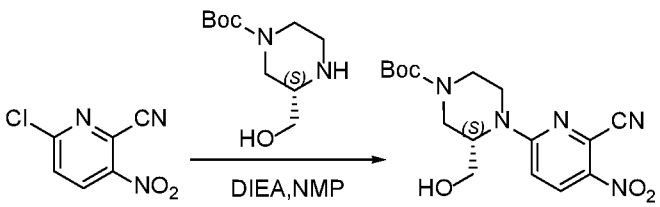
**[0177]** The chemical reactions in the Examples described can be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds of this disclosure are deemed to be within the scope of this disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure can be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction conditions, reagents, and starting materials. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure.

**[0178]** Abbreviations used in the Examples include the following: ACN: acetonitrile; AcOH: acetic acid; BSA: bovine serum albumin; CEMTPP: (carbethoxymethylene)triphenylphosphorane; DCM: dichloromethane; DIEA: diisopropylethylamine; DMF-DMA: dimethylformamide-dimethyl acetal; DMSO: dimethyl sulfoxide; EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; ESI: electrospray ionization; EtOAc: ethyl acetate; EtOH: ethanol or ethyl alcohol; $^1$H NMR: proton nuclear magnetic resonance; HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium); HPLC: high-performance liquid chromatography; LCMS: liquid chromatography–mass spectrometry; MeOH: methanol or methyl alcohol; NBS: N-bromosuccinimide; NMP: N-methyl-2-pyrrolidone; PBS: phosphate-buffered saline; PBST: PBS with Tween 20; Py: pyriding; STAB: sodium triacetoxyborohydride; TEA: triethylamine; TFA trifluoroacetic acid; TFAA: trifluoroacetic anhydride; and THF: tetrahydrofuran.

## SYNTHETIC EXAMPLES

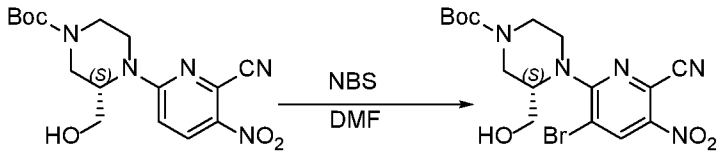
***Example S1: Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one (Compound 1)***

**[0179] Step 1. Synthesis of tert-butyl (3S)-4-(6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



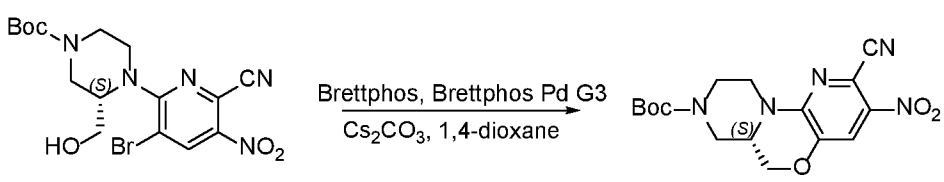
**[0180]** To a solution of 6-chloro-3-nitropyridine-2-carbonitrile (2.0 g, 10.89 mmol) in NMP (20.0 mL) was added tert-butyl (3S)-3-(hydroxymethyl)piperazine-1-carboxylate (5.1 g, 23.97 mmol) and DIEA (5.6 g, 43.58 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl (3S)-4-(6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (3.4 g, 88%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =364.2.

**[0181] Step 2. Synthesis of tert-butyl (3S)-4-(3-bromo-6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



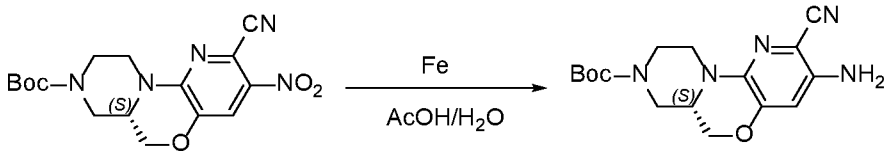

**[0182]** To a solution of tert-butyl (3S)-4-(6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (3.4 g, 9.59 mmol) in DMF (20.0 mL) was added NBS (3.4 g, 19.19 mmol) at room temperature under $N_2$. The reaction mixture was stirred at room temperature for 48 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl (3S)-4-(3-bromo-6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (2.0 g, 47%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =442.1.

**[0183] Step 3. Synthesis of tert-butyl (S)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



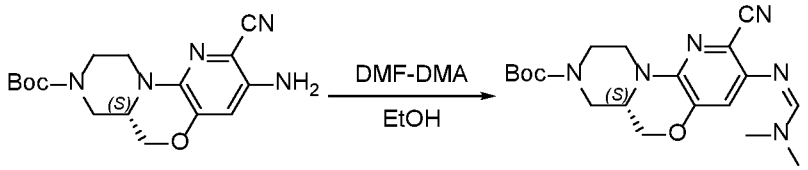
**[0184]** To a solution of tert-butyl (3S)-4-(3-bromo-6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.6 g, 3.61 mmol) in 1,4-dioxane (20.0 mL) was added BrettPhos (388.3 mg, 0.72 mmol), $Cs_2CO_3$ (3.5 g, 10.85 mmol) and BrettPhos Pd G3 (327.9 mg, 0.36 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford tert-butyl (S)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (486.0 mg, 37%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =362.2.

**[0185] Step 4. Synthesis of (S)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0186]** To a solution of tert-butyl (S)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (456.0 mg, 1.26 mmol) in AcOH (10.0 mL) was added Fe (352.3 mg, 6.31 mmol) and $H_2O$ (0.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (92/8, v/v) to afford tert-butyl (S)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate ( 315.0 mg, 75%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =332.2.

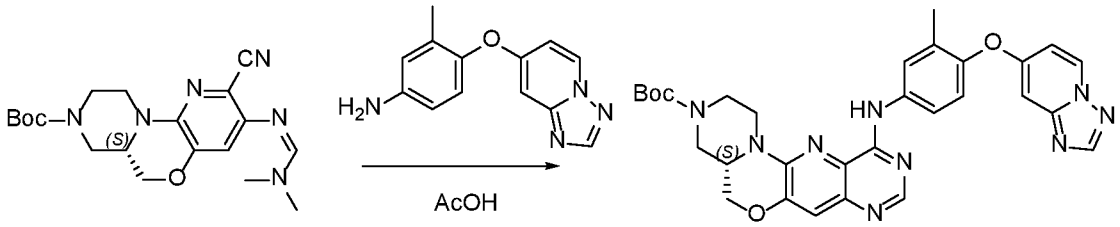
**[0187] Step 5. Synthesis of tert-butyl (S,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0188]** To a solution of tert-butyl (S)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (295.0 mg, 0.89 mmol) in EtOH (5.0 mL) was

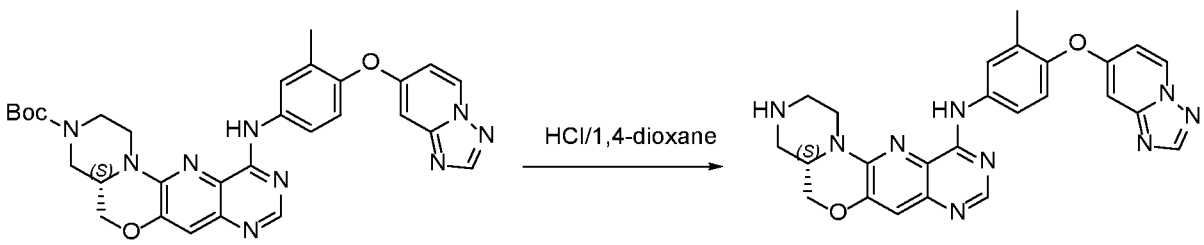
added DMF-DMA (530.4 mg, 4.45 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (S,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (281.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =387.2.

**[0189] Step 6. Synthesis of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**



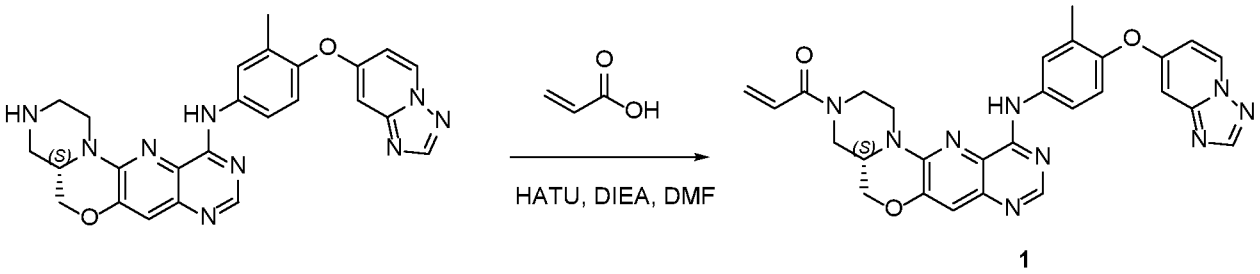

**[0190]** To a solution of tert-butyl (S,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (260.0 mg, 0.67 mmol) in AcOH (5.0 mL) was added 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (323.2 mg, 1.34 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (139.0 mg, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =582.2.

**[0191] Step 7. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**



**[0192]** The solution of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (115.0 mg, 0.19 mmol) in HCl/1,4-dioxane (5.0 mL, 4 mol/L) was stirred at room temperature for 1 h. After the reaction was completed, The pH value of the mixture was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (64.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.2

**[0193] Step 8. Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one (Compound 1)**



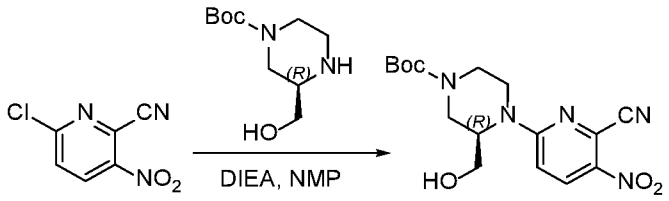

1

**[0194]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (50.0 mg, crude) in DMF (5.0 mL) was added acrylic acid (8.2 mg, 0.11 mmol), DIEA (67.1 mg, 0.52 mmol) and HATU (47.3 mg, 0.12 mmol) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 37% B in 8 min; Wave Length: 254 nm) to afford (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one **(Compound 1)** (17.4 mg, 31%) as a white solid. LCMS

(ESI, m/z): $[M+H]^+$ = 536.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.35 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.42 - 8.38 (m, 2H), 8.01 - 7.97 (m, 2H), 7.27 - 7.21 (m, 2H), 7.04 - 6.85 (m, 2H), 6.79 (s, 1H), 6.22 - 6.18 (m, 1H), 5.79 - 5.76 (m, 1H), 5.22 - 5.13 (m, 1H), 4.69 - 4.41 (m, 2H), 4.33 - 4.26 (m, 1H), 4.15 - 4.10 (m, 1H), 3.72 - 3.64 (m, 1H), 3.09 - 2.91 (m, 2H), 2.68 - 2.62 (m, 1H), 2.21 (s, 3H).

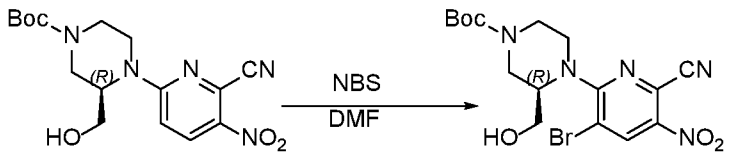
***Example S2: Synthesis of (R)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one (Compound 2)***

**[0195] Step 1. Synthesis of tert-butyl (R)-4-(6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**




**[0196]** To a solution of 6-chloro-3-nitropicolinonitrile (1.0 g, 5.46 mmol) in NMP (10.0 mL) was added tert-butyl (R)-3-(hydroxymethyl)piperazine-1-carboxylate (2.6 g, 12.02 mmol) and DIEA (2.1 g, 16.39 mmol) at room temperature. The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (21/79, v/v) to afford tert-butyl (R)-4-(6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.8 g, 90%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 364.2.

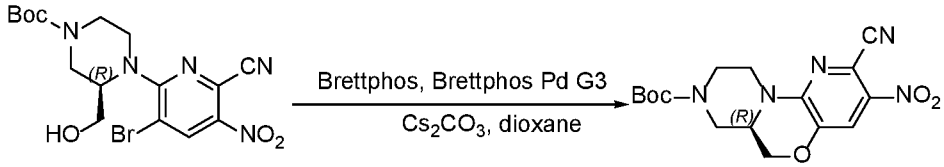
**[0197] Step 2. Synthesis of tert-butyl (R)-4-(3-bromo-6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**




**[0198]** To a solution of tert-butyl (R)-4-(6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.2 g, 3.31 mmol) in DMF (12.0 mL) was added NBS (1.2 g, 6.61 mmol) at room temperature. The mixture was stirred at room temperature for

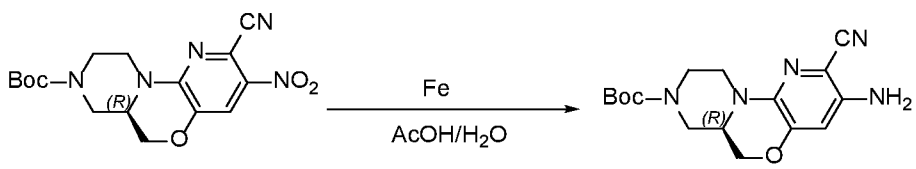
72 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford tert-butyl (R)-4-(3-bromo-6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (700.0 mg, 47%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 442.1.

**[0199] Step 3. Synthesis of tert-butyl (R)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0200]** To a solution of tert-butyl (R)-4-(3-bromo-6-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (700 mg, 1.58 mmol) in 1,4-dioxane (7.0 mL) was added $Cs_2CO_3$ (1544.1 mg, 4.74 mmol), Brettphos (169.8 mg, 0.32 mmol) and Brettphos Pd G3 (143.5 mg, 0.16 mmol) at room temperature under $N_2$. The mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford tert-butyl (R)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (360.0 mg, 47%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 362.1.

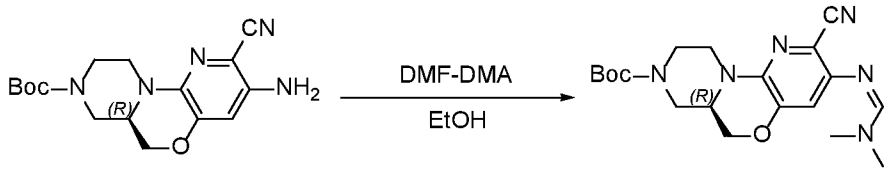
**[0201] Step 4. Synthesis of tert-butyl (R)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0202]** To a solution of tert-butyl (R)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (360.0 mg, 0.99 mmol) in AcOH/$H_2O$ (5.0 mL/0.1 mL) was added Fe (278.5 mg, 4.97 mmol) at room temperature. The mixture was stirred

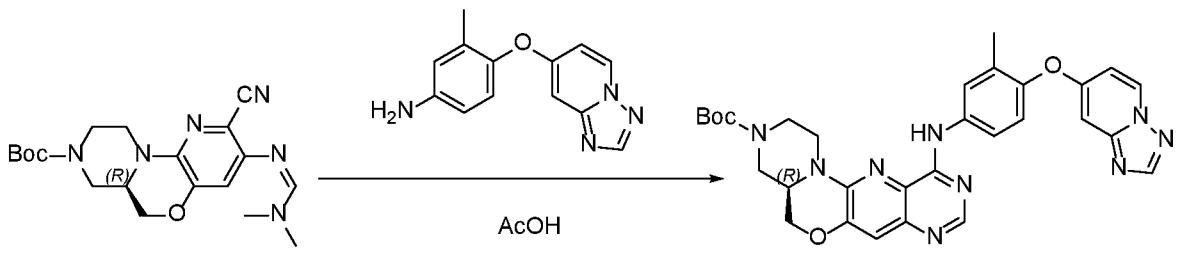
at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (59/41, v/v) to afford tert-butyl (R)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (280.0 mg, 84%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 332.2.

**[0203] Step 5. Synthesis of tert-butyl (R,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0204]** To a solution of tert-butyl (R)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (280.0 mg, 0.84 mmol) in EtOH (5.0 mL) was added DMF-DMA (301.1 mg, 2.53 mmol) at room temperature. The mixture was stirred at 80 °C for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (58/42, v/v) to afford tert-butyl (R,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (220.0 mg, 67%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 387.2.

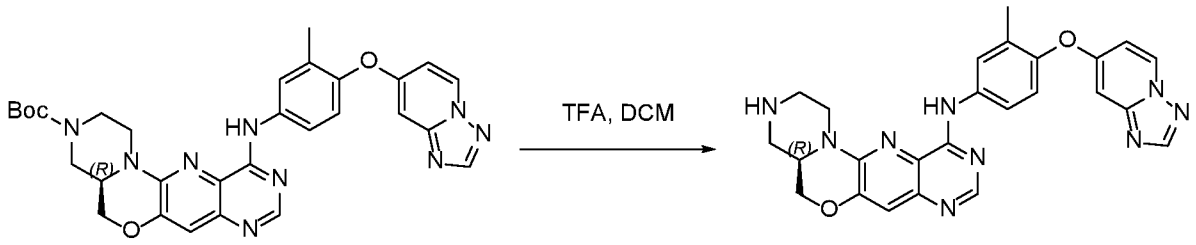
**[0205] Step 6. Synthesis of tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**




**[0206]** To a solution of tert-butyl (R,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (220.0 mg, 0.57 mmol) in AcOH (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (273.6 mg, 1.14 mmol) at room temperature. The mixture was stirred at 85 °C for

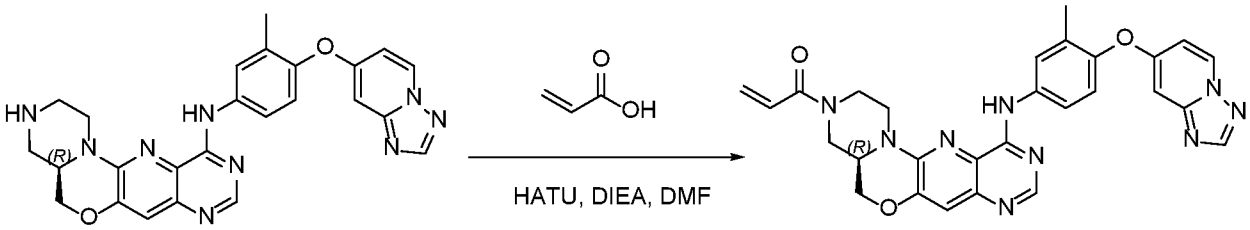
16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (76/24, v/v) to afford tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (200.0 mg, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 582.2.

**[0207] Step 7. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**




**[0208]** To a solution of tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (200.0 mg, 0.34 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with aq. $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (65/35, v/v) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (90.0 mg, 54%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.2.

**[0209] Step 8. Synthesis of (R)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one (Compound 2)**

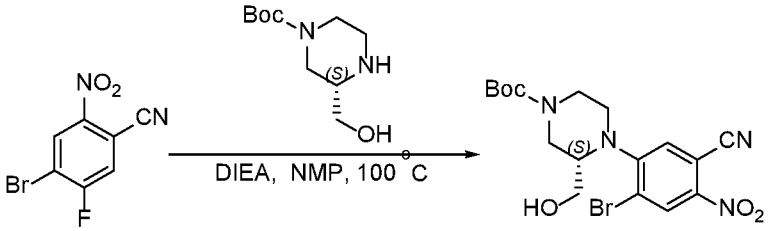



2

**[0210]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (90.0 mg, 0.19 mmol) in DMF (2.0 mL) was added acrylic acid (15.0 mg, 0.21 mmol), DIEA (122.6 mg, 0.95 mmol) and HATU (85.1 mg, 0.22 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: Column: (YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 10 min; Wave Length: 254 nm) to afford (R)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one **(Compound 2)** (28.8 mg, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 536.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.34 (s, 1H), 8.93 (d, $J$ = 7.2 Hz, 1H), 8.42 - 8.38 (m, 2H), 8.01 - 7.97 (m, 2H), 7.27 - 7.20 (m, 2H), 7.04 - 7.02 (m, 1H), 6.94 - 6.82 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 6.22 - 6.18 (m, 1H), 5.79 - 5.76 (m, 1H), 5.22 - 5.09 (m, 1H), 4.69 - 4.49 (m, 2H), 4.33 - 4.22 (m, 1H), 4.15 - 4.10 (m, 1H), 3.73 - 3.60 (m, 1H), 3.09 - 2.91 (m, 2H), 2.71 - 2.65 (m, 1H), 2.20 (s, 3H).

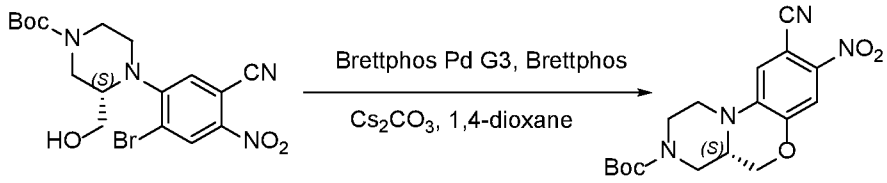
***Example S3: Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one (Compound 3)***

**[0211]** **Step 1. Synthesis of tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



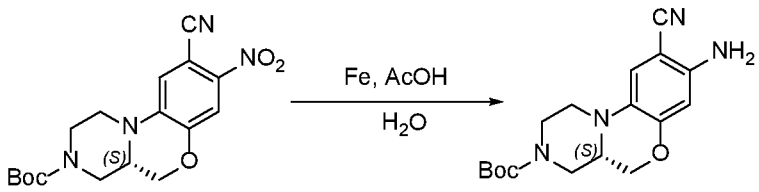
**[0212]** To a solution of 4-bromo-5-fluoro-2-nitrobenzonitrile (1.0 g, 4.08 mmol) in NMP (10.0 mL) was added tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (4.4 g, 20.41 mmol) and DIEA (2.6 g, 20.41 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (70/10, v/v) to afford tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.1 g, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.2.

**[0213] Step 2. Synthesis of tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



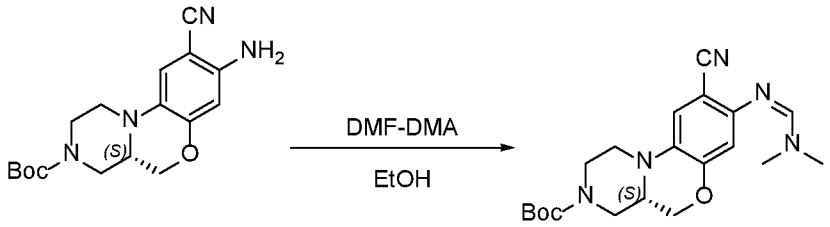

**[0214]** To a solution of tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (500.0 mg, 1.13 mmol) in dioxane (10.0 mL) was added BrettPhos (243.2 mg, 0.45 mmol), $Cs_2CO_3$ (922.9 mg, 2.83 mmol) and BrettPhos Pd G3 (205.4 mg, 0.22 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (340.0 mg, 73%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.3.

**[0215] Step 3. Synthesis of tert-butyl (S)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



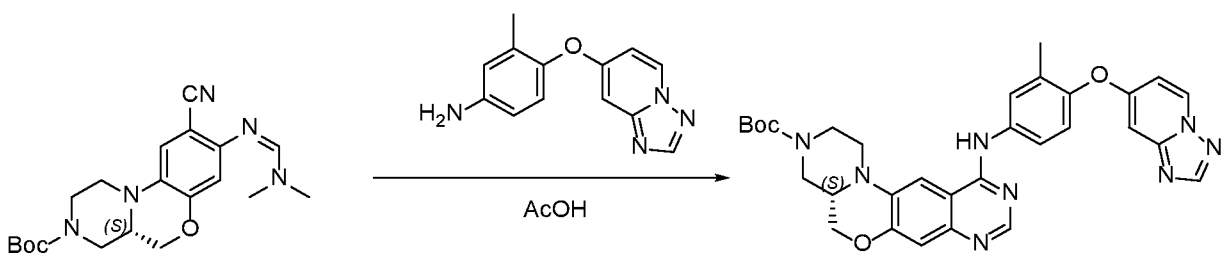
**[0216]** To a solution of tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (400.0 mg, 1.11 mmol) in HOAc (10.0 mL) and $H_2O$ (0.5 mL) was added Fe (309.9 mg, 5.55 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (S)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (320.0 mg, 84%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =331.3.

**[0217] Step 4. Synthesis of tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



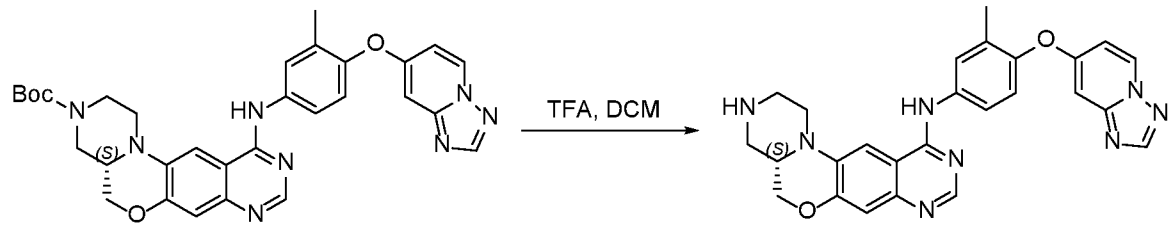

**[0218]** To a solution of tert-butyl (S)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (300.0 mg, 0.91 mmol) in EtOH (5.0 mL) was added DMF-DMA (331.8 mg, 4.54 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (320.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =386.2.

**[0219] Step 5. Synthesis of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**



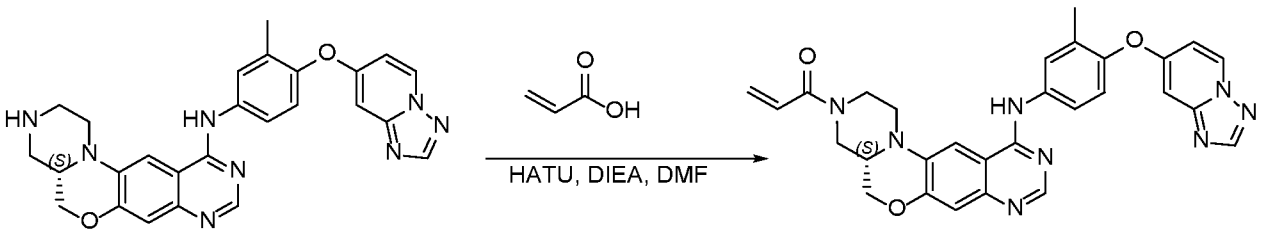
**[0220]** To a solution of tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (300.0 mg, crude) in acetic acid (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (186.9 mg, 0.77 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (94/6, v/v) to afford tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (420.0 mg, 93%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =581.3.

**[0221] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine**




**[0222]** To a solution of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (300.0 mg, 0.54 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (40/60, v/v) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (200.0 mg, 55%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.3

**[0223] Step 7. Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one (Compound 3)**

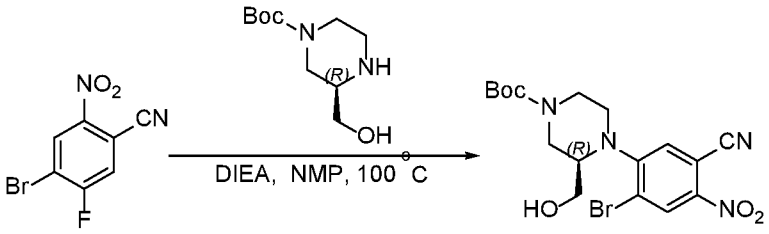



3

**[0224]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (100.0 mg, 0.20 mmol) in DMF (5.0 mL) was added acrylic acid (15.0 mg, 0.20 mmol), DIEA (32.2 mg, 0.25 mmol) and HATU (158.2 mg, 0.41 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (55/45, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 40% B in 8 min; Wave Length: 254 nm) to afford (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one **(Compound 3)** (2.9 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 535.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.46 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.38 (s, 2H), 7.81 - 7.77 (m, 3H), 7.21 (d, $J$ = 8.4 Hz, 1H), 7.05 - 7.02 (m, 2H), 7.00 - 6.90 (m, 1H), 6.80 (d, $J$ = 2.4 Hz, 1H), 6.22 - 6.18 (m, 1H), 5.79 - 5.76 (m, 1H), 4.70 - 4.53 (m, 2H), 4.35 - 4.28 (m, 1H), 4.19 - 4.10 (m, 2H), 3.09 - 3.02 (m, 1H), 2.89 - 2.82 (m, 1H), 2.21 (s, 3H).

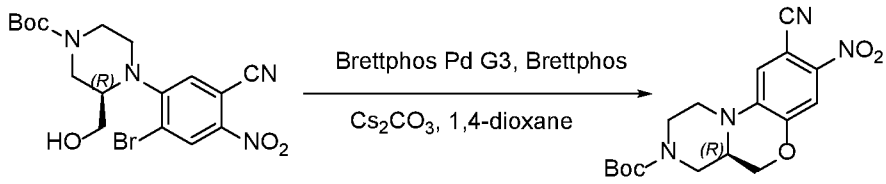
***Example S4: Synthesis of (R)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one (Compound 4)***

**[0225]** **Step 1. Synthesis of tert-butyl (R)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



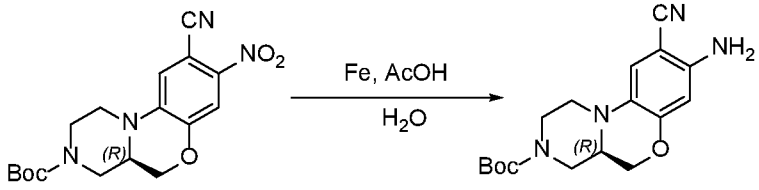

**[0226]** To a solution of 4-bromo-5-fluoro-2-nitrobenzonitrile (1.0 g, 4.08 mmol) in NMP (10.0 mL) was added tert-butyl (R)-3-(hydroxymethyl)piperazine-1-carboxylate (4.4 g, 20.41 mmol) and DIEA (2.6 g, 20.41 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (70/10, v/v) to afford tert-butyl (R)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.0 g, 58%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.2.

**[0227]** **Step 2. Synthesis of tert-butyl (R)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



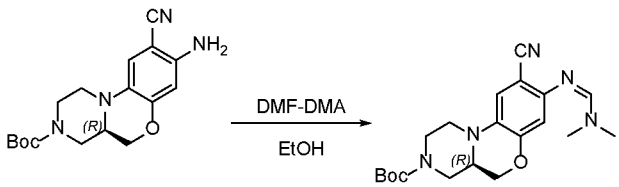

**[0228]** To a solution of tert-butyl (R)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (500.0 mg, 1.13 mmol) in dioxane (10.0 mL) was added BrettPhos (243.2 mg, 0.45 mmol), $Cs_2CO_3$ (922.9 mg, 2.83 mmol) and BrettPhos Pd G3 (205.4 mg, 0.22 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h under $N_2$. After the reaction was completed, the resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (R)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (360.0 mg, 88%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.3.

**[0229]** **Step 3. Synthesis of tert-butyl (R)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



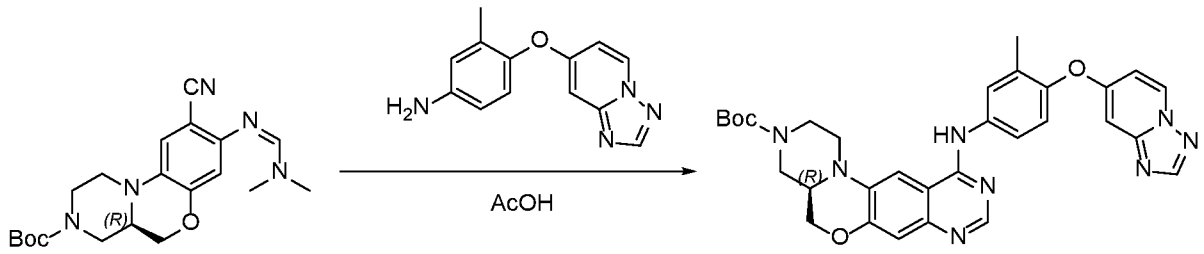

**[0230]** To a solution of tert-butyl (R)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (400.0 mg, 1.11 mmol) in AcOH (10.0 mL) and $H_2O$ (0.5 mL) was added Fe (309.9 mg, 5.55 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (R)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (300.0 mg, 81%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =331.3.

**[0231] Step 4. Synthesis of tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**




**[0232]** To a solution of tert-butyl (R)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (300.0 mg, 0.91 mmol) in EtOH (5.0 mL) was added DMF-DMA (331.8 mg, 4.54 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (270.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =386.2.

**[0233] Step 5. Synthesis of tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**



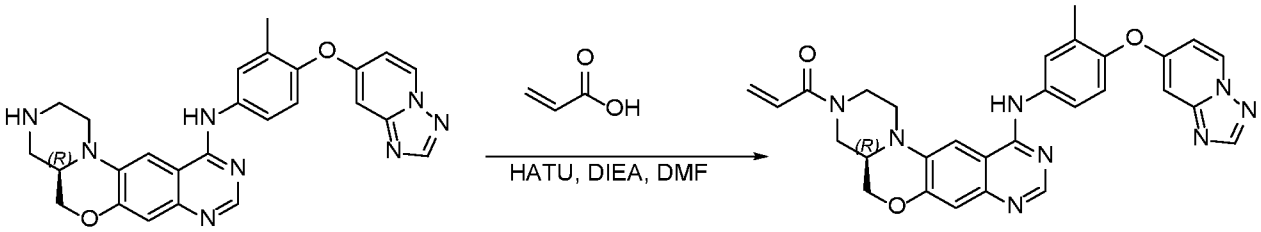

**[0234]** To a solution of tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (300.0 mg, 0.77 mmol) in acetic acid (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (186.9 mg, 0.77 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (350.0 mg, 80%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =581.3.

**[0235] Step 6. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine**


**[0236]** To a solution of tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (300.0 mg, 0.54 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (50/50, v/v) to afford (R)-N-(4-

([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (200.0 mg, 55%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.3

**[0237] Step 7. Synthesis of (R)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one (Compound 4)**

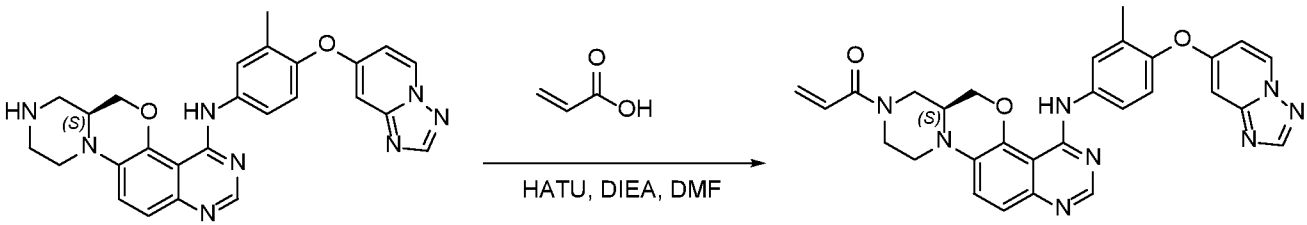



4

**[0238]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (100.0 mg, 0.20 mmol) in DMF (5.0 mL) was added acrylic acid (15.0 mg, 0.20 mmol), DIEA (32.2 mg, 0.25 mmol) and HATU (158.2 mg, 0.41 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 40% B in 8 min; Wave Length: 254 nm) to afford (R)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one **(Compound 4)** (4.7 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 535.4. $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.63 (d, $J$ = 8.0 Hz, 1H), 8.22 - 8.18 (m, 2H), 7.63 - 7.55 (m, 3H), 7.08 - 6.96 (m, 3H), 6.81 - 6.73 (m, 2H), 6.21 - 6.16 (m, 1H), 5.74 - 5.71 (m, 1H), 4.72 - 4.40 (m, 2H), 4.39 - 4.36 (m, 1H), 4.27 - 4.16 (m, 1H), 4.08 - 4.03 (m, 2H), 3.53 - 3.42 (m, 0.5H), 3.03 - 2.99 (m, 1H), 2.83 - 2.80 (m, 1H), 2.62 - 2.53 (m, 0.5H), 2.14 (s, 3H).

***Example S5: Synthesis of (S)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 5)***

**[0239] Step 1. Synthesis of (S)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 5)**

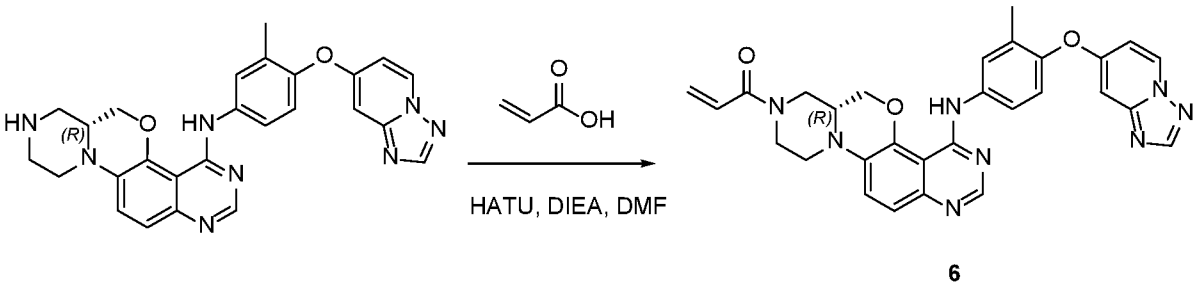



**5**

**[0240]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (30.0 mg, 0.06 mmol) in DMF (2.0 mL) was added acrylic acid (5.4 mg, 0.07 mmol), DIEA (24.2 mg, 0.18 mmol) and HATU (47.5 mg, 0.12 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at 0 °C for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3OH/H_2O$ (80/20, v/v) and then purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 43% B in 8 min; Wave Length: 254 nm) to afford (S)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one **(Compound 5)** (3.0 mg, 9%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 535.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.92 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.38 - 8.37 (m, 2H), 7.88 - 7.82 (m, 2H), 7.65 (d, $J$ = 9.2 Hz, 1H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.95 - 6.88 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 6.21 - 6.16 (m, 1H), 5.77 - 5.74 (m, 1H), 4.79 - 4.74 (m, 1H), 4.55 - 4.52 (m, 1H), 4.28 - 4.22 (m, 2H), 4.09 - 3.98 (m, 1H), 3.32 - 3.24 (m, 1H), 3.09 - 2.90 (m, 1H), 2.81 - 2.75 (m, 1H), 2.70 - 2.64 (m, 1H), 2.19 (s, 3H).

***Example S6: Synthesis of (R)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 6)***

**[0241] Step 1. Synthesis of (R)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 6)**

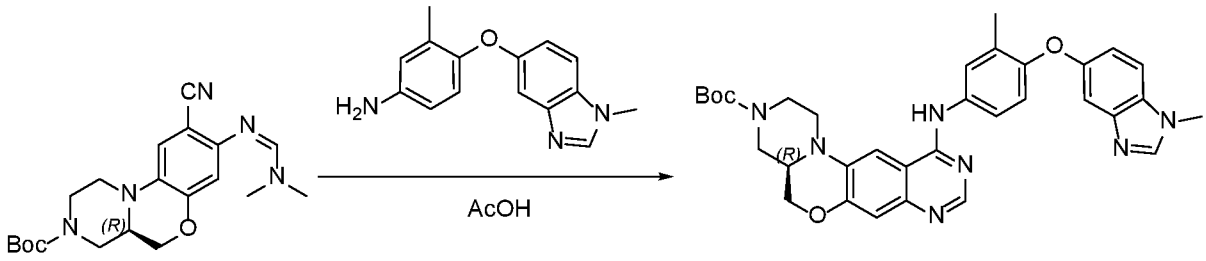



6

**[0242]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, 0.21 mmol) in DMF (8.0 mL) was added acrylic acid (18.0 mg, 0.25 mmol), HATU (119.7 mg, 0.32 mmol) and DIEA (135.5 mg, 1.05 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 20% B in 10 min; Wave Length: 254 nm) to afford (R)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one **(Compound 6)** (3.5 mg, 2%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 535.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.93 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.38 (s, 2H), 7.88 - 7.83 (m, 2H), 7.66 (d, $J$ = 9.2 Hz, 1H), 7.35 - 7.33 (m, 1H), 7.22 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.95 - 6.88 (m, 1H), 6.80 (s, 1H), 6.21 - 6.16 (m, 1H), 5.77 - 5.75 (m, 1H), 4.77 - 4.73 (m, 1H), 4.55 - 4.52 (m, 1H), 4.31 - 4.19 (m, 2H), 4.07 - 3.94 (m, 1H), 3.07 - 2.62 (m, 3H), 2.20 (s, 3H).

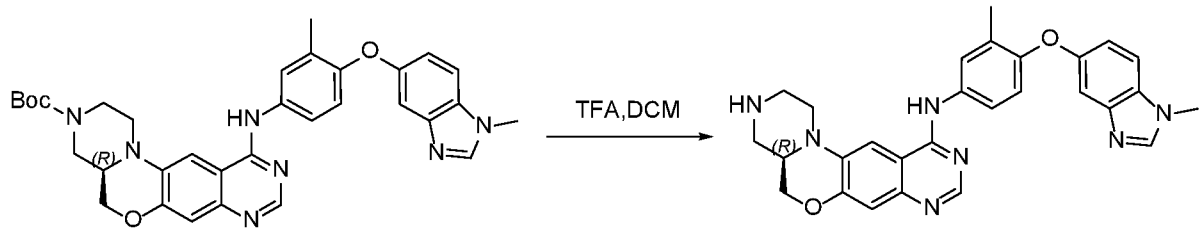
***Example S7: Synthesis of (R)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one (Compound 7)***

**[0243] Step 1. Synthesis of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**




**[0244]** To a solution of tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (290.0 mg, 0.75 mmol) in acetic acid (5.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (190.5 mg, 0.75 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (250.0 mg, 55%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =594.3.

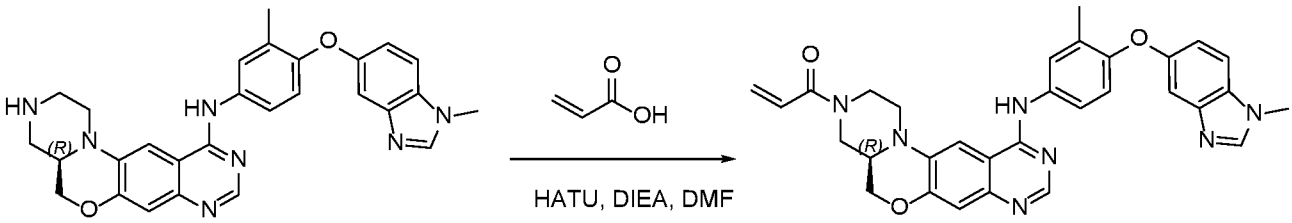
**[0245] Step 2. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine**




**[0246]** To a solution of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (250.0 mg, 0.42 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room

temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (50/50, v/v) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (150.0 mg, 74%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.2

**[0247] Step 3. Synthesis of (R)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one (Compound 7)**



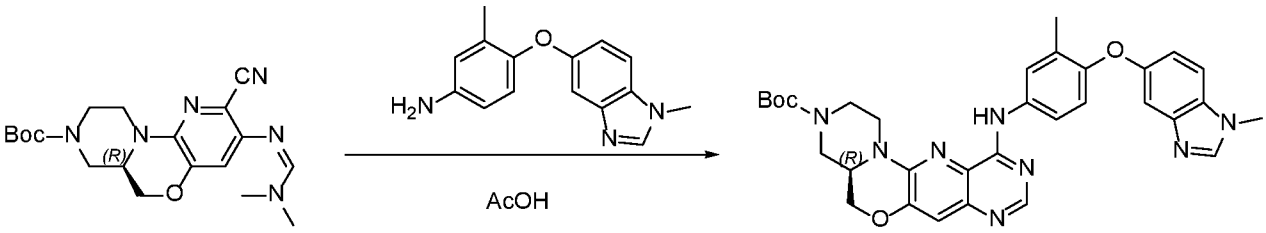

7

**[0248]** To a solution of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (100.0 mg, 0.20 mmol) in DMF (5.0 mL) was added acrylic acid (15.0 mg, 0.20 mmol), DIEA (32.2 mg, 0.25 mmol) and HATU (158.2 mg, 0.41 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (70/30, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15% B to 30% B in 10 min; Wave Length: 254 nm) to afford (R)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)prop-2-en-1-one **(Compound 7)** (15.3 mg, 2%) as a yellow solid. LCMS (ESI, m/z):

$[M+H]^+$ = 548.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.62 (s, 1H), 8.40 (s, 1H), 8.19 (s, 1H), 7.79 (s, 1H), 7.67 (d, $J$ = 2.0 Hz, 1H), 7.59 - 7.57 (m, 2H), 7.11 (d, $J$ = 2.0 Hz, 1H), 7.04 - 7.00 (m, 2H), 6.92 - 6.87 (m, 2H), 6.22 - 6.18 (m, 1H), 5.79 - 5.76 (m, 1H), 4.67 - 4.53 (m, 2H), 4.36 - 4.27 (m, 1H), 4.16 - 4.03 (m, 2H), 3.85 (s, 3H), 3.00 - 2.86 (m, 1H), 2.83 - 2.68 (m, 1H), 2.25 (s, 3H).

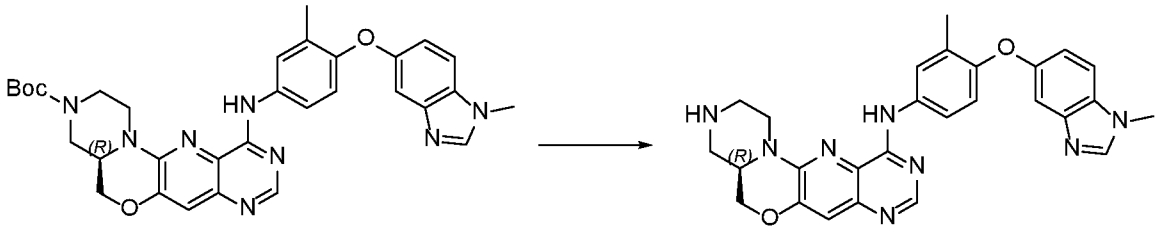
***Example S8: Synthesis of (R)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one (Compound 8)***

**[0249] Step 1. Synthesis of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**



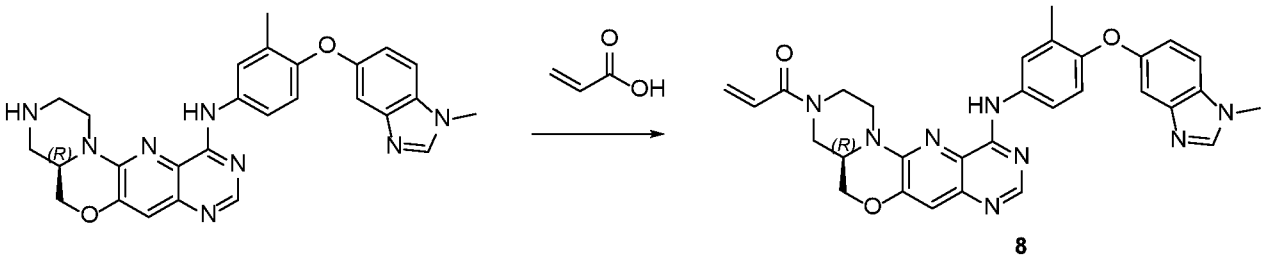

**[0250]** To a mixture of tert-butyl (R,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (850.0 mg, 2.20 mmol) in acetic acid (10.0 mL) was added 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (557.1 mg, 2.20 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (7/1, v/v) to afford tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (1.0 g, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 595.2.

**[0251] Step 2. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**



**[0252]** To a mixture of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (900.0 mg, 1.51 mmol) in DCM (6.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was basified to pH=8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (64/36, v/v) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (700.0 mg, 93%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2.

**[0253] Step 3. Synthesis of (R)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one (Compound 8)**



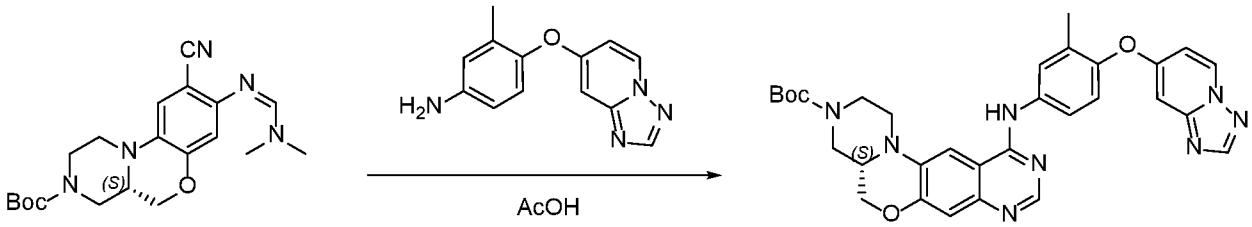
**8**

**[0254]** To a stirred mixture of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (310.0 mg, 0.63 mmol) and acrylic acid (90.3 mg, 1.25 mmol) in pyridine (6.0 mL) was added EDCI (240.3 mg, 1.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (63/37, v/v) and then purified by Prep-HPLC with

the following conditions:(Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 42% B in 8 min; Wave Length: 254 nm) to afford (R)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)prop-2-en-1-one **(Compound 8)** (47.8 mg, 13%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 549.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.28 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 7.84 - 7.79 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.26 (s, 1H), 7.07 (s, 1H), 7.01 - 6.89 (m, 3H), 6.22 - 6.18 (m, 1H), 5.79 - 5.76 (m, 1H), 5.22 - 5.09 (m, 1H), 4.68 - 4.49 (m, 2H), 4.33 - 4.21 (m, 1H), 4.15 - 4.07 (m, 1H), 3.84 (s, 3H), 3.68 - 3.53 (m, 1H), 3.09 - 2.89 (m, 2H), 2.69 - 2.61 (m, 1H), 2.25 (s, 3H).

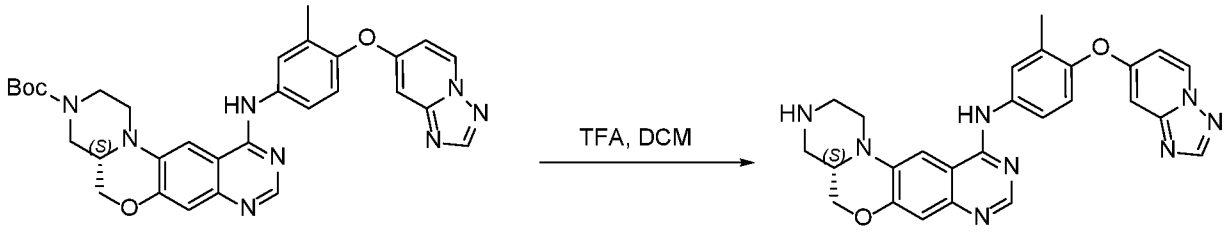
***Example S9: Synthesis of (S,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 9)***

**[0255] Step 1. Synthesis of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**



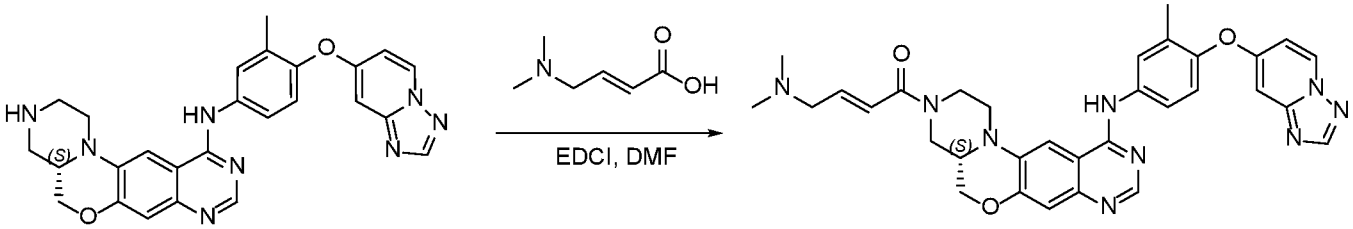

**[0256]** A mixture of tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate and 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (0.9 g, 3.74 mmol) in acetic acid (15.0 mL) was stirred at 90 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (5/1, v/v) to afford tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (1.5 g, 83%) as an brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 581.3.

**[0257] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine**




**[0258]** A mixture of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (1.4 g, 0.08 mmol) in TFA (7.0 mL) and DCM (15.0 mL) was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was neutralized to Ph=7 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (60/40, v/v) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (800.0 mg, 69%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.3.

**[0259] Step 3. Synthesis of (S,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 9)**



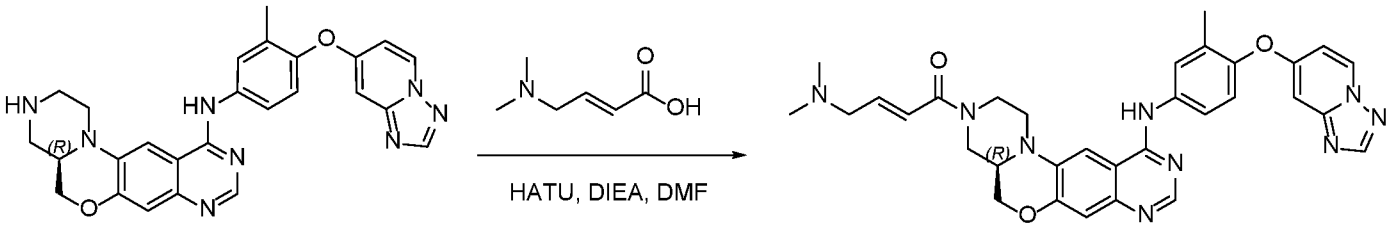

9

**[0260]** To a stirred mixture of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (200.0 mg, 0.42 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (53.7 mg, 0.42 mmol) in DMF (3.0 mL) was added EDCI (159.5 mg, 0.83 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (70/30, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield

RP18 OBD Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 50% B in 8 min; Wave Length: 254 nm) to afford (S,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 9)** (46.1 mg, 18%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ = 592.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.44 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.39 - 8.37 (m, 2H), 7.84 - 7.76 (m, 3H), 7.21 (d, $J$ = 8.4 Hz, 1H), 7.04 - 7.02 (m, 2H), 6.80 (d, $J$ = 2.4 Hz, 1H), 6.75 - 6.65 (m, 2H), 4.62 - 4.51 (m, 2H), 4.35 - 4.24 (m, 1H), 4.16 - 4.07 (m, 2H), 3.23 - 3.13 (m, 2H), 3.06 (d, $J$ = 3.6 Hz, 2H), 2.99 - 2.84 (m, 2H), 2.33 - 2.13 (m, 9H).

***Example S10: Synthesis of (R,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 10)***

**[0261] Step 1. Synthesis of (R,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 10)**



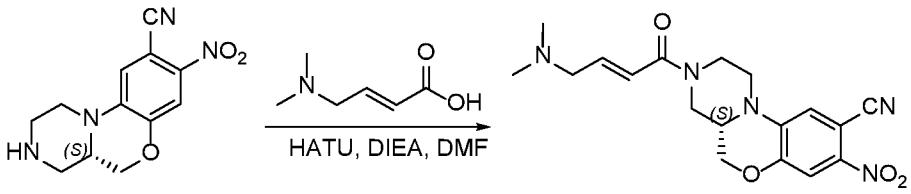

10

**[0262]** To a stirred mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (180.0 mg, 0.36 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (96.8 mg, 0.75 mmol) in DMF (6.0 mL) was added DIEA (145.2 mg, 1.13 mmol) and HATU (284.9 mg, 0.75 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (47/53, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 68% B to 72% B in 12 min; Wave Length: 254 nm) to afford (R,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-

tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 10)** (24.0 mg, 10%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 592.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.42 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.39 - 8.38 (m, 2H), 7.84 - 7.76 (m, 3H), 7.21 (d, $J$ = 8.4 Hz, 1H), 7.05 - 7.02 (m, 2H), 6.80 (d, $J$ = 2.4 Hz, 1H), 6.76 - 6.65 (m, 2H), 4.67 - 4.51 (m, 2H), 4.41 - 4.22 (m, 1H), 4.16 - 4.05 (m, 2H), 3.08 (d, $J$ = 4.0 Hz, 2H), 3.04 - 2.94 (m, 1H), 2.89 - 2.82 (m, 1H), 2.61 - 2.54 (m, 2H), 2.18 - 2.16 (m, 9H).

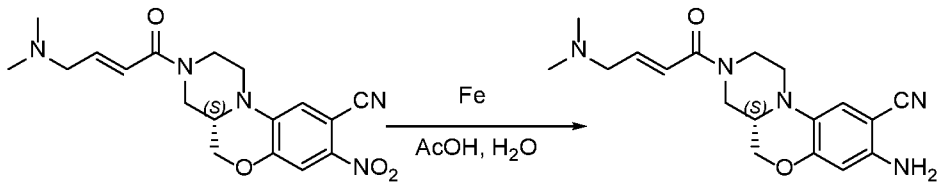
***Example S11: Synthesis of (S,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-en-1-one (Compound 11)***

**[0263] Step 1. Synthesis of (S,E)-3-(4-(dimethylamino)but-2-enoyl)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile**



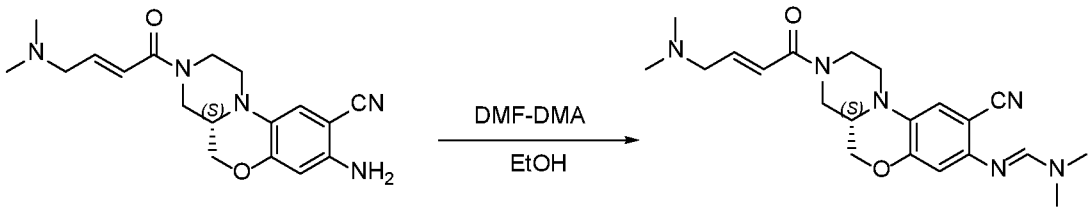

**[0264]** To a solution of (S)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (300.0 mg, 1.15 mmol) in DMF (5.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (163.8 mg, 1.27 mmol), DIEA (893.9 mg, 6.92 mmol) and HATU (526.0 mg, 1.38 mmol) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) to afford (S,E)-3-(4-(dimethylamino)but-2-enoyl)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (343.0 mg, 80%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 372.2.

**[0265] Step 2. Synthesis of (S,E)-8-amino-3-(4-(dimethylamino)but-2-enoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile**




**[0266]** To a solution of (S,E)-3-(4-(dimethylamino)but-2-enoyl)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (333.0 mg, 0.93 mmol) in AcOH (10.0 mL) and $H_2O$ (0.5 mL) was added Fe (260.2 mg, 4.67 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) to afford (S,E)-8-amino-3-(4-(dimethylamino)but-2-enoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (280.0 mg, 88%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =342.2.

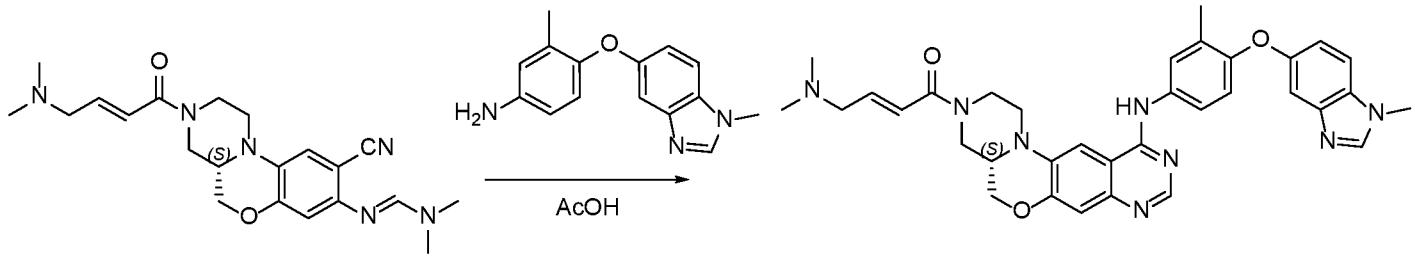
**[0267] Step 3. Synthesis of (E)-N'-((S)-9-cyano-3-((E)-4-(dimethylamino)but-2-enoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide**




**[0268]** To a solution of (S,E)-8-amino-3-(4-(dimethylamino)but-2-enoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (270.0 mg, 0.83 mmol) in EtOH (5.0 mL) was added DMF-DMA (491.4 mg, 4.13 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford (E)-N'-((S)-9-cyano-3-((E)-4-(dimethylamino)but-2-enoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (190.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =397.2.

**[0269] Step 4. Synthesis of (S,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-**

**tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-en-1-one (Compound 11)**

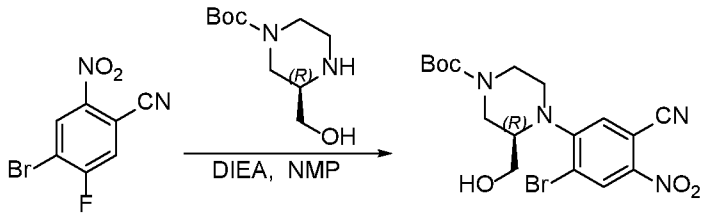



11

**[0270]** To a solution of (E)-N'-((S)-9-cyano-3-((E)-4-(dimethylamino)but-2-enoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (190.0 mg, crude) in HOAc (5.0 mL) was added 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (242.8 mg, 0.96 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 19 x 250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 32% B to 32% B in 15 min; Wave Length: 254 nm) to afford (S,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-en-1-one **(Compound 11)** (2.3 mg, 1%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 605.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.37 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.74 - 7.68 (m, 2H), 7.62 - 7.56 (m, 2H), 7.09 (d, $J$ = 2.0 Hz, 1H), 7.02 - 6.99 (m, 2H), 6.88 (d, $J$ = 8.8 Hz, 1H), 6.70 - 6.68 (m, 2H), 4.62 - 4.49 (m, 2H), 4.38 - 4.08 (m, 3H), 3.84 (s, 3H), 3.25 - 3.17 (m, 2H), 3.06 (d, $J$ = 3.6 Hz, 2H), 3.02 - 2.96 (m, 1H), 2.87 - 2.76 (m, 1H), 2.25 - 2.16 (m, 9H).

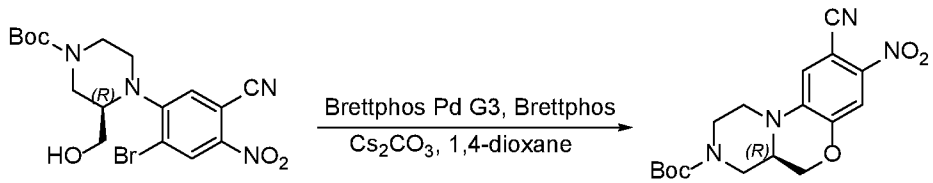
***Example S12: Synthesis of (R,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-en-1-one (Compound 12)***

**[0271]** **Step 1. Synthesis of tert-butyl (3R)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



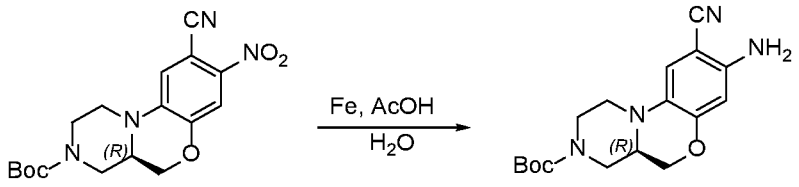

**[0272]** To a solution of 4-bromo-5-fluoro-2-nitrobenzonitrile (1.0 g, 4.08 mmol) in NMP (20.0 mL) was added tert-butyl (3R)-3-(hydroxymethyl)piperazine-1-carboxylate (4.4 g, 20.41 mmol) and DIEA (2.6 g, 20.41 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/$H_2O$ (3/1, v/v) to afford tert-butyl (3R)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.1 g, 61%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.1.

**[0273] Step 2. Synthesis of tert-butyl (R)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



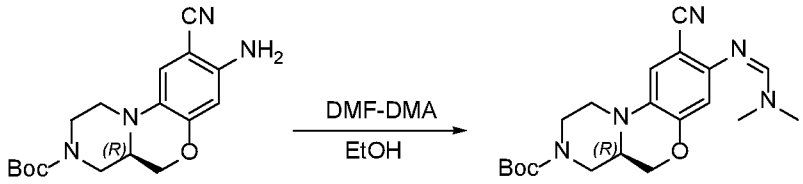

**[0274]** To a solution of tert-butyl (3R)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.1 g, 2.49 mmol) in dioxane (30.0 mL) was added $Cs_2CO_3$ (2.0 g, 6.23 mmol), BrettPhos (535.2 mg, 1.00 mmol) and BrettPhos Pd G3 (451.9 mg, 0.50 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 1 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl (R)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (700.0 mg, 78%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.1.

**[0275] Step 3. Synthesis of tert-butyl (R)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



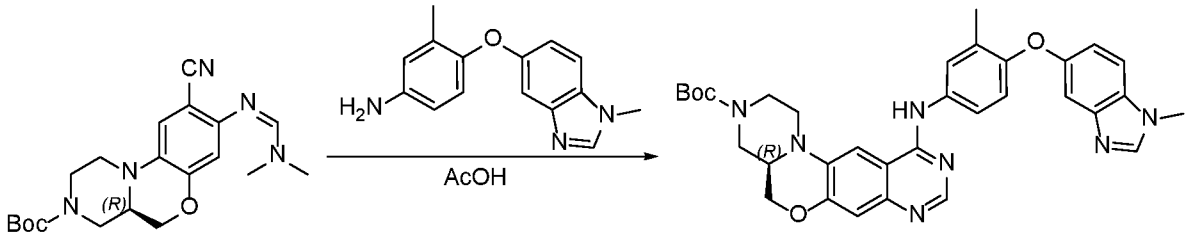

**[0276]** To a solution of tert-butyl (R)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (680.0 mg, 1.89 mmol) in AcOH (10.0 mL) was added Fe (526.9 mg, 9.44 mmol) and water (0.3 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (20/1, v/v) to afford tert-butyl (R)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (500.0 mg, 80%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =331.2.

**[0277] Step 4. Synthesis of tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



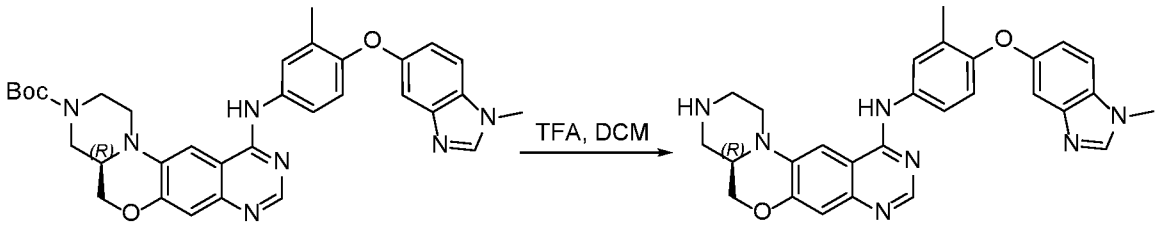

**[0278]** To a solution of tert-butyl (R)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (480.0 mg, 1.45 mmol) in EtOH (10.0 mL) was added DMF-DMA (167.9 mg, 1.41 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (520.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =386.2.

**[0279] Step 5. Synthesis of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**




**[0280]** To a solution of tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (200.0 mg, crude) in AcOH (10.0 mL) was added 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (131.4 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (100.0 mg, 32%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =594.3.

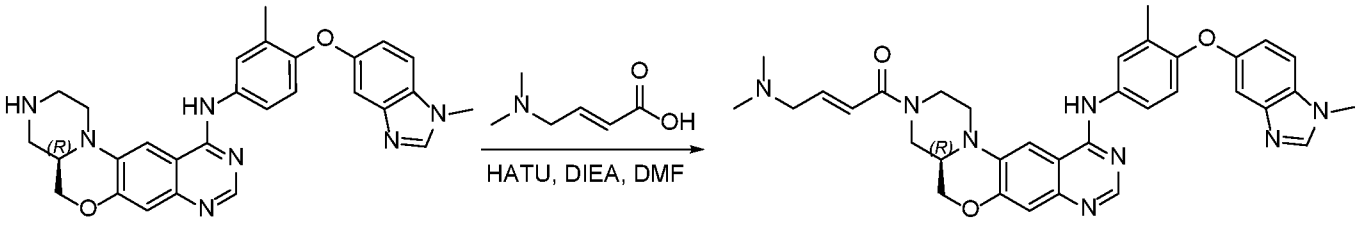
**[0281] Step 6. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine**




**[0282]** To a solution of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (90.0 mg, 0.15 mmol) in DCM (6.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was diluted with $H_2O$. The pH value of the mixture was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-

hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (60.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =494.2.

**[0283] Step 7. Synthesis of (R,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-en-1-one (Compound 12)**

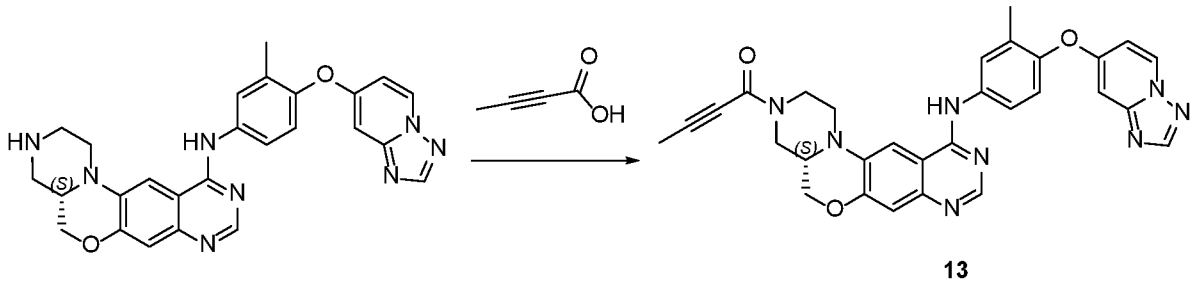



12

**[0284]** To a solution of (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (32.2 mg, 0.19 mmol) in DMF (6.0 mL) was added HATU (92.5 mg, 0.24 mmol), (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (80.0 mg, crude) and DIEA (62.9 mg, 0.47 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash chromatography with acetonitrile/water (3/7, v/v) and then purified by Prep-HPLC with the following condition (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 70% B to 85% B in 12 min; Wave Length: 254 nm) to afford (R,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-en-1-one **(Compound 12)** (10.1 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =605.5. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.37 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 7.74 (d, $J$ = 3.6 Hz, 1H), 7.68 (d, $J$ = 2.4 Hz, 1H), 7.64 - 7.56 (m, 2H), 7.10 (d, $J$ = 2.0 Hz, 1H), 7.02 - 6.99 (m, 2H), 6.87 (d, $J$ = 8.8 Hz, 1H), 6.71 - 6.69 (m, 2H), 4.67 - 4.50 (m, 2H), 4.39 - 4.23 (m, 1H), 4.11 - 4.06 (m, 2H), 3.84 (s, 3H), 3.30 - 3.14 (m, 2H), 3.06 (d, $J$ = 4.4 Hz, 2H), 2.99 - 2.91 (m, 1H), 2.89 - 2.82 (m, 1H), 2.25 (s, 3H), 2.17 (s, 6H).

***Example S13: Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-yn-1-one (Compound 13)***

**[0285] Step 1. Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-yn-1-one (Compound 13)**

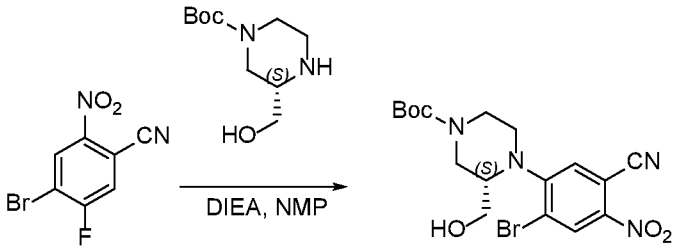


13

**[0286]** To a stirred mixture of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (200.0 mg, 0.42 mmol) and 2-butynoic acid (34.9 mg, 0.42 mmol) in DMF (3.0 mL) was added EDCI (159.6 mg, 0.83 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (60/40, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 8 min; Wave Length: 254 nm) to afford (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-yn-1-one **(Compound 13)** (22.1 mg, 9%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 547.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.43 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.40 - 8.38 (m, 2H), 7.85 - 7.76 (m, 3H), 7.22 - 7.20 (m, 1H), 7.05 - 7.02 (m, 2H), 6.80 (d, $J$ = 2.4 Hz, 1H), 4.56 - 4.42 (m, 3H), 4.19 - 4.08 (m, 2H), 3.53 - 3.44 (m, 1H), 3.20 - 3.14 (m, 0.5H), 3.09 - 2.98 (m, 1H), 2.95 - 2.78 (m, 1H), 2.68 - 2.60 (m, 0.5H), 2.20 (s, 3H), 2.07 (d, $J$ = 1.2 Hz, 3H).

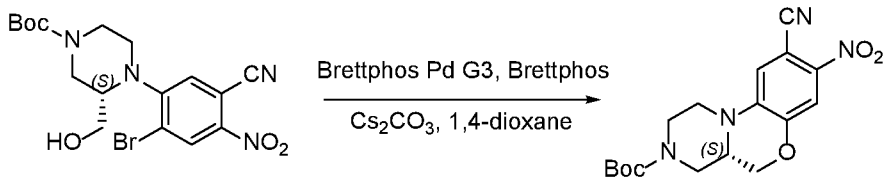
***Example S14: Synthesis of (S)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-yn-1-one (Compound 14)***

**[0287] Step 1. Synthesis of tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



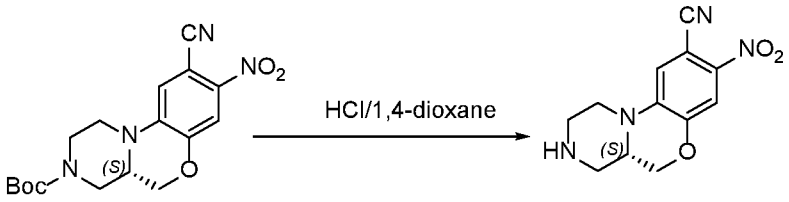

**[0288]** To a solution of 4-bromo-5-fluoro-2-nitrobenzonitrile (4.0 g, 21.79 mmol) in NMP (30.0 mL) was added tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (5.1 g, 23.97 mmol) and DIEA (11.2 g, 87.16 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was cooled to room temperature and diluted with $H_2O$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.8 g, 60%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.1.

**[0289] Step 2. Synthesis of tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



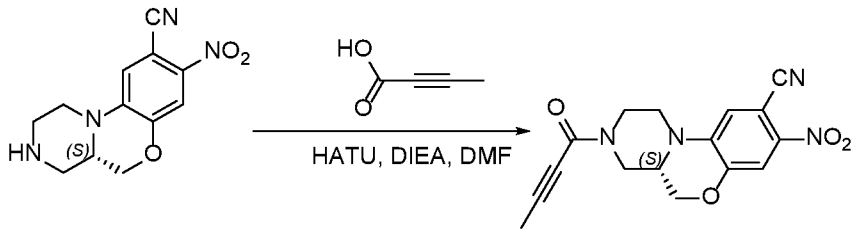

**[0290]** To a solution of tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.8 g, 10.87 mmol) in dioxane (100.0 mL) was added BrettPhos (1.2 g, 2.28 mmol), $Cs_2CO_3$ (10.3 g, 31.87 mmol) and BrettPhos Pd G3 (1.1 g, 1.20 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (2.5 g, 63%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.1.

**[0291] Step 3. Synthesis of (S)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile**



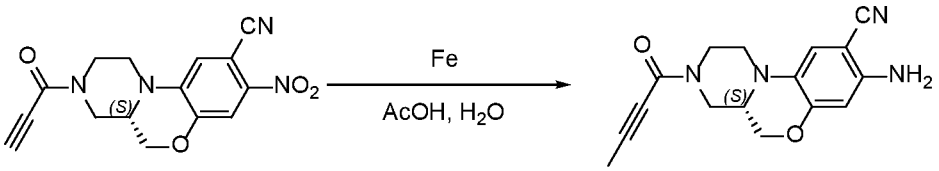

**[0292]** The solution of tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (800.0 mg, 2.22 mmol) in HCl/1,4-dioxane (10.0 mL, 4 mol/L) was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was adjusted pH to 8 with $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (329.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 261.1.

**[0293] Step 4. Synthesis of (S)-3-(but-2-ynoyl)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile**



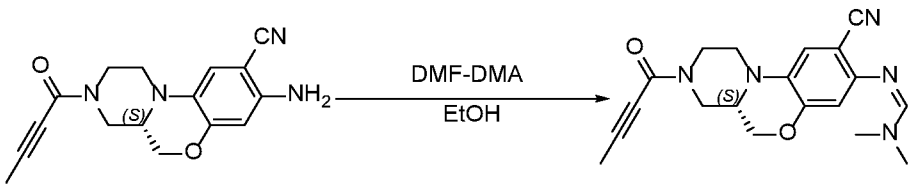

**[0294]** To a solution of (S)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (200.0 mg, 0.76 mmol) in DMF (5.0 mL) was added but-2-ynoic acid (71.0 mg, 0.84 mmol), DIEA (496.6 mg, 3.84 mmol) and HATU (350.6 mg, 0.92 mmol) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-3-(but-2-ynoyl)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (203.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 327.2.

**[0295] Step 5. Synthesis of (S)-8-amino-3-(but-2-ynoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile**



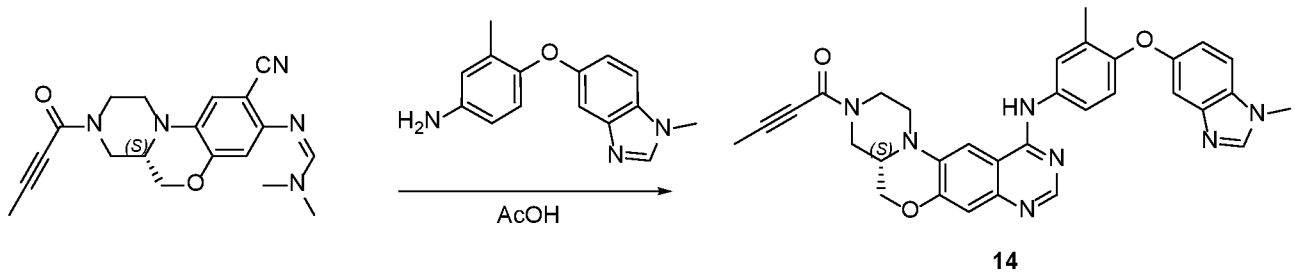

**[0296]** To a solution of (S)-3-(but-2-ynoyl)-8-nitro-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (267.0 mg, 0.81 mmol) in HOAc (10.0 mL) and $H_2O$ (0.5 mL) was added Fe (228.4 mg, 4.09 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) to afford (S)-8-amino-3-(but-2-ynoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile ( 189.0 mg, 78%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =297.1.

**[0297] Step 6. Synthesis of (S,Z)-N'-(3-(but-2-ynoyl)-9-cyano-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide**




**[0298]** To a solution of (S)-8-amino-3-(but-2-ynoyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-9-carbonitrile (179.0 mg, 0.60 mmol) in EtOH (5.0 mL) was added DMF-DMA (359.9 mg, 3.02 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford (S,Z)-N'-(3-(but-2-ynoyl)-9-cyano-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (141.5 mg, crude) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =352.2.

**[0299] Step 7. Synthesis of (S)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-yn-1-one (Compound 14)**

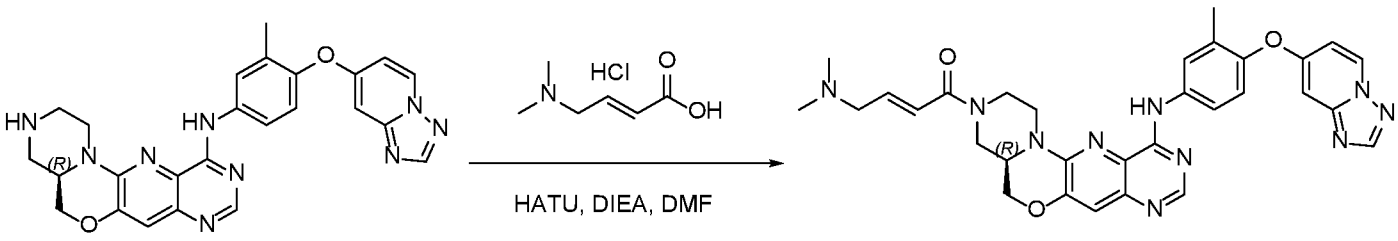



14

**[0300]** To a solution of (S,Z)-N'-(3-(but-2-ynoyl)-9-cyano-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (201.0 mg, 0.57 mmol) in HOAc (5.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (289.7 mg, 1.14 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XSelect CSH Prep C18 OBD Column, 19 x 250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 60% B to 65% B in 14 min; Wave Length: 254 nm) to afford (S)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-3(4H)-yl)but-2-yn-1-one **(Compound 14)** (51.2 mg, 16%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 560.3. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 9.35 (d, $J$ = 6.0 Hz, 1H), 8.35 (d, $J$ = 3.2 Hz, 1H), 8.17 (s, 1H), 7.76 (d, $J$ = 6.4 Hz, 1H), 7.70 - 7.68 (m, 1H), 7.64 - 7.60 (m, 1H), 7.57 (d, $J$ = 8.8 Hz, 1H), 7.10 (d, $J$ = 2.4 Hz, 1H), 7.03 - 6.99 (m, 2H), 6.90 - 6.87 (m, 1H), 4.56 - 4.44 (m, 3H), 4.19 - 4.08 (m, 2H), 3.85 (s, 3H), 3.53 - 3.42 (m, 1H), 3.12 - 2.96 (m, 1H), 2.93 - 2.74 (m, 1H), 2.67 - 2.61 (m, 1H), 2.26 (s, 3H), 2.08 (s, 3H).

***Example S15: Synthesis of (R,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 15)***

**[0301] Step 1. Synthesis of (R,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 15)**

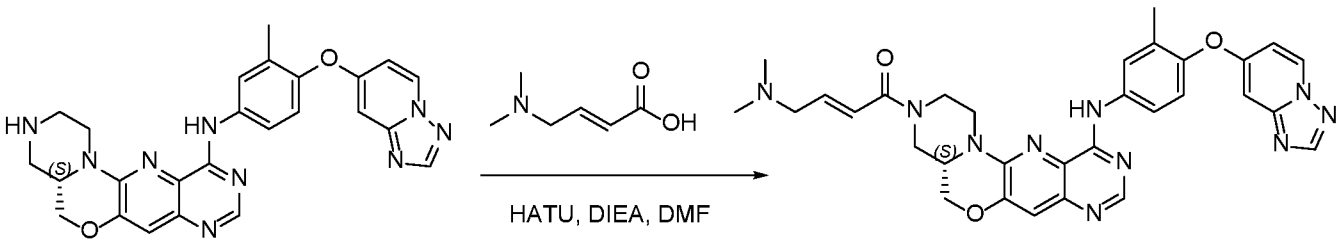



15

**[0302]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (110.0 mg, 0.23 mmol) in DMF (2.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (41.4 mg, 0.25 mmol) DIEA (237.4 mg, 1.84 mmol) and HATU (104.9 mg, 0.28 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (XBridge Shield RP18 OBD Column, 19x250 mm, 10 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 66% B to 72% B in 8 min; Wave Length: 254 nm) to (R,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 15)** (26.2 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 593.5. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.33 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 8.02 - 7.97 (m, 2H), 7.27 - 7.20 (m, 2H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 6.74 - 6.71 (m, 2H), 5.22 - 5.13 (m, 1H), 4.67 - 4.54 (m, 2H), 4.32 - 4.28 (m, 1H), 4.14 - 4.09 (m, 1H), 3.68 - 3.61 (m, 1H), 3.07 - 2.89 (m, 4H), 2.20 (s, 3H), 2.17 (s, 6H).

***Example S16: Synthesis of (S,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 16)***

**[0303] Step 1. Synthesis of (S,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 16)**

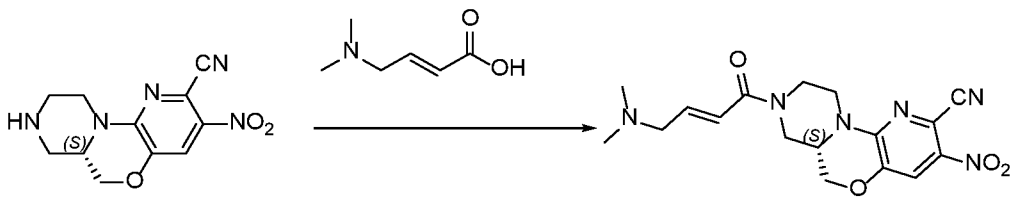



16

**[0304]** To a solution of (2E)-4-(dimethylamino)but-2-enoic acid (35.1 mg, 0.27 mmol) in DMF (5.0 mL) was added (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (119.0 mg, 0.24 mmol) DIEA (159.7 mg, 1.23 mmol) and HATU (112.7 mg, 0.29 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN -----Preparative; Flow rate: 60 mL/min; Gradient: 32% B to 47% B in 8 min; Wave Length: 254 nm) to afford (S,E)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 16)** (20.9 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =593.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.35 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 8.02 - 7.97 (m, 2H), 7.28 (s, 1H), 7.22 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.8 Hz, 1H), 6.74 - 6.67 (m, 2H), 5.21 - 5.13 (m, 1H), 4.68 - 4.56 (m, 2H), 4.35 - 4.19 (s, 1H), 4.15 - 4.10 (m, 1H), 3.69 - 3.58 (m, 1H), 3.08 (d, $J$ = 4.0 Hz, 2H), 3.05 - 2.92 (m, 2H), 2.64 - 2.58 (m, 1H), 2.21 - 2.18 (m, 9H).

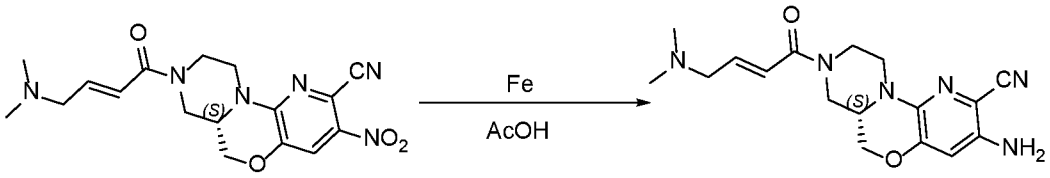
***Example S17: Synthesis of (S,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)but-2-en-1-one (Compound 17)***

**[0305] Step 1. Synthesis of (S,E)-8-(4-(dimethylamino)but-2-enoyl)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**



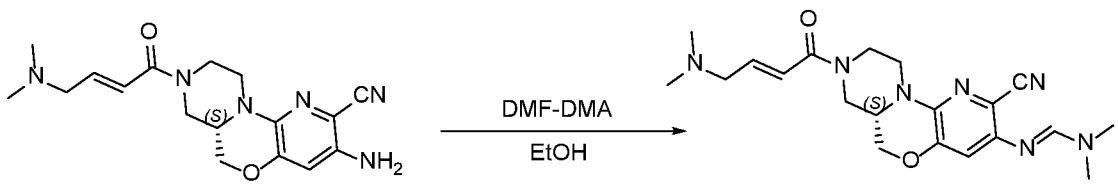
**[0306]** To a stirred mixture of (S)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (300.0 mg, 1.15 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (148.3 mg, 1.145 mmol) in DMF (4.0 mL) was added EDCI (440.3 mg, 2.29 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (70/30, v/v) to afford (S,E)-8-(4-(dimethylamino)but-2-enoyl)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (280.0 mg, 65%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 373.1.

**[0307] Step 2. Synthesis of (S,E)-3-amino-8-(4-(dimethylamino)but-2-enoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**



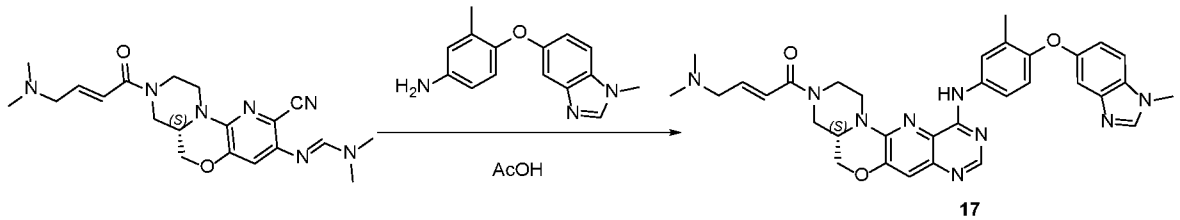

**[0308]** To a stirred mixture of (S,E)-8-(4-(dimethylamino)but-2-enoyl)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (260.0 mg, 0.69 mmol) in acetic acid (10.0 mL) and $H_2O$ (0.6 mL) was added Fe (389.9 mg, 6.98 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (9/1, v/v) to afford (S,E)-3-amino-8-(4-(dimethylamino)but-2-enoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (200.0 mg, 83%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 343.1.

**[0309] Step 3. Synthesis of (E)-N'-((S)-2-cyano-8-((E)-4-(dimethylamino)but-2-enoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**



**[0310]** A mixture of (S,E)-3-amino-8-(4-(dimethylamino)but-2-enoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (180.0 mg, 0.52 mmol) and DMF-DMA (62.6 mg, 0.52 mmol) in ethanol (8.0 mL) was stirred at 90 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford (E)-N'-((S)-2-cyano-8-((E)-4-(dimethylamino)but-2-enoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (200.0 mg, 95%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 398.1.

**[0311] Step 4. Synthesis of (S,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)but-2-en-1-one (Compound 17)**

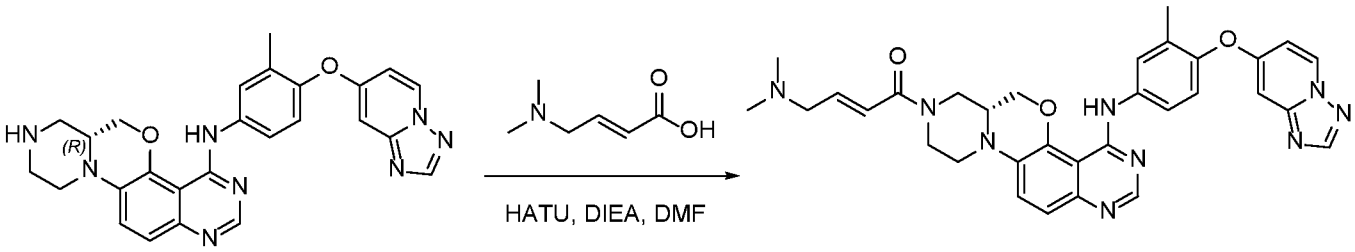



17

**[0312]** A mixture of (E)-N'-((S)-2-cyano-8-((E)-4-(dimethylamino)but-2-enoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (100.0 mg, 0.25 mmol) and 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (63.7 mg, 0.25 mmol) in acetic acid (5.0 mL) was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (60/40, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 42% B in 8 min; Wave Length: 254 nm) to afford (S,E)-4-(dimethylamino)-1-(11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)but-2-en-1-one **(Compound 17)** (6.9 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 606.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.27 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 7.84 - 7.80 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.26 (s, 1H), 7.07 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.90 (d, $J$ = 8.8 Hz, 1H), 6.75 - 6.68 (m, 2H), 5.16 - 5.13 (m, 1H), 4.65 - 4.54 (m, 2H), 4.29 - 4.24 (m, 1H), 4.13 - 4.08 (m, 1H), 3.84 (s, 3H), 3.68 - 3.53 (m, 1H), 3.07 - 2.85 (m, 5H), 2.24 (s, 3H), 2.16 (s, 6H).

***Example S18: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 18)***

**[0313] Step 1. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 18)**

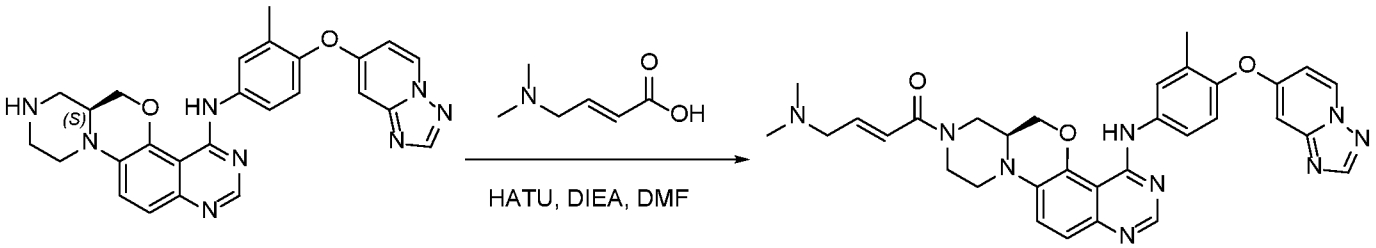



18

**[0314]** To a mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (150.0 mg, 0.31 mmol) in DMF (6.0 mL) was added HATU (189.9 mg, 0.49 mmol), (E)-4-(dimethylamino)but-2-enoic acid (80.5 mg, 0.62 mmol) and DIEA (403.5 mg, 3.10 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by reverse phase flash chromatography with ACN/$H_2O$ (52/48, v/v) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 18)** (35.0 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 592.3. $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.75 (d, $J$ = 8.0 Hz, 1H), 8.38 - 8.30 (m, 2H), 7.80 - 7.77 (m, 2H), 7.64 - 7.62 (m, 1H), 7.39 - 7.36 (m, 1H), 7.19 - 7.17 (m, 1H), 7.10 - 7.07 (m, 1H), 6.88 - 6.83 (m, 3H), 4.85 - 4.66 (m, 2H), 4.38 - 4.27 (m, 2H), 4.10 - 4.07 (m, 1H), 3.53 - 3.49 (m, 2H), 3.23 - 3.01 (m,1H), 2.92 - 2.72 (m, 2H), 2.55 (s, 6H), 2.26 (s, 3H).

***Example S19: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one formate (Compound 19)***

**[0315] Step 1. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one formate (Compound 19)**

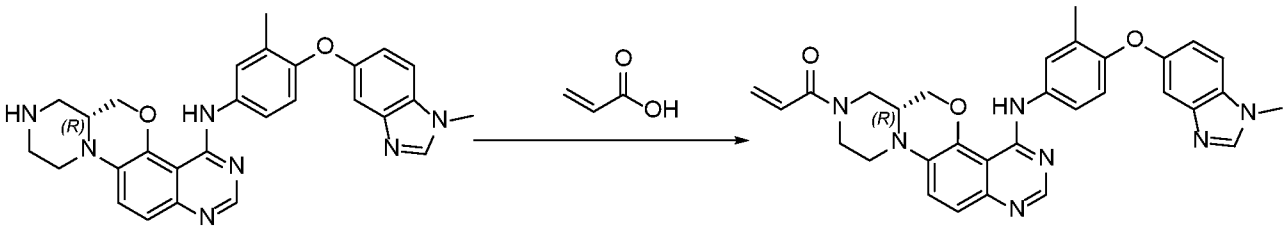



19

**[0316]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (24.0 mg, 0.05 mmol) in DMF (3.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid (12.9 mg, 0.1 mmol), DIEA (32.2 mg, 0.25 mmol) and HATU (30.3 mg, 0.08 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 0.5 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3OH/H_2O$ (80/20, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 20% B in 10 min; Wave Length: 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one formate **(Compound 19)** (3.3 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 592.3. $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.75 (d, $J$ = 7.6 Hz, 1H), 8.50 (s, 1H), 8.34 - 8.30 (m, 2H), 7.80 - 7.77 (m, 2H), 7.64 - 7.62 (m, 1H), 7.38 (d, $J$ = 8.8 Hz, 1H), 7.18 (d, $J$ = 8.4 Hz, 1H), 7.10 - 7.07 (m, 1H), 6.88 - 6.78 (m, 3H), 4.79 - 4.66 (m, 2H), 4.38 - 4.27 (m, 2H), 4.10 - 4.07 (m, 1H), 3.50 - 3.44 (m, 2H), 3.20 - 3.05 (m, 1H), 2.92 - 2.78 (m, 2H), 2.55 (s, 6H), 2.26 (s, 3H).

***Example S20: Synthesis of (R)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 20)***

**[0317] Step 1. Synthesis of (R)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 20)**

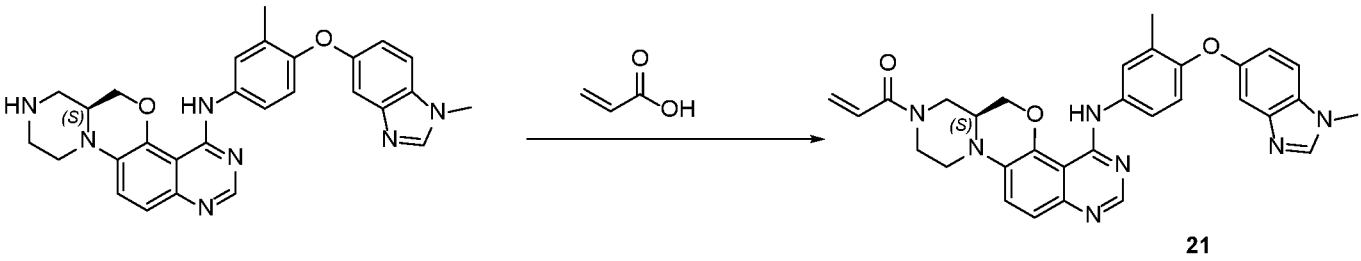


**20**

**[0318]** To a stirred mixture of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (80.0 mg, 0.16 mmol) and acrylic acid (11.6 mg, 0.16 mmol) in pyridine (4.0 mL) was added EDCI (62.1 mg, 0.32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (70/30, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 42% B in 8 min; Wave Length: 254 nm) to afford (R)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one **(Compound 20)** (5.2 mg, 5%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 548.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.82 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.70 - 7.62 (m, 3H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.31 (d, $J$ = 9.2 Hz, 1H), 7.09 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.96 - 6.87 (m, 2H), 6.21 - 6.16 (m, 1H), 5.77 - 5.74 (m, 1H), 4.79 - 4.73 (m, 1H), 4.58 - 4.49 (m, 1H), 4.29 - 4.18 (m, 2H), 4.07 - 4.01 (m, 1H), 3.84 (s, 3H), 3.27 - 3.19 (m, 1H), 3.10 - 2.88 (m, 1H), 2.83 - 2.64 (m, 2H), 2.25 (s, 3H).

***Example S21: Synthesis of (S)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 21)***

**[0319] Step 1. Synthesis of (S)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one (Compound 21)**

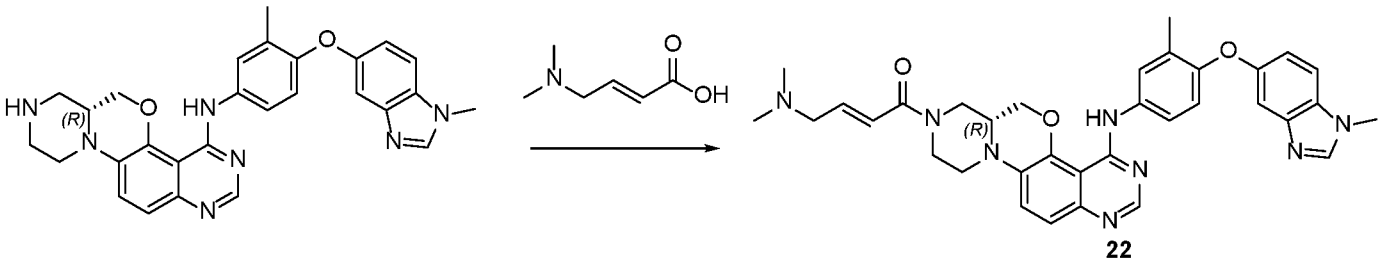



21

**[0320]** To a stirred mixture of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (80.0 mg, 0.16 mmol) and acrylic acid (11.6 mg, 0.16 mmol) in pyridine (4.0 mL) was added EDCI (62.1 mg, 0.32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (70/30, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 42% B in 8 min; Wave Length: 254 nm) to afford (S)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)prop-2-en-1-one **(Compound 21)** (21.4 mg, 24%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 548.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.81 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.70 - 7.62 (m, 3H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.31 (d, $J$ = 8.8 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.86 (m, 3H), 6.20 - 6.16 (m, 1H), 5.77 - 5.74 (m, 1H), 4.78 - 4.73 (m, 1H), 4.54 - 4.51 (m, 1H), 4.28 - 4.21 (m, 2H), 4.09 - 4.03 (m, 1H), 3.84 (s, 3H), 3.27 - 3.17 (m, 1H), 3.10 - 2.89 (m, 1H), 2.82 - 2.64 (m, 2H), 2.24 (s, 3H).

***Example S22: Synthesis of (R,E)-4-(dimethylamino)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)but-2-en-1-one (Compound 22)***

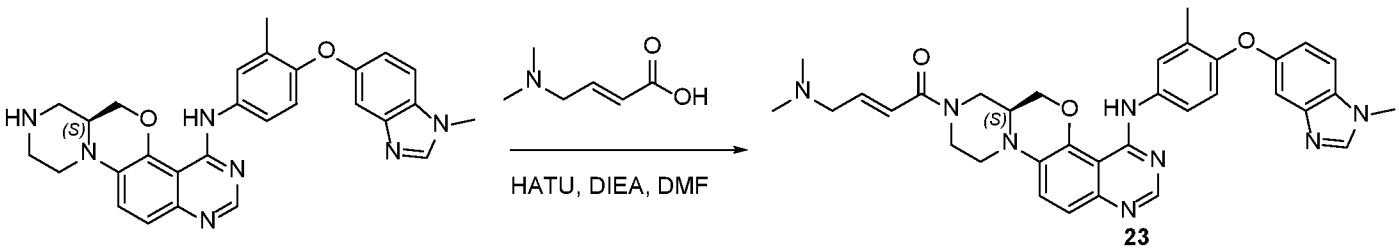
**[0321] Step 1. Synthesis of (R,E)-4-(dimethylamino)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)but-2-en-1-one (Compound 22)**




**[0322]** To a stirred mixture of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (120.0 mg, 0.24 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (31.4 mg, 0.24 mmol) in DMF (4.0 mL) was added DIEA (125.6 mg, 0.97 mmol) and HATU (184.9 mg, 0.48 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (70/30, v/v) and then purified by Prep-HPLC with the following conditions Column: (XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 8 min; Wave Length: 254 nm) to afford (R,E)-4-(dimethylamino)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)but-2-en-1-one **(Compound 22)** (20.8 mg, 13%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ = 605.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.82 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.71 - 7.54 (m, 4H), 7.31 (d, $J$ = 8.8 Hz, 1H), 7.09 (d, $J$ = 2.4 Hz, 1H), 7.01 - 6.97 (m, 1H), 6.88 (d, $J$ = 8.4 Hz, 1H), 6.74 - 6.63 (m, 2H), 4.78 - 4.74 (m, 1H), 4.53 - 3.37 (m, 1H), 4.29 - 4.20 (m, 2H), 4.06 - 4.02 (m, 1H), 3.84 (s, 3H), 3.29 - 3.23 (m, 2H), 3.05 (d, $J$ = 4.4 Hz, 2H), 2.95 - 2.57 (m, 2H), 2.25 (s, 3H), 2.15 (s, 6H).

***Example S23: Synthesis of (S,E)-4-(dimethylamino)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)but-2-en-1-one (Compound 23)***

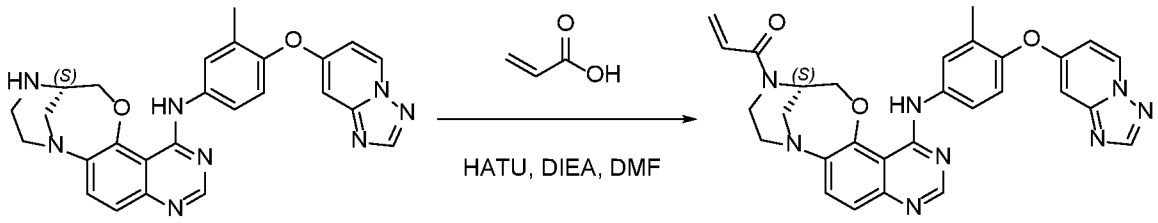
**[0323] Step 1. Synthesis of (S,E)-4-(dimethylamino)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)but-2-en-1-one (Compound 23)**




**[0324]** A mixture of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (150.0 mg, 0.30 mmol), (2E)-4-(dimethylamino)but-2-enoic acid (117.7 mg, 0.91 mmol), HATU (288.9 mg, 0.76 mmol) and DIEA (196.4 mg, 1.52 mmol) in DMF (10.0 mL) was stirred at room temperature for 1h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19×250 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 75% B to 85% B in 10 min, 220 nm) to afford (S,E)-4-(dimethylamino)-1-(4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)but-2-en-1-one **(Compoun 23)** (24.6 mg, 13%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 605.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.82 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.70 - 7.62 (s, 3H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.31 (d, $J$ = 9.2 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.88 (d, $J$ = 8.8 Hz, 1H), 6.73 - 6.64 (m, 2H), 4.77 - 4.73 (m, 1H), 4.53 - 4.45 (m, 1H), 4.29 - 4.24 (m, 2H), 4.07 - 4.02 (m, 1H), 3.84 (s, 3H), 3.29 - 3.18 (s, 2H), 3.06 (d, $J$ = 4.4 Hz, 2H), 2.91 - 2.76 (m, 1H), 2.25 (s, 3H), 2.17 (s, 6H).

***Example S24: Synthesis of 1-((3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 24)***

**[0325] Step 1. Synthesis of 1-((3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 24)**

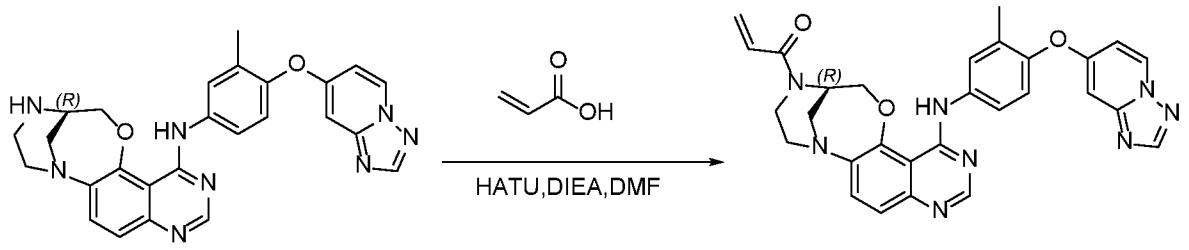



**24**

**[0326]** To a solution of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (100.0 mg, 0.21 mmol) in DMF (5.0 mL) was added acrylic acid (15.0 mg, 0.20 mmol), DIEA (270.9 mg, 2.10 mmol) and HATU (79.8 mg, 0.23 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (65/35, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 8 min; Wave Length: 254 nm) to afford 1-((3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one **(Compound 24)** (6.1 mg, 5%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 535.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.14 - 10.10 (m, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.00 - 7.91 (m, 1H), 7.88 - 7.80 (m, 1H), 7.61 (d, $J$ = 9.2 Hz, 1H), 7.43 (d, $J$ = 9.2 Hz, 1H), 7.23 - 7.20 (m, 1H), 7.04 - 7.02 (m, 1H), 6.85 - 6.77 (m, 2H), 6.18 - 6.14 (m, 1H), 5.75 - 5.73 (m, 1H), 5.11 - 4.72 (m, 2H), 4.46 - 4.38 (m, 1H), 4.18 - 4.08 (m, 1H), 3.89 - 3.69 (m, 2H), 2.21 (s, 3H).

***Example S25: Synthesis of 1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 25)***

**[0327] Step 1. Synthesis of 1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 25)**

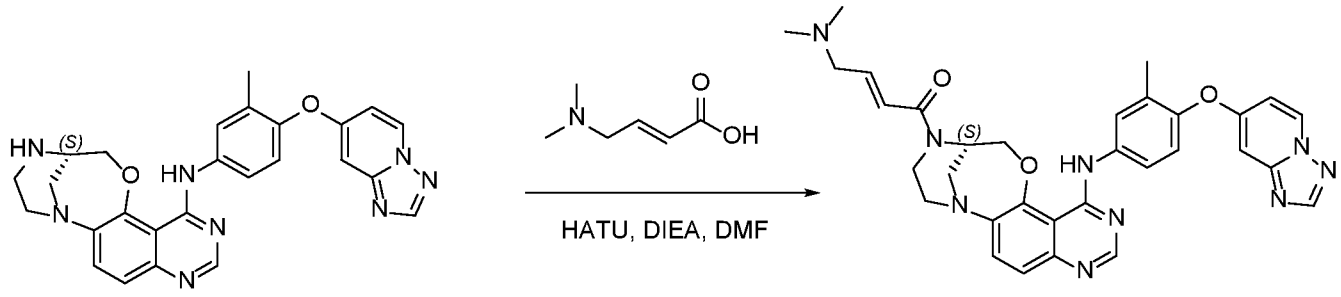



**25**

**[0328]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (100.0 mg, 0.21 mmol) in DMF (8.0 mL) was added acrylic acid (16.5 mg, 0.23 mmol), HATU (95.0 mg, 0.25 mmol) and DIEA (269.0 mg, 2.08 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 8 min; Wave Length: 254 nm) to afford 1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one **(Compound 25)** (15.3 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 535.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.13 - 10.10 (m, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.00 - 7.91 (m, 1H), 7.85 - 7.83 (m, 1H), 7.60 (d, $J$ = 9.2 Hz, 1H), 7.43 (d, $J$ = 9.2 Hz, 1H), 7.23 - 7.19 (m, 1H), 7.04 - 7.02 (m, 1H), 6.84 - 6.77 (m, 2H), 6.18 - 6.14 (m, 1H), 5.75 - 5.73 (m, 1H), 5.08 - 4.74 (m, 2H), 4.43 - 4.40 (m, 1H), 4.19 - 4.08 (m, 1H), 3.81 - 3.68 (m, 2H), 3.41 - 3.37 (m, 1H), 3.25 - 3.17 (m, 1H), 2.21 (s, 3H).

***Example S26: Synthesis of (E)-1-((3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 26)***

**[0329] Step 1. Synthesis of (E)-1-((3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 26)**

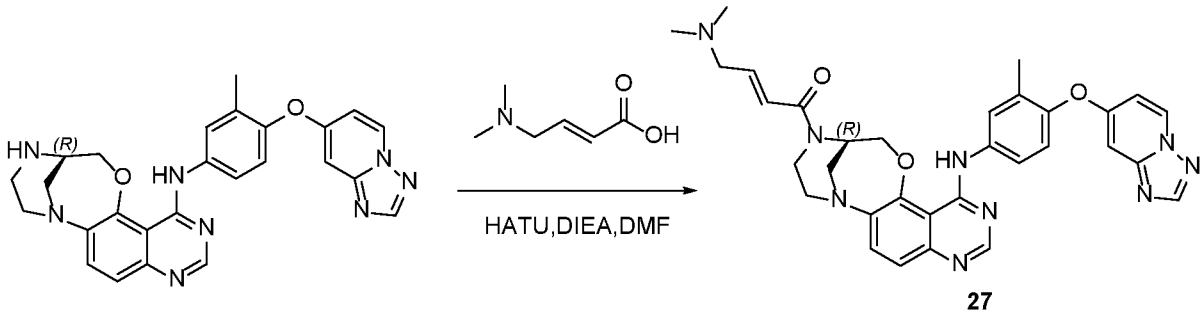



26

**[0330]** To a solution of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (92.4 mg, 0.19 mmol) in DMF (5.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid (29.8 mg, 0.23 mmol), DIEA (248.5 mg, 1.92 mmol) and HATU (109.6 mg, 0.28 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at 0 °C for 30 min. After the reaction was completed, the mixture was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 50% B in 8 min; Wave Length: 254 nm) to afford (E)-1-((3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 26)** (11.3 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 592.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.13 - 10.09 (m, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.00 - 7.90 (m, 1H), 7.85 (s, 1H), 7.60 (d, $J$ = 9.2 Hz, 1H), 7.43 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 7.23 - 7.20 (m, 1H), 6.79 (d, $J$ = 2.8 Hz, 1H), 6.70 - 6.57 (m, 2H), 5.09 - 5.02 (m, 2H), 4.72 - 4.41 (m, 1H), 4.17 - 4.07 (m, 1H), 3.80 - 3.68 (m, 2H), 3.07 - 3.03 (m, 2H), 2.21 - 2.15 (m, 9H).

***Example S27: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 27)***

**[0331] Step 1. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 27)**

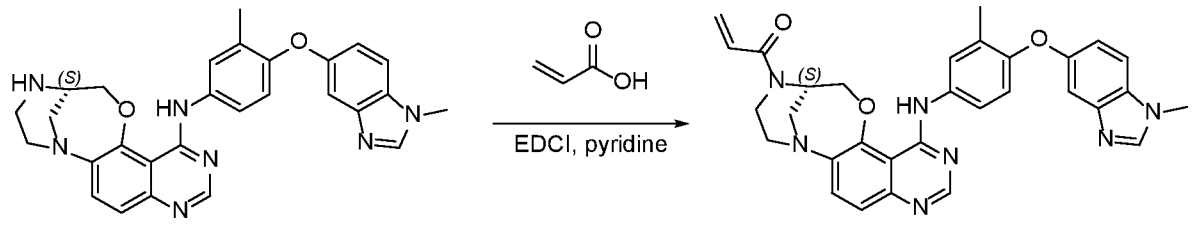



27

**[0332]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (34.0 mg, 0.07 mmol) in DMF (5.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid (10.1 mg, 0.08 mmol), HATU (32.3 mg, 0.09 mmol) and DIEA (91.5 mg, 0.71 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 35% B in 8 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 27)** (11.8 mg, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 592.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.14 - 10.09 (m, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.00 - 7.90 (m, 1H), 7.85 (s, 1H), 7.60 (d, $J$ = 8.8 Hz, 1H), 7.43 (d, $J$ = 9.2 Hz, 1H), 7.23 - 7.19 (m, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 6.67 - 6.61 (m, 2H), 5.09 - 4.73 (m, 2H), 4.46 - 4.38 (m, 1H), 4.20 - 4.07 (m, 1H), 3.83 - 3.70 (m, 2H), 3.05 - 3.03 (m, 2H), 2.21 - 2.15 (m, 9H).

***Example S28: Synthesis of 1-((3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 28)***

**[0333] Step 1. Synthesis of 1-((3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 28)**

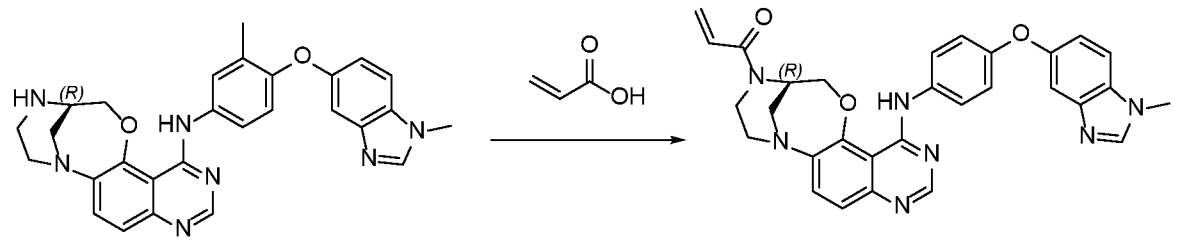



**28**

**[0334]** To a solution of (3S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (150.0 mg, 0.30 mmol) and acrylic acid (21.9 mg, 0.30 mmol) in pyridine (2.0 mL) was added EDCI (116.5 mg, 0.61 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 50% B in 8 min; Wave Length: 254 nm) to afford 1-((3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one **(Compound 28)** (30.2 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 548.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.02 - 9.98 (m, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 7.79 - 7.71 (m, 2H), 7.59 - 7.55 (m, 2H), 7.40 (d, $J$ = 8.8 Hz, 1H), 7.08 (s, 1H), 6.99 (d, $J$ = 8.8 Hz, 1H), 6.88 - 6.77 (m, 2H), 6.17 - 6.13 (m, 1H), 5.74 - 5.71 (m, 1H), 5.06 - 4.73 (m, 2H), 4.44 - 4.35 (m, 1H), 4.18 - 4.06 (m, 2H), 3.84 (s, 3H), 3.81 - 3.66 (m, 2H), 3.39 - 3.33 (m, 1H), 3.23 - 3.15 (m, 1H), 2.24 (s, 3H).

***Example S29: Synthesis of 1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 29)***

**[0335] Step 1. Synthesis of 1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one (Compound 29)**

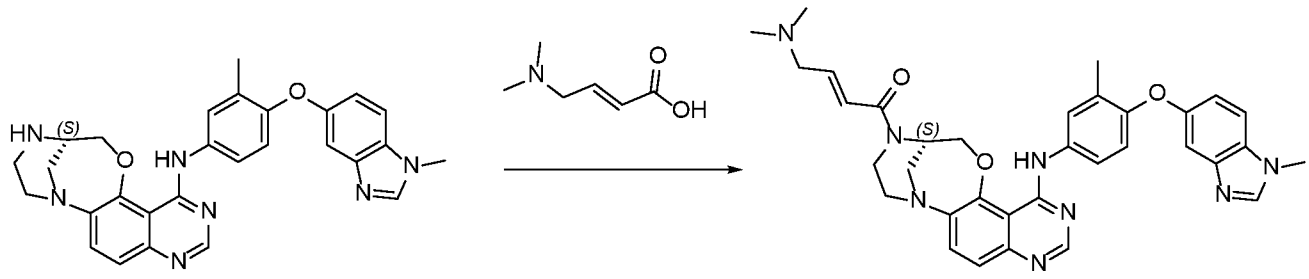


29

**[0336]** To a solution of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (155.0 mg, 0.31 mmol) in pyridine (3.0 mL) were added acrylic acid (45.3 mg, 0.63 mmol) and EDCI (120.4 mg, 0.63 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 50% B in 8 min; Wave Length: 254 nm) to afford 1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)prop-2-en-1-one **(Compound 29)** (47.5 mg, 27%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 548.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.05 - 9.98 (m, 1H), 8.42 (s, 1H), 8.17 (s, 1H), 7.79 - 7.71 (m, 2H), 7.60 - 7.55 (m, 2H), 7.41 - 7.38 (m, 1H), 7.08 (d, $J$ = 2.4 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.89 - 6.76 (m, 2H), 6.15 (d, $J$ = 15.0 Hz, 1H), 5.75 - 5.71 (m, 1H), 5.05 - 4.71 (m, 2H), 4.44 - 4.36 (m, 1H), 4.18 - 4.05 (m, 2H), 3.83 (s, 3H), 3.79 - 3.65 (m, 2H), 3.43 - 3.33 (m, 1H), 3.22 - 3.15 (m, 1H), 2.24 (s, 3H).

***Example S30: Synthesis of (E)-4-(dimethylamino)-1-((3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 30)***

**[0337] Step 1. Synthesis of (E)-4-(dimethylamino)-1-((3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 30)**

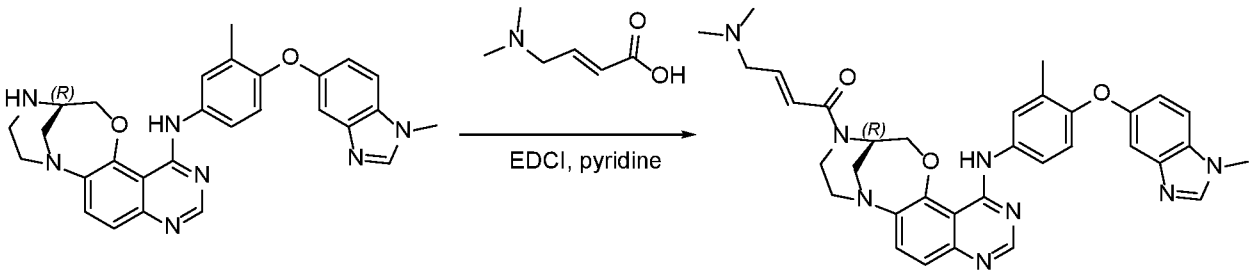


30

**[0338]** To a mixture of (3S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (150.0 mg, 0.30 mmol) and (E)-4-(dimethylamino)but-2-enoic acid (39.2 mg, 0.30 mmol) in pyridine (2.0 mL) was added EDCI (116.5 mg, 0.61 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure The residue was purified by Prep-HPLC with the following conditions: (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 35% B to 45% B in 12 min; Wave Length: 254 nm) to afford (E)-4-(dimethylamino)-1-((3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one **(Compound 30)** (17.2 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 605.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.04 - 9.98 (m, 1H), 8.42 (s, 1H), 8.17 (s, 1H), 7.82 - 7.69 (m, 2H), 7.59 - 7.55 (m, 2H), 7.40 (d, $J$ = 8.8 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.91 - 6.85 (m, 1H), 6.69 - 6.54 (m, 2H), 5.10 - 4.69 (m, 2H), 4.46 - 4.34 (m, 1H), 4.21 - 4.02 (m, 1H), 3.84 (s, 3H), 3.82 - 3.63 (m, 2H), 3.49 - 3.36 (m, 1H), 3.24 - 3.12 (m, 1H), 3.04 (d, $J$ = 4.0 Hz, 2H), 2.25 (s, 3H), 2.16 - 2.14 (m, 6H).

***Example S31: Synthesis of (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 31)***

**[0339] Step 1. Synthesis of (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 31)**

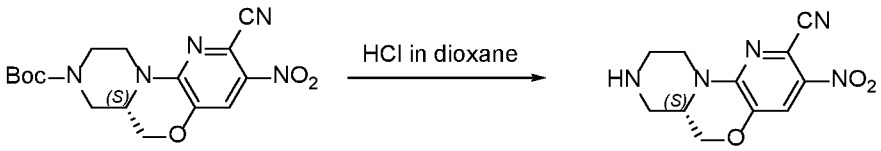



31

**[0340]** To a solution of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (200.0 mg, 0.40 mmol) in pyridine (4.0 mL) were added (E)-4-(dimethylamino)but-2-enoic acid (104.6 mg, 0.81 mmol) and EDCI (155.4 mg, 0.81 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 37% B in 8 min; Wave Length: 254 nm) to afford (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one **(Compound 31)** (23.8 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 605.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.07 - 9.97 (m, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 7.78 - 7.71 (m, 2H), 7.64 - 7.55 (m, 2H), 7.39 (d, $J$ = 8.8 Hz, 1H), 7.07 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.89 - 6.85 (m, 1H), 6.68 - 6.56 (m, 2H), 5.09 - 4.73 (m, 2H), 4.44 - 4.36 (m, 1H), 4.19 - 4.06 (m, 2H), 3.84 (s, 3H), 3.78 - 3.64 (m, 2H), 3.43 - 3.38 (m, 1H), 3.22 - 3.14 (m, 1H), 3.04 - 3.02 (m, 2H), 2.24 (s, 3H), 2.16 - 2.14 (m, 6H).

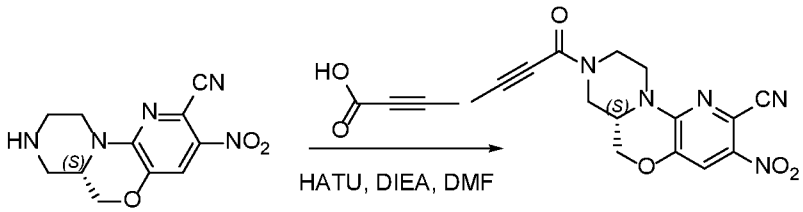
***Example S32: Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)but-2-yn-1-one (Compound 32)***

**[0341]** **Step 1. Synthesis of (S)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**



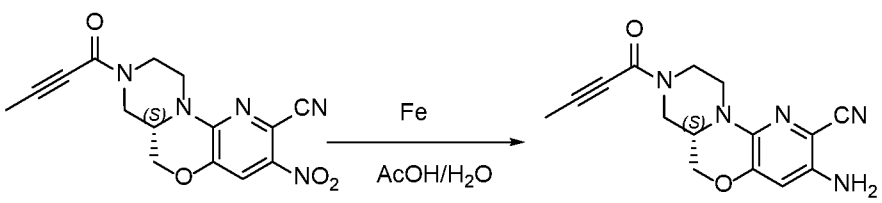
**[0342]** The solution of tert-butyl (S)-2-cyano-3-nitro-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (510.0 mg, 1.41 mmol) in HCl/1,4-dioxane (3.0 mL, 4 mol/L) was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was adjusted pH to 8 with $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (270.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 262.1.

**[0343] Step 2. Synthesis of (S)-8-(but-2-ynoyl)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**



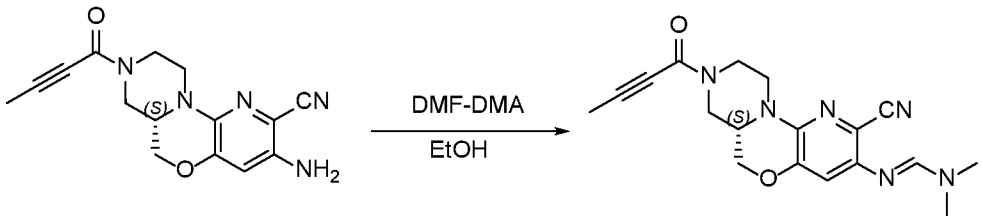

**[0344]** To a solution of (S)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (270.0 mg, crude) in DMF (5.0 mL) was added 2-butynoic acid (95.6 mg, 1.14 mmol), DIEA (1.1 g, 8.27 mmol) and HATU (471.6 mg, 1.24 mmol) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-8-(but-2-ynoyl)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (265.0 mg, 78%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =328.1.

**[0345] Step 3. Synthesis of (S)-3-amino-8-(but-2-ynoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**



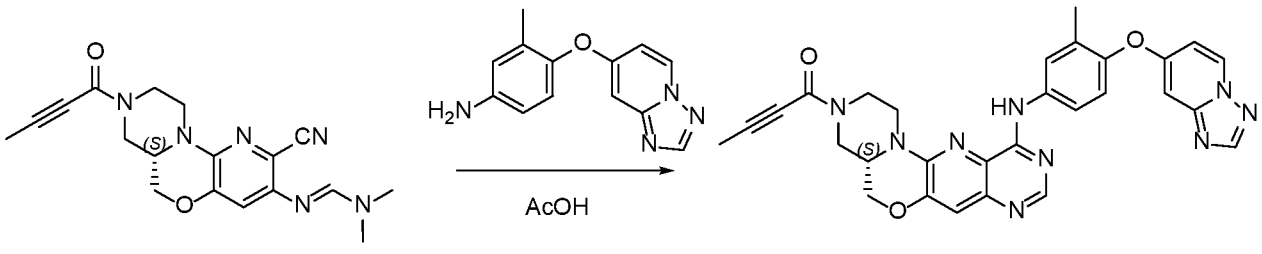
**[0346]** To a solution of (S)-8-(but-2-ynoyl)-3-nitro-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (260.0 mg, 0.80 mmol) in AcOH (10.0 mL) and $H_2O$ (0.5 mL) was added Fe (221.8 mg, 3.97 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) to afford (S)-3-amino-8-(but-2-ynoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (160.0 mg, 87%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =298.1.

**[0347] Step 4. Synthesis of (S,E)-N'-(8-(but-2-ynoyl)-2-cyano-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**




**[0348]** To a solution of (S)-3-amino-8-(but-2-ynoyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (150.0 mg, 0.50 mmol) in EtOH (5.0 mL) was added DMF-DMA (300.6 mg, 2.53 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (45/55, v/v) to afford (S,E)-N'-(8-(but-2-ynoyl)-2-cyano-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (139.0 mg, 78%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =353.2.

**[0349] Step 5. Synthesis of (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)but-2-yn-1-one (Compound 32)**

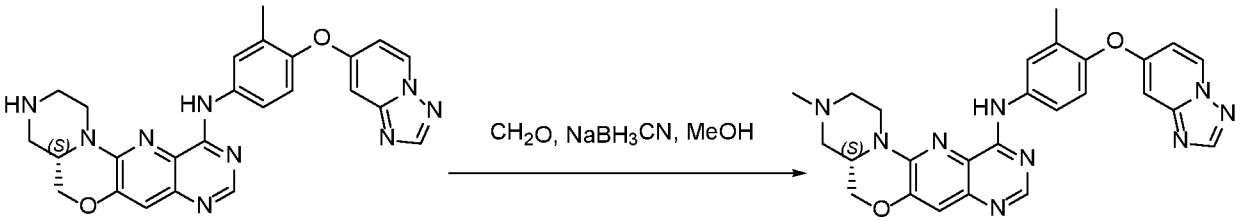



**32**

**[0350]** To a solution of (S,E)-N'-(8-(but-2-ynoyl)-2-cyano-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (139.0 mg, 0.39 mmol) in AcOH (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (189.5 mg, 0.79 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 41% B in 8 min; Wave Length: 254 nm) to afford (S)-1-(11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-3(4H)-yl)but-2-yn-1-one **(Compound 32)** (42.4 mg, 19%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 548.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.35 - 9.32 (m, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.43 - 8.38 (m, 2H), 8.05 - 7.97 (m, 2H), 7.29 (s, 1H), 7.23 -7.21 (m, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 5.24 - 5.21 (m, 1H), 4.58 - 4.41 (m, 3H), 4.15 - 4.12 (m, 1H), 3.74 - 3.51 (m, 1H), 3.18 - 2.84 (m, 2H), 2.72 - 2.66 (m, 1H), 2.21 (s, 3H), 2.08 (s, 3H).

***Example S33: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 33)***

**[0351]** **Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 33)**



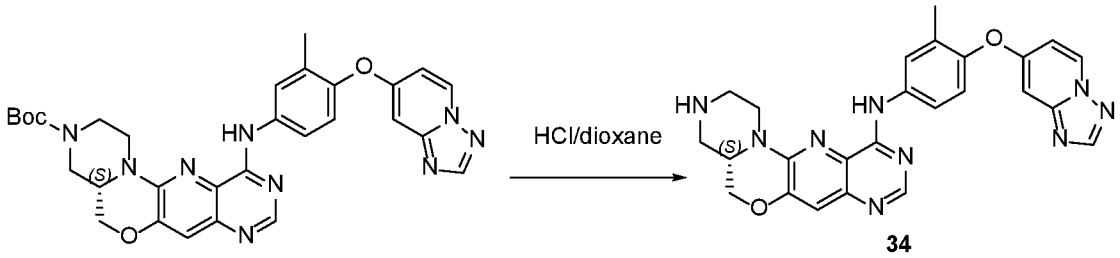

**33**

**[0352]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (100.0 mg, 0.21 mmol) in MeOH/THF (2.0 mL/12.0 mL) was added HCHO (156.0 mg, 30%) at room temperature. The resulting mixture was stirred at 0 °C for 1 h. To the above mixture was

added $NaBH_3CN$ (58.7 mg, 0.94 mmol) at 0 °C. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was quenched with $H_2O$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 42% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 33)** (23.3 mg, 22%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =496.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.30 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.41 - 8.38 (m, 2H), 8.02 - 7.97 (m, 2H), 7.23 - 7.20 (m, 2H), 7.04 - 7.01 (m, 1H), 6.78 (d, $J$ = 2.8 Hz, 1H), 5.05 - 5.02 (m, 1H), 4.48 - 4.44 (m, 1H), 4.09 - 4.04 (m, 1H), 3.66 - 3.61 (m, 1H), 2.98 - 2.91 (m, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 2.13 - 2.07 (m, 1H), 1.78 - 1.70 (m, 1H).

***Example S34: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 34)***

**[0353] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 34)**



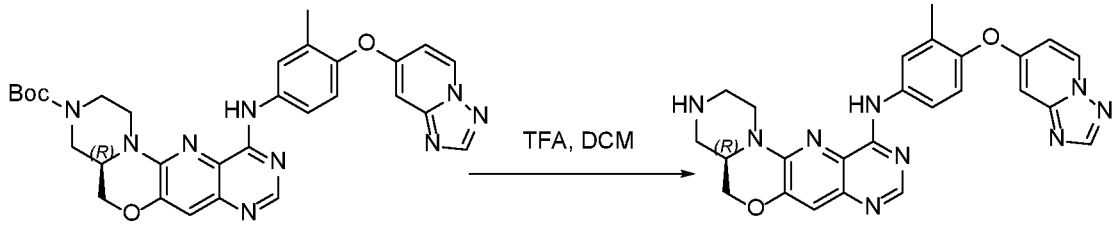

**34**

**[0354]** A solution of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (90.0 mg, 0.16 mmol) in HCl/1,4-dioxane (15.0 mL, 4 mol/L) was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with aq. $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was

washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 34)** (19.3 mg, 26%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =482.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.27 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.40 - 8.38 (m, 2H), 8.02 - 7.97 (m, 2H), 7.21 - 7.15 (m, 2H), 7.04 - 7.02 (m, 1H), 6.79 - 6.71 (m, 1H), 4.98 - 4.95 (m, 1H), 4.44 - 4.41 (m, 1H), 4.04 - 3.97 (m, 1H), 3.52 - 3.47 (m, 1H), 3.11 - 3.01 (m, 2H), 2.84 - 2.69 (m, 3H), 2.39 - 2.33 (m, 1H), 2.20 (s, 3H).

***Example S35: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 35)***

**[0355] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 35)**



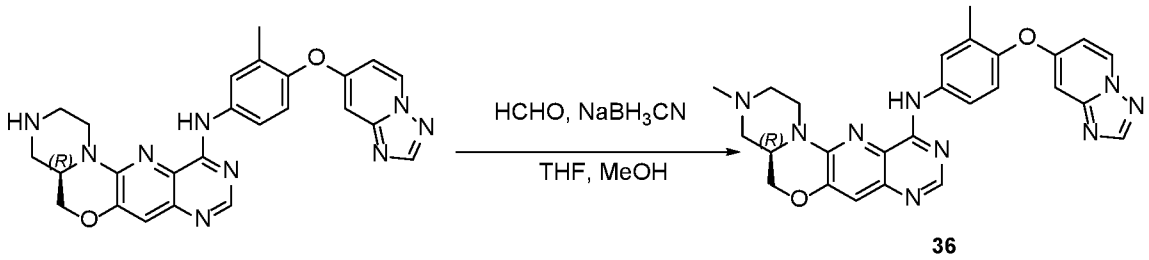

35

**[0356]** To a solution of tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (240.0 mg, 0.41 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with aq. $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (46/54, v/v) and

then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 35)** (19.2 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.27 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.40 - 8.38 (m, 2H), 8.02 - 7.97 (m, 2H), 7.21 - 7.19 (m, 2H), 7.04 - 7.02 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 4.98 - 4.95 (m, 1H), 4.44 - 4.41 (m, 1H), 4.04 - 3.99 (m, 1H), 3.52 - 3.47 (m, 1H), 3.11 - 3.01 (m, 2H), 2.81 - 2.68 (m, 2H), 2.39 - 2.36 (m, 1H), 2.19 (s, 3H).

***Example S36: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 36)***

**[0357] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 36)**



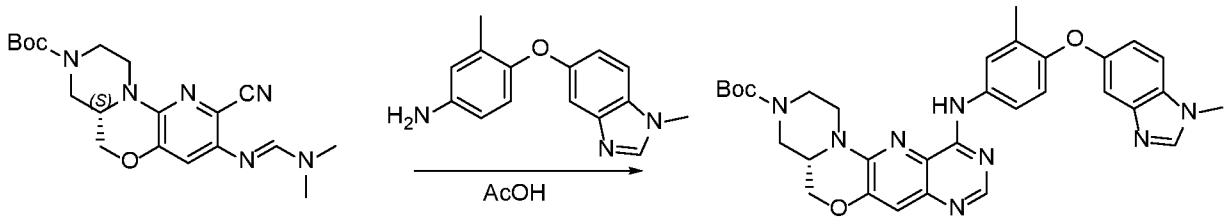

36

**[0358]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (80.0 mg, 0.17 mmol) in THF/MeOH (8.0 mL/2.0 mL) was added HCHO (124.7 mg, 30%) at room temperature. The mixture was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (47.0 mg, 0.75 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 41% B in 8 min; Wave Length: 254

nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 36)** (29.7 mg, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 496.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.31 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.40 - 8.37 (m, 2H), 8.00 - 7.96 (m, 2H), 7.23 - 7.19 (m, 2H), 7.03 - 7.01 (m, 1H), 6.77 (s, 1H), 5.04 - 5.01 (m, 1H), 4.46 - 4.42 (m, 1H), 4.08 - 4.02 (m, 1H), 3.65 - 3.58 (m, 1H), 2.97 - 2.90 (m, 3H), 2.27 (s, 3H), 2.19 (s, 3H), 2.12 - 2.09 (m, 1H), 1.78 - 1.73 (m, 1H).

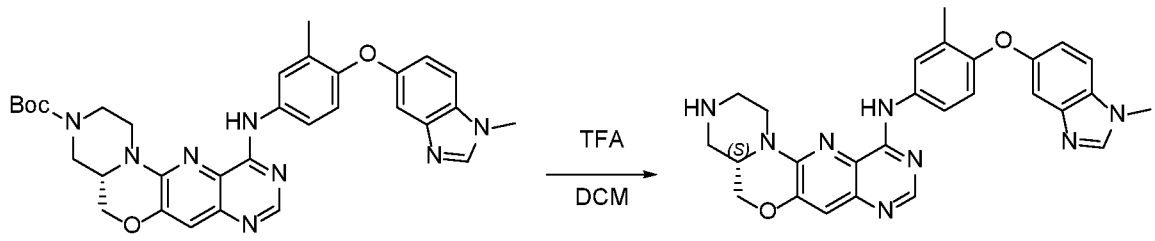
***Example S37: Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 37)***

**[0359] Step 1. Synthesis of tert-butyl (S)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**




**[0360]** To a solution of tert-butyl (S,E)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (500.0 mg, 1.29 mmol) in AcOH (10.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (660.0 mg, 2.59 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (80/20, v/v) to afford tert-butyl (S)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (250.0 mg, 32%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =595.3.

**[0361] Step 2. Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 37)**

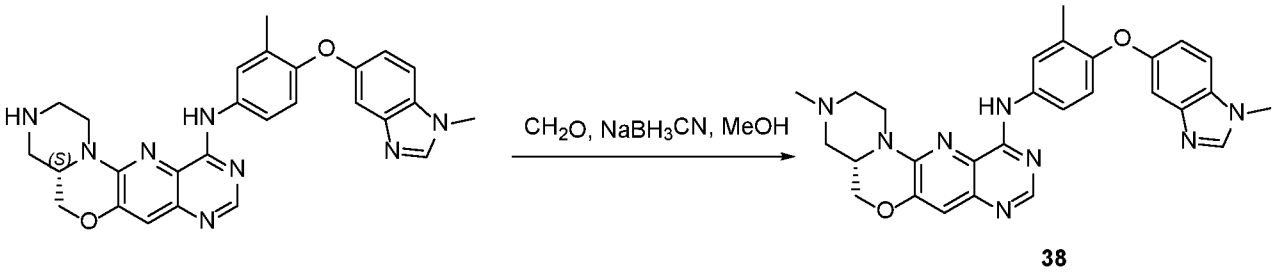



37

**[0362]** To a solution of tert-butyl (S)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (250.0 mg, 0.42 mmol) in DCM (5.0 mL) was added TFA (2.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was adjusted pH to 8 with $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 37)** (44.8 mg, 19%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.16 (s, 1H), 8.35 (s, 1H), 8.16 (s, 1H), 7.84 - 7.79 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.19 (s, 1H), 7.07 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.89 (d, $J$ = 8.8 Hz, 1H), 4.95 - 4.92 (m, 1H), 4.43 - 4.40 (m, 1H), 4.03 - 3.98 (m, 1H), 3.84 (s, 3H), 3.50 - 3.45 (m, 1H), 3.10 - 3.00 (m, 2H), 2.80 - 2.71 (m, 2H), 2.39 - 2.33 (m, 1H), 2.24 (s, 3H).

***Example S38: Synthesis of (S)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 38)***

**[0363] Step 1. Synthesis of (S)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 38)**

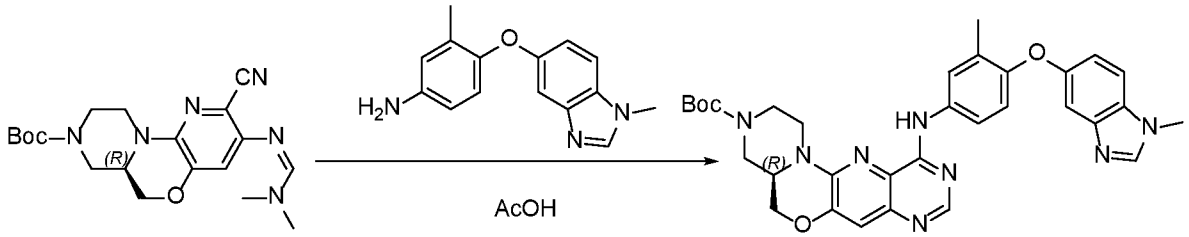



38

**[0364]** To a solution of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (150.0 mg, 0.30 mmol) in MeOH (5.0 mL) was added HCHO (230.7 mg, 30%) at room temperature. The mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (86.9 mg, 1.38 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN -----Preparative; Flow rate: 60 mL/min; Gradient: 37% B to 43% B in 8 min; Wave Length: 254 nm) to afford (S)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 38)** (9.1 mg, 5%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =509.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.21 (s, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 7.84 - 7.78 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.21 (s, 1H), 7.07 (d, $J$ = 2.4 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.89 (d, $J$ = 8.8 Hz, 1H), 5.03 - 5.00 (m, 1H), 4.47 - 4.43 (m, 1H), 4.08 - 4.03 (m, 1H), 3.84 (s, 3H), 3.68 - 3.57 (m, 1H), 2.97 - 2.90 (m, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 2.12 - 2.06 (m, 1H), 1.79 - 1.76 (m, 1H).

***Example S39: Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 39)***

**[0365] Step 1. Synthesis of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**




**[0366]** To a solution of tert-butyl (R,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (130.0 mg, 0.34 mmol) in AcOH (3.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (170.4 mg, 0.67 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (65/35, v/v) to afford tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (110.0 mg, 54%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 595.3.

**[0367] Step 2. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 39)**

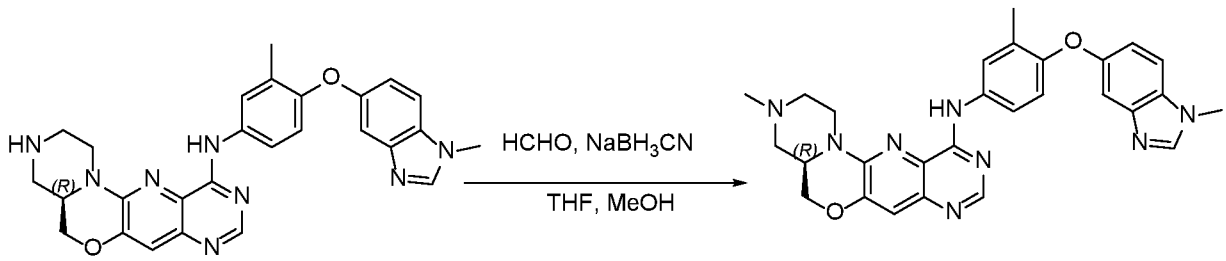

39

**[0368]** To a solution of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (110.0 mg, 0.19 mmol) in DCM (3.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The resulting mixture was adjusted pH to 8.0 with aq. $NaHCO_3$ and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by

reverse phase flash column chromatography with $CH_3CN/H_2O$ (40/60, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 37% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 39)** (10.6 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.18 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 7.84 - 7.80 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.19 (s, 1H), 7.07 (d, $J$ = 1.6 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 4.96 - 4.93 (m, 1H), 4.44 - 4.40 (m, 1H), 4.03 - 3.94 (m, 1H), 3.84 (s, 3H), 3.50 - 3.45 (m, 1H), 3.10 - 2.92 (m, 2H), 2.89 - 2.68 (m, 3H), 2.38 - 2.33 (m, 1H), 2.24 (s, 3H).

***Example S40: Synthesis of (R)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 40)***

**[0369] Step 1. Synthesis of (R)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 40)**



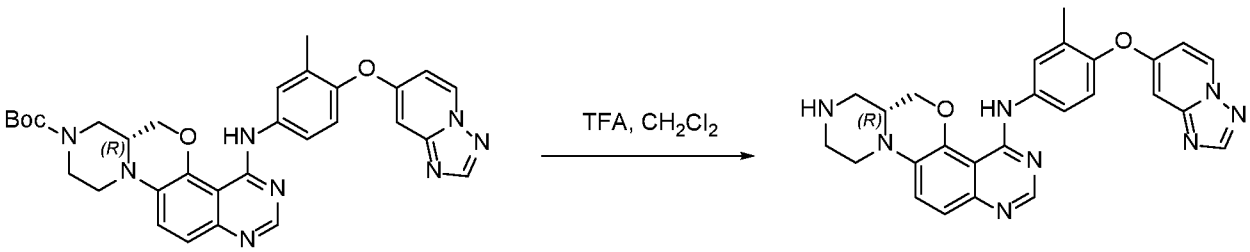

**40**

**[0370]** To a solution of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (80.0 mg, 0.16 mmol) in THF/MeOH (4.0 mL/1.0 mL) was added HCHO (121.3 mg, 30%) at room temperature. The mixture was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (45.7 mg, 0.73 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm;

Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 40% B in 8 min; Wave Length: 254 nm) to afford (R)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 40)** (8.8 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 509.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.22 (s, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 7.84 - 7.79 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.21 (s, 1H), 7.07 (d, $J$ = 1.6 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 5.03 - 5.00 (m, 1H), 4.47 - 4.43 (m, 1H), 4.08 - 4.03 (m, 1H), 3.84 (s, 3H), 3.64 - 3.59 (m, 1H), 2.96 - 2.90 (m, 3H), 2.33 - 2.24 (m, 6H), 2.11 - 2.05 (m, 1H), 1.79 - 1.73 (m, 1H).

***Example S41: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine diformic acid (Compound 41)***

**[0371] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine diformic acid (Compound 41)**



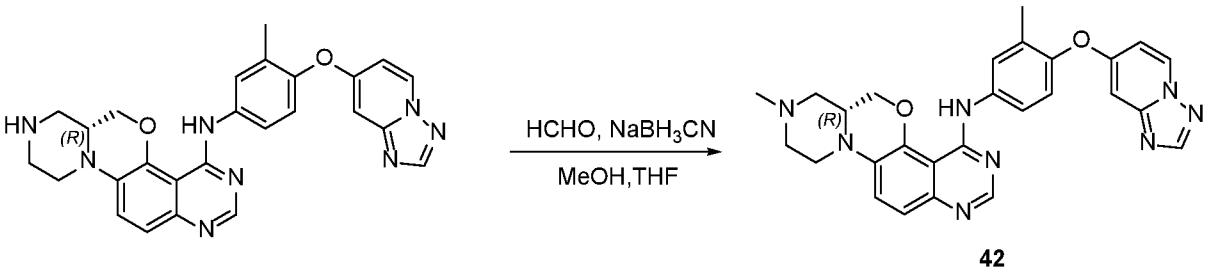

41

**[0372]** To a solution of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (50.0 mg, 0.09 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 10% B to 30% B in 10 min; Wave Length: 254 nm) to afford (R)-N-(4-

([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine diformic acid **(Compound 41)** (3.2 mg, 6%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.96 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.37 (d, $J$ = 4.8 Hz, 2H), 8.23 (s, 2H), 7.91 - 7.88 (m, 1H), 7.83 (d, $J$ = 2.4 Hz, 1H), 7.58 (d, $J$ = 9.2 Hz, 1H), 7.31 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.01 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.70 - 4.67 (m, 1H), 4.21 - 4.16 (m, 1H), 3.85 - 3.82 (m, 2H), 3.09 - 3.04 (m, 3H), 2.82 - 2.68 (s, 3H), 2.20 (s, 3H).

***Example S42: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-methyl-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 42)***

**[0373] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-methyl-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 42)**



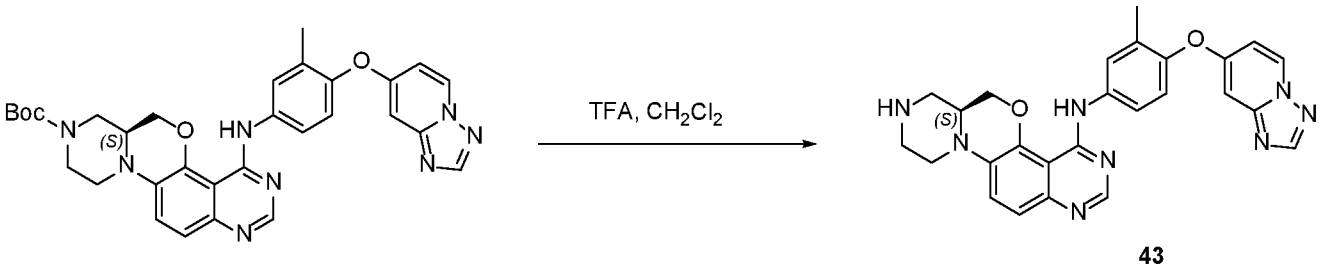

42

**[0374]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (90.0 mg, 0.19 mmol) in MeOH (1.0 mL) and THF (5.0 mL) was added HCHO (16.8 mg, 30%) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (52.9 mg, 0.84 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 38% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-methyl-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 42)** (6.2 mg, 6%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2. $^1$H NMR (400 MHz,

DMSO-$d_6$): δ 9.95 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.37 (d, $J$ = 3.6 Hz, 2H), 7.91 - 7.88 (m, 1H), 7.83 (d, $J$ = 2.4 Hz, 1H), 7.61 (d, $J$ = 9.2 Hz, 1H), 7.31 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.00 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.73 - 4.70 (m, 1H), 4.25 - 4.20 (m, 1H), 3.93 - 3.90 (m, 1H), 2.92 - 2.87 (m, 2H), 2.83 - 2.77 (m, 1H), 2.27 (s, 3H), 2.20 (s, 3H), 2.14 - 2.11 (m, 1H), 1.85 - 1.80 (m, 1H).

***Example S43: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 43)***

**[0375] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 43)**



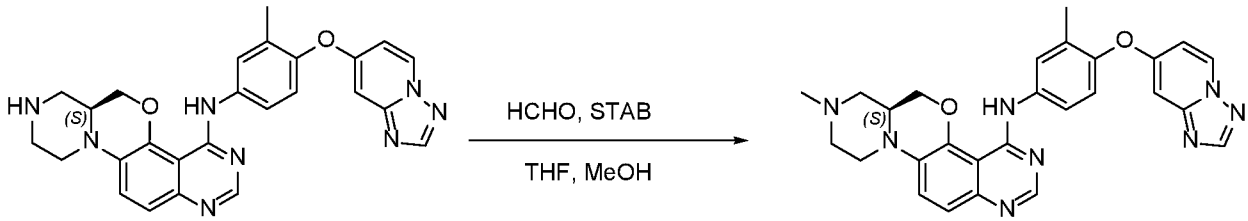

43

**[0376]** To a solution of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (50.0 mg, 0.13 mmol) in $CH_2Cl_2$ (5.0 mL) was added TFA (2.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 38% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 43)** (11.5 mg, 18%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.96 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.38 - 8.36 (m, 2H), 7.91 - 7.88 (m, 1H), 7.83 (d, $J$ = 2.0 Hz, 1H), 7.59 (d, $J$ = 9.2 Hz, 1H), 7.31 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.01

(m, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 4.70 - 4.67 (m, 1H), 4.22 - 4.17 (m, 1H), 3.86 - 3.83 (m, 1H), 3.18 - 3.13 (m, 1H), 3.08 - 3.00 (m, 2H), 2.82 - 2.76 (m, 1H), 2.20 (s, 3H).

***Example S44: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-methyl-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 44)***

**[0377] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-methyl-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 44)**

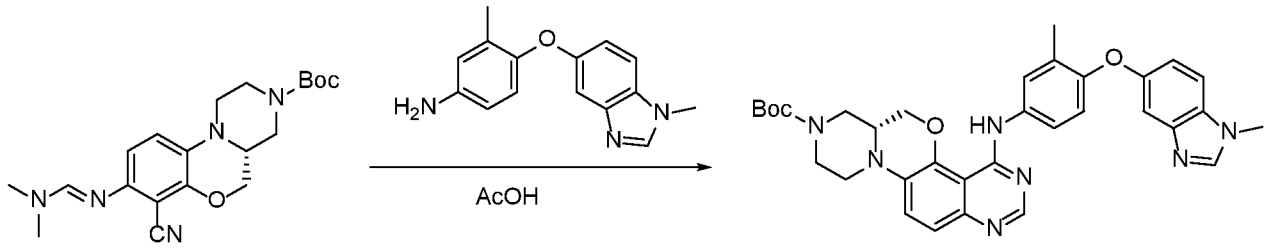



**44**

**[0378]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (40.0 mg, 0.08 mmol) in THF (5.0 mL) and methanol (1.0 mL) was added formaldehyde (5.0 mg, 40%) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Then STAB (79.3 mg, 0.37 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (90/10, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 38% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-methyl-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 44)** (3.0 mg, 7%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.94 (s, 1H), 8.93 (d, *J* = 6.8 Hz, 1H), 8.37 - 8.35 (m, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.78 (s, 1H), 4.71 - 4.68 (m, 1H), 4.23 - 4.19 (m, 1H), 3.92 - 3.89 (m, 1H), 2.89 - 2.76 (m, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.15 - 2.09 (m, 1H), 1.84 - 1.78 (m, 1H).

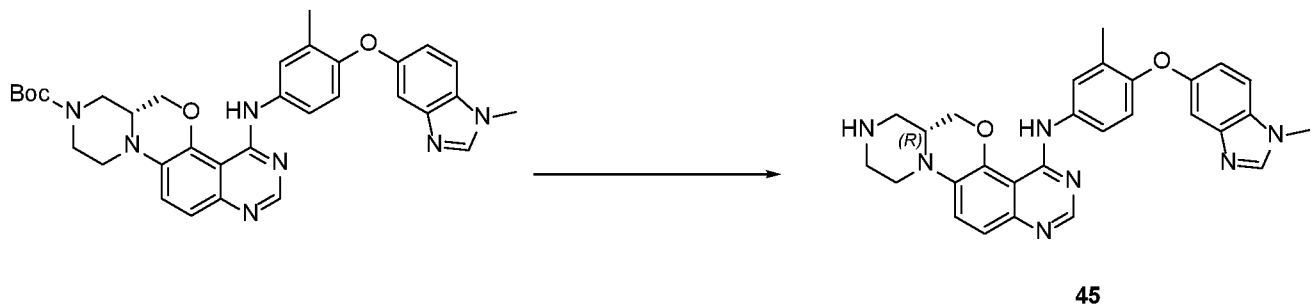
***Example S45: Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 45)***

**[0379] Step 1. Synthesis of tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**




**[0380]** A mixture of tert-butyl (R,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (260.0 mg, 0.67 mmol) and 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (170.8 mg, 0.67 mmol) in acetic acid (8.0 mL) was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (9/1, v/v) to afford tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (180.0 mg, 44%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

**[0381] Step 2. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 45)**



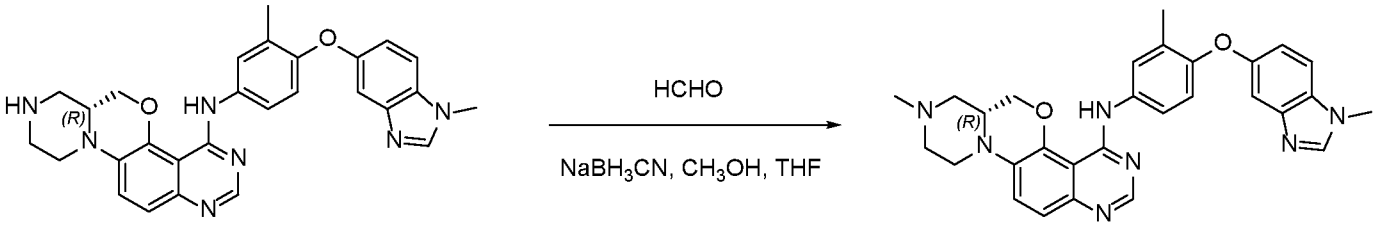

**45**

**[0382]** A mixture of tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (160.0 mg, 0.27 mmol) and TFA (1.5 mL) in DCM (3.0 mL) was stirred at

room temperature for 1 h. After the reaction was completed, the resulting mixture was neutralized to pH=8 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (40/60, v/v) and then purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 69% B to 69% B in 11 min; Wave Length: 254 nm) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 45)** (10.7 mg, 7%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.85 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 7.70 - 7.68 (m, 2H), 7.57 - 7.55 (m, 2H), 7.28 (d, $J$ = 8.8 Hz, 1H), 7.08 (d, $J$ = 2.4 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.88 (d, $J$ = 8.4 Hz, 1H), 4.68 - 4.65 (m, 1H), 4.19 - 4.14 (m, 1H), 3.84 - 3.81 (m, 4H), 3.16 - 2.98 (m, 3H), 2.78 - 2.64 (m, 2H), 2.45 - 2.40 (m, 1H), 2.24 (s, 3H).

***Example S46: Synthesis of (R)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 46)***

**[0383] Step 1. Synthesis of (R)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 46)**



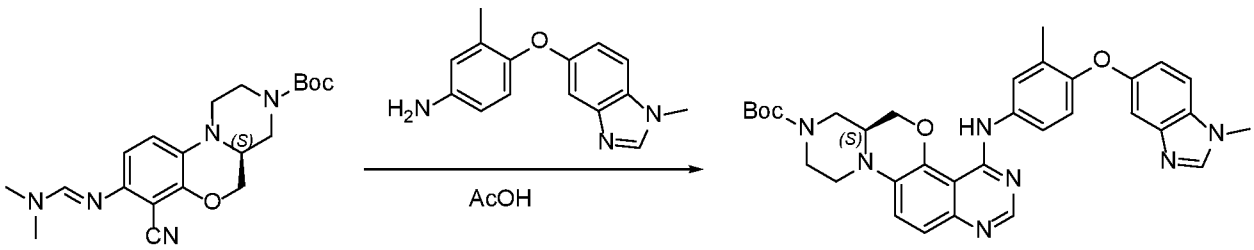

**46**

**[0384]** A mixture of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, 0.20 mmol) and HCHO (45.6 mg, 40% in $H_2O$) in THF (4.0 mL) and MeOH (1.0 mL) was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (57.3 mg, 0.91 mmol) was added to the mixture at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was diluted with $H_2O$ and then

extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 34% B in 8 min; Wave Length: 254 nm) to afford (R)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 46)** (17.8 mg, 17%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ = 508.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.84 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.70 - 7.67 (m, 2H), 7.59 - 7.55 (m, 2H), 7.28 (d, $J$ = 9.2 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.70 - 4.67 (m, 1H), 4.23 - 4.18 (m, 1H), 3.92 - 3.89 (m, 1H), 3.84 (s, 3H), 3.27 - 3.22 (m, 1H), 2.91 - 2.86 (m, 2H), 2.82 - 2.76 (m, 1H), 2.26 - 2.24 (m, 6H), 2.16 - 2.09 (m, 1H), 1.84 - 1.77 (m, 1H).

***Example S47: Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 47)***

**[0385] Step 1. Synthesis of tert-butyl (S)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**




**[0386]** A mixture of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (900.0 mg, 0.26 mmol) and 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (591.4 mg, 2.33 mmol ) in acetic acid (10.0 mL) was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (9/1, v/v) to afford tert-butyl (S)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (500.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

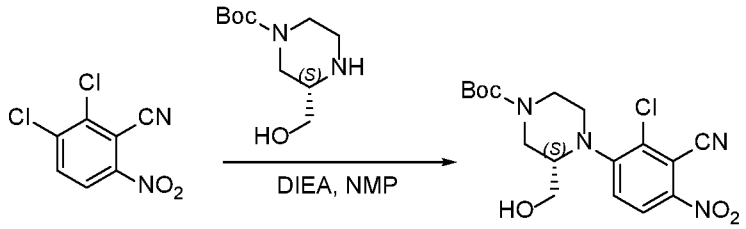
**[0387] Step 2. Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 47)**

47

**[0388]** A mixture of tert-butyl (S)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (70.0 mg, 0.11 mmol) in DCM (3.0 mL) and TFA (1.5 mL) was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was neutralized to pH=8 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (40/60, v/v) and then purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 35% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 47)** (13.6 mg, 23%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.85 (s, 1H), 8.31 (s, 1H), 8.16 (s, 1H), 7.70 - 7.68 (m, 2H), 7.57 - 7.54 (m, 2H), 7.27 (d, $J$ = 9.2 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.68 - 4.64 (m, 1H), 4.19 - 4.13 (m, 1H), 3.84 - 3.78 (m, 4H), 3.14 - 2.95 (m, 3H), 2.80 - 2.72 (m, 1H), 2.68 - 2.60 (m, 1H), 2.43 - 2.36 (m, 1H), 2.24 (s, 3H).

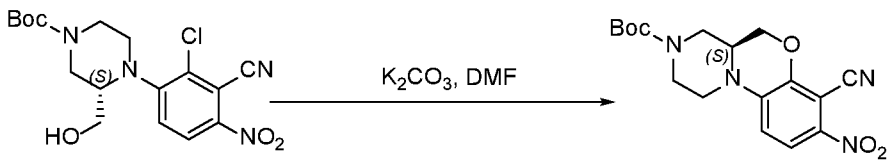
***Example S48: Synthesis of (S)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 48)***

**[0389] Step 1. Synthesis of tert-butyl (3S)-4-(2-chloro-3-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



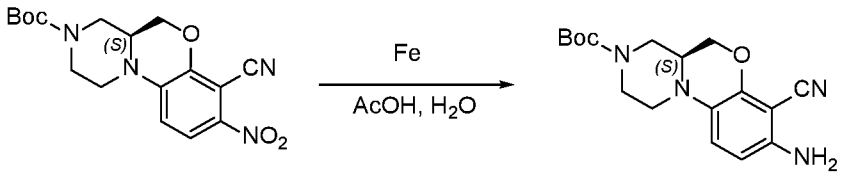

**[0390]** A mixture of 2,3-dichloro-6-nitrobenzonitrile (5.0 g, 23.04 mmol), tert-butyl (3S)-3-(hydroxymethyl)piperazine-1-carboxylate (12.6 g, 57.60 mmol) and DIEA (14.9 g, 115.20 mmol) in NMP (100.0 mL) was stirred at 100 °C for 16 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) to afford tert-butyl (3S)-4-(2-chloro-3-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (3.2 g, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 397.1.

**[0391] Step 2. Synthesis of tert-butyl (S)-7-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



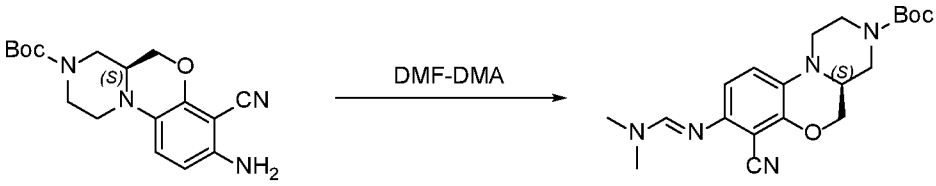

**[0392]** A mixture of tert-butyl (3S)-4-(2-chloro-3-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (3.2 g, 8.06 mmol) and $K_2CO_3$ (3.3 g, 24.19 mmol) in DMF (20.0 mL) was stirred at 120 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (S)-7-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (1.7 g, 58%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 361.1

**[0393] Step 3. Synthesis of tert-butyl (S)-8-amino-7-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



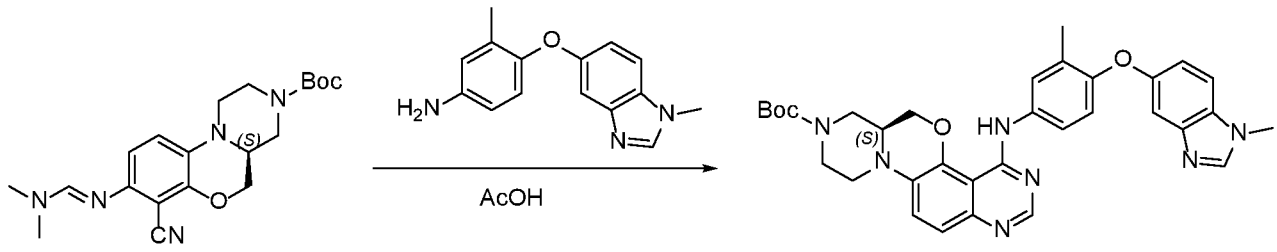

**[0394]** A mixture of tert-butyl (S)-7-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (1.7 g, 4.71 mmol) and Fe (2.6 g, 47.17 mmol) in AcOH (20.0 mL) and $H_2O$ (1.0 mL) was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (90/10, v/v) to afford tert-butyl (S)-8-amino-7-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (1.0 g, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 331.2.

**[0395] Step 4. Synthesis of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



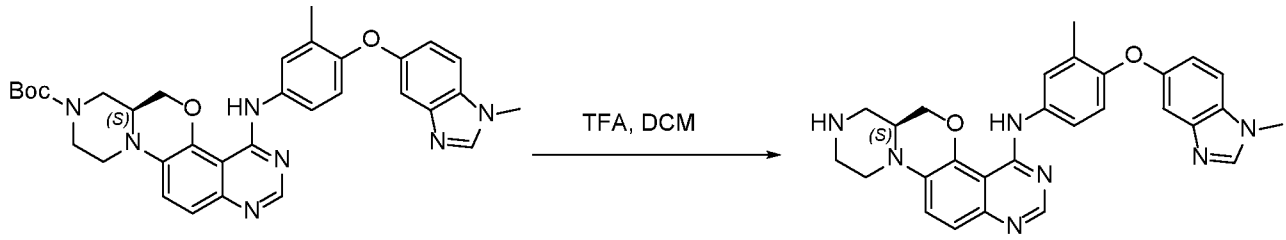

**[0396]** A mixture of tert-butyl (S)-8-amino-7-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (900.0 mg, 2.72 mmol) and DMF-DMA (486.9 mg, 4.08 mmol) in dioxane (10.0 mL) was stirred at 90 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (92/8, v/v) to afford tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (500.0 mg, 47%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 386.2.

**[0397] Step 5. Synthesis of tert-butyl (S)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**



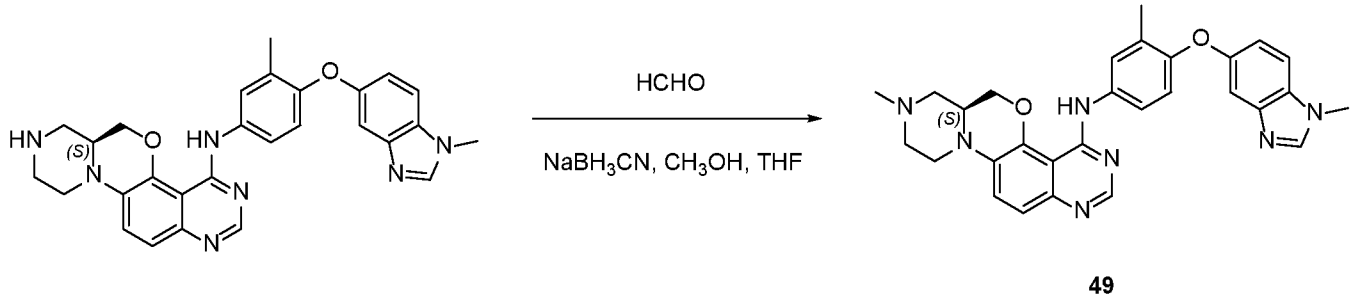

**[0398]** A mixture of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (800.0 mg, 2.07 mmol) and 3-methyl-4-[(1-methyl-1,3-benzodiazol-5-yl)oxy]aniline (525.7 mg, 2.07 mmol) in $CH_3OH$ (20.0 mL, 493.97 mmol) was stirred at 85°C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (90/10, v/v) to afford tert-butyl (S)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (500.0 mg, 40%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 594.2$.

**[0399] Step 6. Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0400]** A solution of tert-butyl (S)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (500.0 mg, 0.84 mmol) and TFA (5.0 mL) in $CH_2Cl_2$ (5.0 mL) was stirred at room temperature for 1 h. After the reaction was completed, the mixture was acidified to pH=7 with saturated $NaHCO_3$ (aq.), the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (84/16, v/v) to afford (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (300.0 mg, 72%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 494.2$

**[0401] Step 7. Synthesis of (S)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 48)**

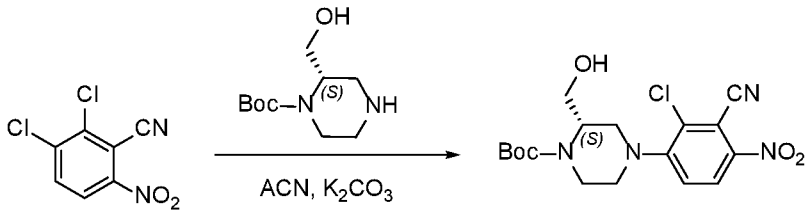



49

**[0402]** A mixture of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (150.0 mg, 0.30 mmol) and HCHO (68.4 mg, 40% in $H_2O$) in THF (4.0 mL) and $CH_3OH$ (1.0 mL) was stirred at room temperature for 1 h. Then $NaBH_3CN$ (85.9 mg, 1.36 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for additional 1 h. After the reaction was completed, the reaction mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30×150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 45% B in 8 min, 254 nm) to afford (S)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 48)** (29.6 mg, 18%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 508.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.84 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 7.70 - 7.67 (m, 2H), 7.59 - 7.55 (m, 2H), 7.28 (d, $J$ = 9.2 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.70 - 4.67 (m, 1H), 4.23 - 4.18 (m, 1H), 3.92 - 3.89 (m, 1H), 3.84 (s, 3H), 3.27 - 3.23 (m, 1H), 2.91 - 2.86 (m, 2H), 2.82 - 2.76 (m, 1H), 2.26 - 2.24 (m, 6H), 2.16 - 2.12 (m, 1H), 1.84 - 1.78 (m, 1H).

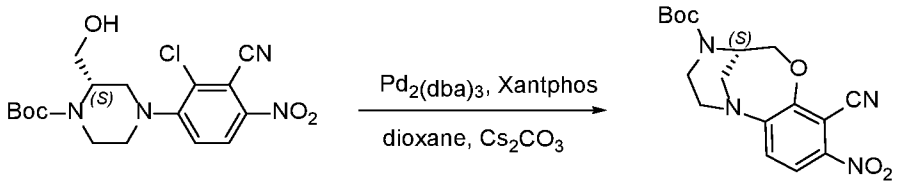
***Example S49: Synthesis of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 49)***

**[0403] Step 1. Synthesis of tert-butyl (S)-4-(2-chloro-3-cyano-4-nitrophenyl)-2-(hydroxymethyl)piperazine-1-carboxylate**



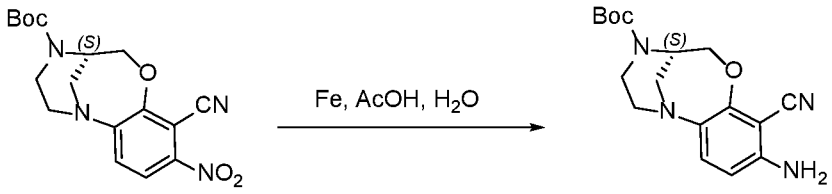

**[0404]** To a solution of 2,3-dichloro-6-nitrobenzonitrile (10.0 g, 46.08 mmol) in ACN (100.0 mL) was added tert-butyl (S)-2-(hydroxymethyl)piperazine-1-carboxylate (9.9 g, 46.08 mmol) and $K_2CO_3$ (12.7 g, 92.16 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (95/5, v/v) to afford tert-butyl (S)-4-(2-chloro-3-cyano-4-nitrophenyl)-2-(hydroxymethyl)piperazine-1-carboxylate (11.0 g, 60%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =397.1.

**[0405] Step 2. Synthesis of tert-butyl (3S)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**



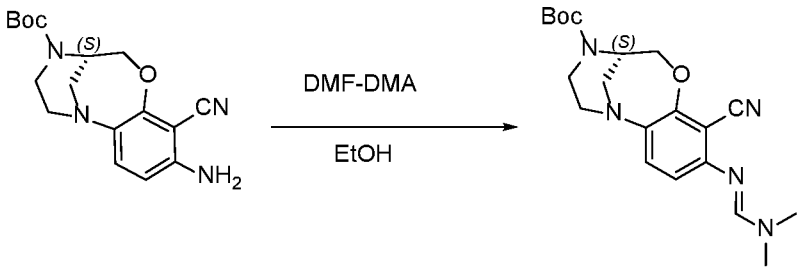

**[0406]** To a solution of tert-butyl (S)-4-(2-chloro-3-cyano-4-nitrophenyl)-2-(hydroxymethyl)piperazine-1-carboxylate (5.0 g, 12.60 mmol) in dioxane (50.0 mL) was added Xantphos (2.9 g, 5.04 mmol), $Cs_2CO_3$ (10.2 g, 31.50 mmol) and $Pd_2(dba)_3$ (2.3 g, 2.52 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3S)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (2.6 g, 60%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.1.

**[0407] Step 3. Synthesis of tert-butyl (3S)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**



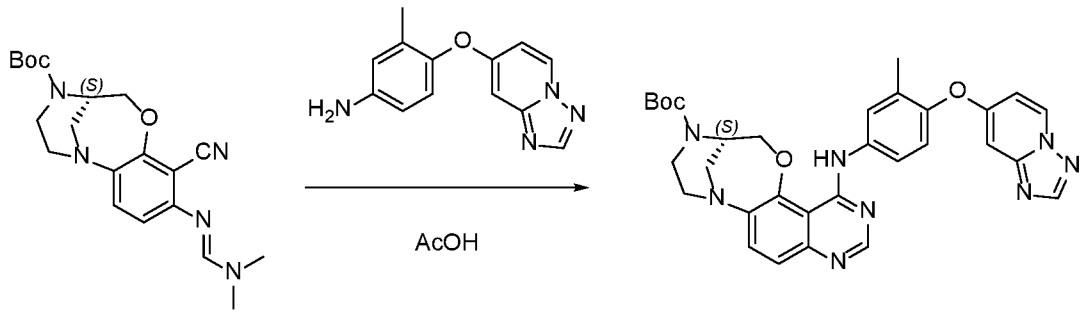

**[0408]** To a solution of tert-butyl (3S)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (2.0 g, 5.55 mmol) in AcOH (20.0 mL) and $H_2O$ (2.0 mL) was added Fe (1.5 g, 27.75 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (3S)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (1.1 g, 59%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =331.2.

**[0409] Step 4. Synthesis of tert-butyl (3S)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**



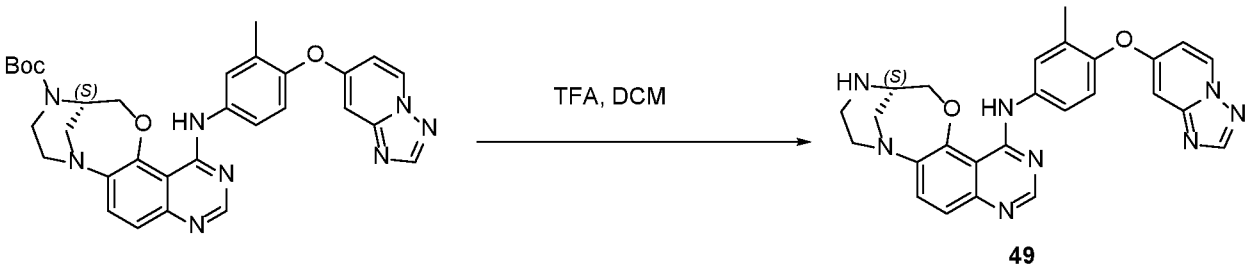

**[0410]** To a solution of tert-butyl (3S)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (2.5 g, 7.56 mmol) in EtOH (25.0 mL) was added DMF-DMA (2.9 mL, 37.83 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (3S)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (1.3 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =386.2.

**[0411] Step 5. Synthesis of tert-butyl (3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0412]** To a solution of tert-butyl (3S)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (2.0 g, 5.18 mmol) in acetic acid (20.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (1.2 g, 5.18 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (93/7, v/v) to afford tert-butyl (3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (1.0 g, 33%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =581.3.

**[0413] Step 6. Synthesis of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 49)**



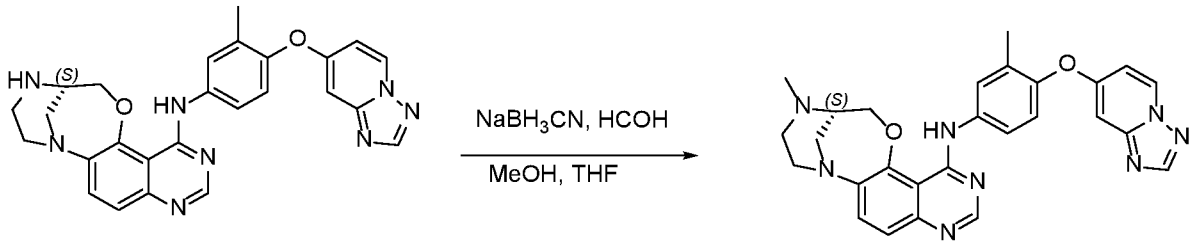

49

**[0414]** To a solution of tert-butyl (3S)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (100.0 mg, 0.17 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium

sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XSelect CSH Prep C18 OBD Column, 19 x 250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 11 min; Wave Length: 254 nm) to afford (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 49)** (9.8 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.21 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 7.96 - 7.93 (m, 1H), 7.84 (d, $J$ = 2.4 Hz, 1H), 7.51 (d, $J$ = 9.2 Hz, 1H), 7.37 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.80 (d, $J$ = 2.4 Hz, 1H), 4.94 - 4.89 (m, 1H), 4.40 - 4.35 (m, 1H), 3.98 - 3.94 (m, 1H), 3.63 - 3.59 (m, 1H), 3.44 - 3.33 (m, 2H), 3.27 - 3.14 (m, 3H), 2.50 - 2.47 (m, 1H), 2.21 (s, 3H).

***Example S50: Synthesis of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-4-methyl-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 50)***

**[0415] Step 1. Synthesis of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-4-methyl-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 50)**



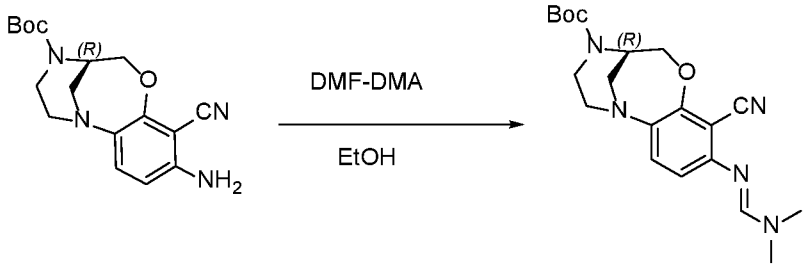

**50**

**[0416]** To a solution of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (80.0 mg, 0.16 mmol) in THF (5.0 mL) and MeOH (1.0 mL) was added formaldehyde (15.0 mg, 40% in $H_2O$) AT ROOM TEMPERATURE. The resulting mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (47.1 mg, 0.74 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography

with acetonitrile/water (30/70, v/v) to afford (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-4-methyl-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 50)** (21.6 mg, 26%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.19 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.45 - 8.38 (m, 2H), 7.97 - 7.95 (m, 1H), 7.83 (s, 1H), 7.53 (d, $J$ = 8.8 Hz, 1H), 7.38 (d, $J$ = 8.8 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (s, 1H), 4.89 - 4.83 (m, 1H), 4.67 - 4.62 (m, 1H), 4.07 - 4.04 (m, 1H), 3.64 - 3.60 (m, 1H), 3.38 - 3.35 (m, 2H), 3.20 - 3.16 (m, 1H), 2.99 - 2.92 (m, 1H), 2.38 - 2.31 (m, 4H), 2.20 (s, 3H).

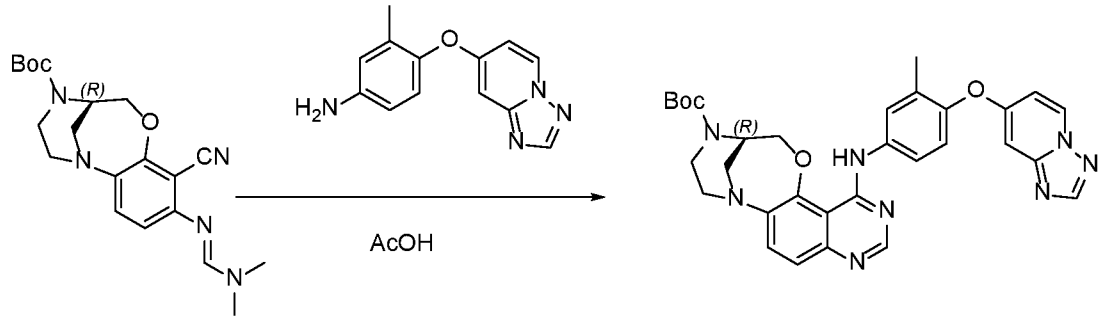
***Example S51: Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 51)***

**[0417] Step 1. Synthesis of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**



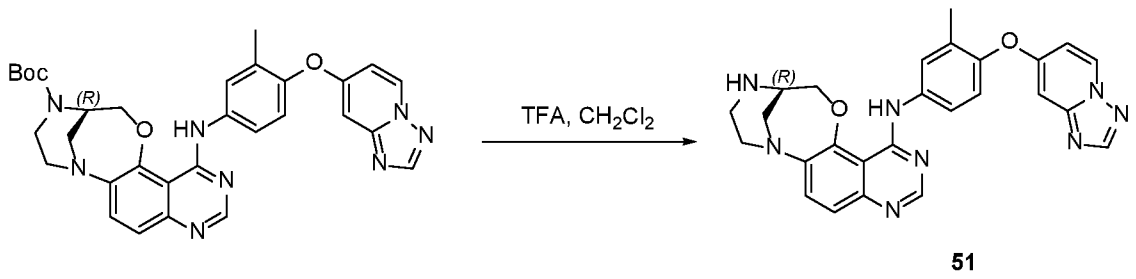

**[0418]** To a solution of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (120.0 mg, 0.36 mmol) in EtOH (5.0 mL) was added DMF-DMA (216.4 mg, 1.82 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (130.0 mg, crude) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 386.2.

**[0419] Step 2. Synthesis of Tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0420]** To a solution of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (120.0 mg, 0.31 mmol) in AcOH (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (78.9 mg, 0.31 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (90.4 mg, 50%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 581.3.

**[0421] Step 3. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 51)**



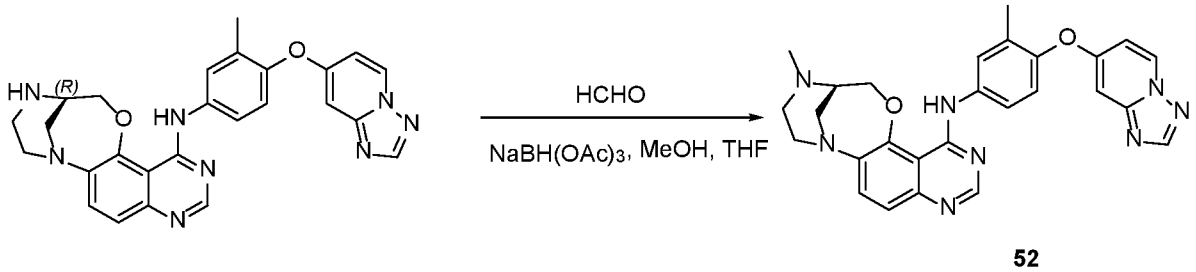

51

**[0422]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (80.0 mg, 0.14 mmol) in $CH_2Cl_2$ (5.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium

sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 15% B in 10 min; Wave Length: 254 nm) to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 51)** (5.4 mg, 8%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.21 (s, 1H), 8.92 (d, $J$ = 8.0 Hz, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 7.95 - 7.92 (m, 1H), 7.84 (s, 1H), 7.51 (d, $J$ = 8.4 Hz, 1H), 7.37 (d, $J$ = 8.8 Hz, 1H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (s, 1H), 4.94 - 4.88 (m, 1H), 4.39 - 4.34 (m, 1H), 3.97 - 3.94 (m, 1H), 3.64 - 3.58 (m, 1H), 3.38 - 3.14 (m, 2H), 2.20 (s, 3H).

***Example S52: Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-4-methyl-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 52)***

**[0423] Step 1. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-4-methyl-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 52)**



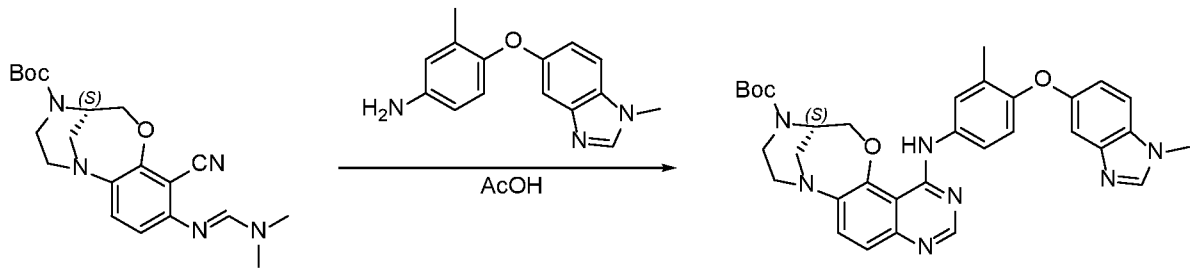

52

**[0424]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (120.0 mg, 0.25 mmol) in THF (25.0 mL) and methanol (5.0 mL) was added formaldehyde solution (22.5 mg, 40% in $H_2O$) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Then $NaBH(OAc)_3$ (238.2 mg, 1.13 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by phase flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC

with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 31% B in 8 min; Wave Length: 254 nm) to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-4-methyl-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 52)** (18.8 mg, 15%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.20 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.45 (s, 1H), 8.38 (s, 1H), 7.97 - 7.95 (m, 1H), 7.83 (d, $J$ = 2.0 Hz, 1H), 7.53 (d, $J$ = 9.2 Hz, 1H), 7.38 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.4 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 4.89 - 4.84 (m, 1H), 4.67 - 4.62 (m, 1H), 4.07 - 4.04 (m, 1H), 3.64 - 3.60 (m, 1H), 3.41 - 3.38 (m, 2H), 3.20 - 3.16 (m, 1H), 3.03 - 2.94 (m, 1H), 2.37 - 2.32 (m, 1H), 2.30 (s, 3H), 2.20 (s, 3H).

***Example S53: Synthesis of (3S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 53)***

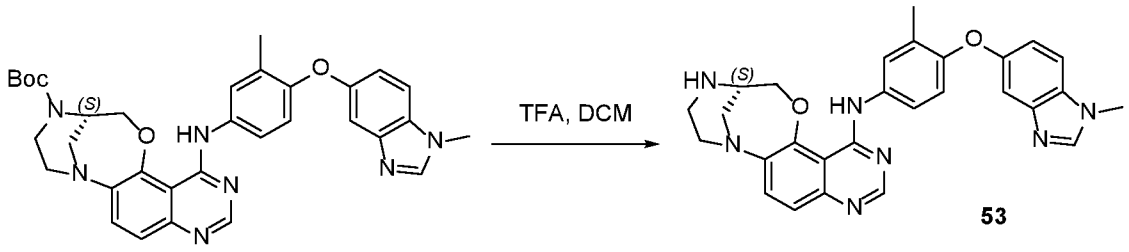
**[0425] Step 1. Synthesis of tert-butyl (3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0426]** To a solution of tert-butyl (3S)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (700.0 mg, 1.81 mmol) in AcOH (10.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (434.5 mg, 1.81 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) to afford tert-butyl (3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-

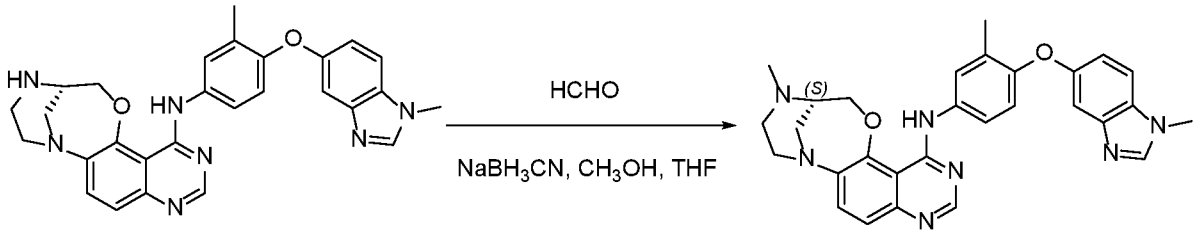
3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (600.0 mg, 55%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

**[0427] Step 2. Synthesis of (3S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 53)**




**[0428]** To a solution of tert-butyl (3S)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (80.0 mg, 0.13 mmol) in DCM (4.0 mL) was added TFA (1.0 mL) at room tempreature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was neutralized to pH = 8 with $NaHCO_3$(aq.). Then the resulting mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 29% B in 8 min, 29% B to 35% B in 15 min; Wave Length: 254 nm) to afford (3S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 53)** (12.3 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.12 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 7.76 - 7.73 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.49 (d, $J$ = 9.2 Hz, 1H), 7.34 (d, $J$ = 8.8 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.89 - 6.87 (m, 1H), 4.91 - 4.86 (m, 1H), 4.39 - 4.34 (m, 1H), 3.96 - 3.93 (m, 1H), 3.84 (s, 3H), 3.61 - 3.58 (m, 1H), 3.43 - 3.35 (m, 1H), 3.33 - 3.29 (m, 1H), 3.23 - 3.13 (m, 1H), 2.47 - 2.43 (m, 1H), 2.23 (s, 3H).

***Example S54: Synthesis of (3S)-4-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 54)***



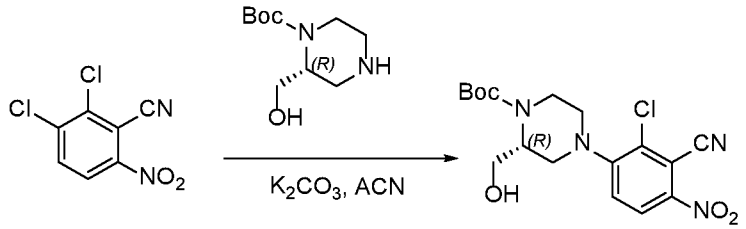

54

**[0429] Step 1. Synthesis of (3S)-4-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 54)**

**[0430]** To a solution of (3S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (150.0 mg, 0.30 mmol) in THF (2.0 mL) and MeOH (0.5 mL) was added formaldehyde (68.4 mg, 40% in $H_2O$) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 2 h. Then $NaBH_3CN$ (85.9 mg, 1.36 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at atroom temperature for additional 1.5 h. After the reaction was completed, the reaction mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure.The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: ACN, Mobile Phase B: Water (0.1% FA); Flow rate: 60 mL/min; Gradient: 3% B to 10% B in 8 min; Wave Length: 254 nm) to afford (3S)-4-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine formic acid **(Compound 54)** (12.9 mg, 8%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 508.2. $^1H$ NMR (400 MHz, Methanol-$d_4$): δ 8.38 (s, 1H), 8.26 (s, 1H), 8.13 (s, 1H), 7.69 (d, $J$ = 2.4 Hz, 1H), 7.61 - 7.55 (m, 3H), 7.42 (d, $J$ = 8.8 Hz, 1H), 7.14 - 7.09 (m, 2H), 6.92 (d, $J$ = 8.4 Hz, 1H), 4.81 - 4.74 (m, 2H), 4.23 - 4.20 (m, 1H), 3.93 (s, 3H), 3.78 - 3.74 (m, 1H), 3.65 - 3.58 (m, 2H), 3.40 - 3.36 (m, 1H), 3.30 - 3.21 (m, 1H), 2.68 - 2.63 (m, 1H), 2.56 (s, 3H), 2.32 (s, 3H).

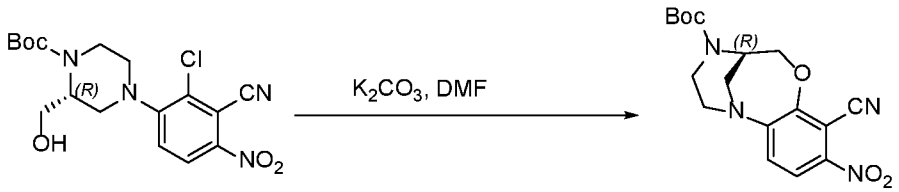
***Example S55: Synthesis of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 55)***

**[0431] Step 1. Synthesis of tert-butyl (R)-4-(2-chloro-3-cyano-4-nitrophenyl)-2-(hydroxymethyl)piperazine-1-carboxylate**




**[0432]** To a solution of 2,3-dichloro-6-nitrobenzonitrile (5.0 g, 23.04 mmol) in acetonitrile (50.0 mL) was added tert-butyl (R)-2-(hydroxymethyl)piperazine-1-carboxylate (7.5 g, 34.56 mmol) and $K_2CO_3$ (9.6 g, 69.12 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl (R)-4-(2-chloro-3-cyano-4-nitrophenyl)-2-(hydroxymethyl)piperazine-1-carboxylate (4.1 g, 44%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 397.1.

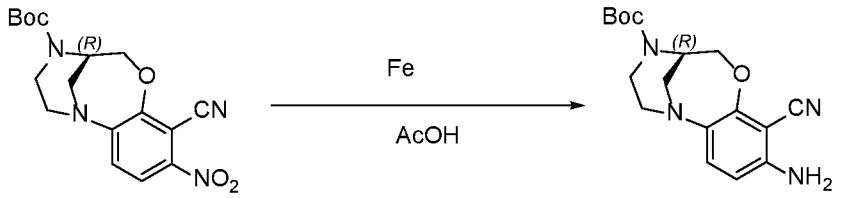
**[0433] Step 2. Synthesis of tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**




**[0434]** To a solution of tert-butyl (R)-4-(2-chloro-3-cyano-4-nitrophenyl)-2-(hydroxymethyl)piperazine-1-carboxylate (4.1 g, 10.33 mmol) in DMF (50.0 mL) was added $K_2CO_3$ (4.3 g, 30.99 mmol) at room temperature. The resulting mixture was stirred at 120 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (10/1, v/v) to afford tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-

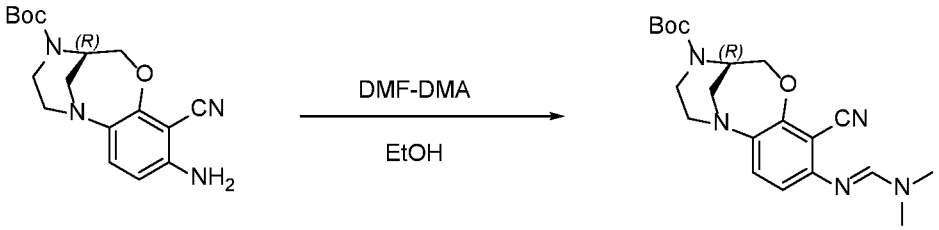
methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (3.0 g, 80%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 361.1.

**[0435] Step 3. Synthesis of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**




**[0436]** To a solution of tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (3.0 g, 8.33 mmol) in acetic acid (30.0 mL) and $H_2O$ (0.6 mL) was added Fe (2.3 g, 41.63 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (2.0 g, 72%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 331.2.

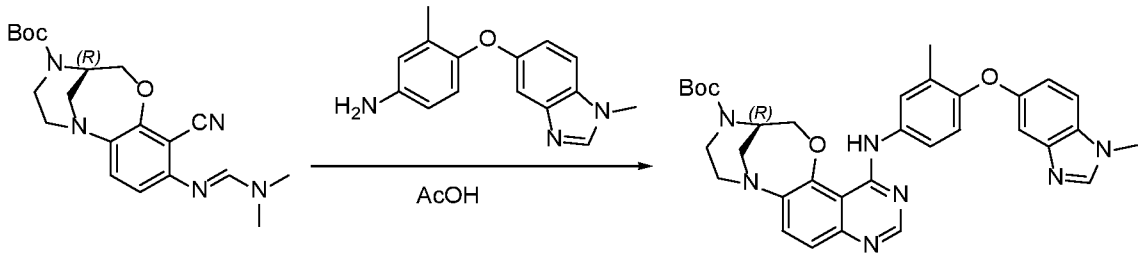
**[0437] Step 4. Synthesis of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**




**[0438]** To a solution of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (2.0 g, 6.05 mmol) in EtOH (20.0 mL) was added DMF-DMA (3.6 g, 30.25 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-

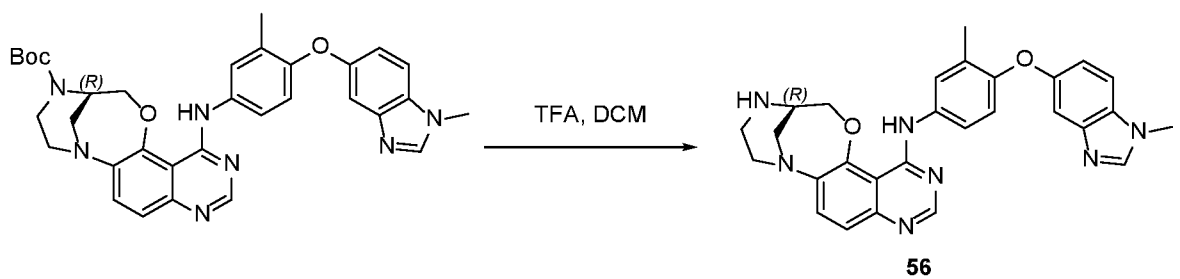
methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (1.8 g, 77%) as a light brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 386.2.

**[0439] Step 5. Synthesis of tert-butyl (3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0440]** To a solution of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (1.0 g, 2.59 mmol) in acetic acid (10.0 mL) were added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (0.66 g, 2.59 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (900.0 mg, 58%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

**[0441] Step 6. Synthesis of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 55)**



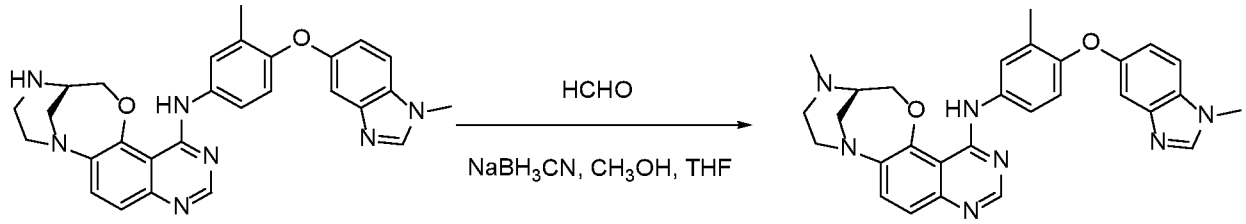

56

**[0442]** To a solution of tert-butyl (3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-

f]quinazoline-4-carboxylate (350.0 mg, 0.59 mmol) in DCM (4.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was neutralized to pH = 8 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 34% B in 8 min; Wave Length: 254 nm) to afford (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 55)** (36.0 mg, 12%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.3. $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.34 (s, 1H), 8.11 (s, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.62 - 7.51 (m, 3H), 7.40 - 7.38 (m, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.11 - 7.08 (m, 1H), 6.91 (d, *J* = 8.8 Hz,1H), 4.54 - 4.49 (m, 1H), 4.14 - 4.11 (m, 1H), 3.92 (s, 3H), 3.72 - 3.69 (m, 1H), 3.54 - 3.37 (m, 4H), 2.62 - 2.58 (m, 1H), 2.31 (s, 3H).

***Example S56: Synthesis of (3R)-4-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 56)***

**[0443] Step 1. Synthesis of (3R)-4-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (Compound 56)**



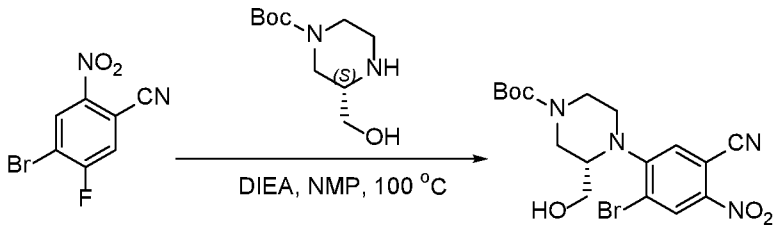

**56**

**[0444]** A mixture of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (90.0 mg, 0.18 mmol) and HCHO (44.9 mg, 40% in $H_2O$) in THF (2.0 mL) and MeOH (0.5 mL) was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (52.8 mg, 0.84 mmol) was added to the mixture at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was quenched with $H_2O$

and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 39% B in 8 min; 254 nm) to afford (3R)-4-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine **(Compound 56)** (16.3 mg, 16%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 508.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.07 (s, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 7.77 - 7.71 (m, 2H), 7.57 - 7.49 (m, 2H), 7.35 (d, $J$ = 9.2 Hz, 1H), 7.08 (d, $J$ = 2.4 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.88 (d, $J$ = 8.8 Hz, 1H), 4.85 - 4.80 (m, 1H), 4.66 - 4.61 (m, 1H), 4.06 - 4.02 (m, 1H), 3.84 (s, 3H), 3.62 - 3.59 (m, 1H), 3.41 - 3.35 (m, 2H), 3.19 - 3.15 (m, 1H), 2.99 - 2.92 (m, 1H), 2.37 - 2.33 (m, 1H), 2.30 (s, 3H), 2.25 (s, 3H).

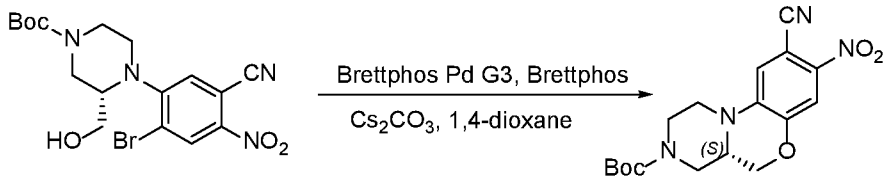
***Example S57: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 57)***

**[0445] Step 1. Synthesis of tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



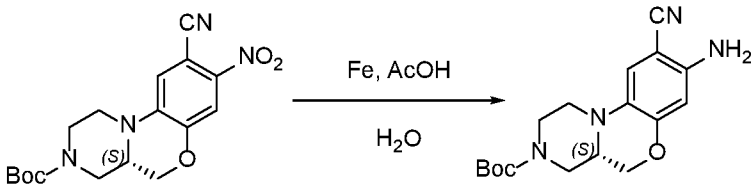

**[0446]** To a solution of 4-bromo-5-fluoro-2-nitrobenzonitrile (2.0 g, 8.16 mmol) in NMP (40.0 mL) was added tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (8.8 g, 40.82 mmol) and DIEA (5.3 g, 40.82 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (2.5 g, 69%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 441.0.

**[0447] Step 2. Synthesis of tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



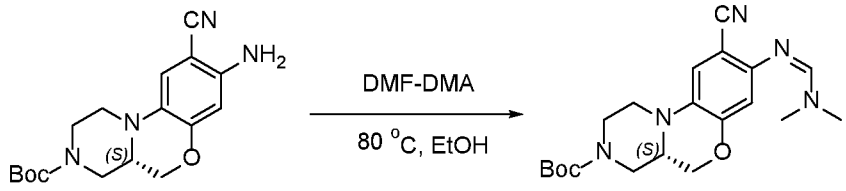

**[0448]** To a solution of tert-butyl (S)-4-(2-bromo-5-cyano-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.7 g, 3.85 mmol) in 1,4-dioxane (20.0 mL) was added BrettPhos (0.4 g, 0.77 mmol), $Cs_2CO_3$ (3.8 g, 11.56 mmol) and BrettPhos Pd G3 (0.4 g, 0.39 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was cooled down to room temperature and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (95/5, v/v) to afford tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (630.0 mg, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 361.1.

**[0449] Step 3. Synthesis of tert-butyl (S)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



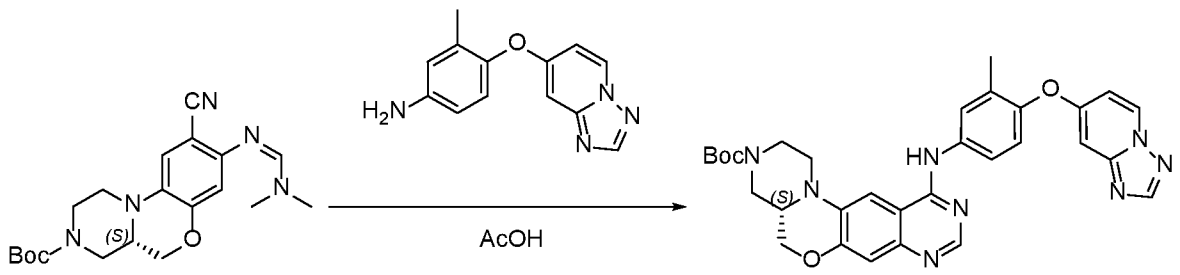

**[0450]** To a solution of tert-butyl (S)-9-cyano-8-nitro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (606.0 mg, 1.68 mmol) in acetic acid (30.0 mL) and water (2.0 mL) was added Fe (469.6 mg, 8.41 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (90/10, v/v) to afford tert-butyl (S)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (476.0 mg, 86%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =331.2.

**[0451] Step 4. Synthesis of tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**




**[0452]** To a solution of tert-butyl (S)-8-amino-9-cyano-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (476.0 mg, 1.44 mmol) in ethanol (20.0 mL) was added DMF-DMA (686.7 mg, 5.76 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (550.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 386.2.

**[0453] Step 5. Synthesis of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**




**[0454]** To a solution of tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (310.0 mg, crude) in acetic acid (10.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (193.2 mg, 0.80 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (93.7 mg, 20%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =581.3.

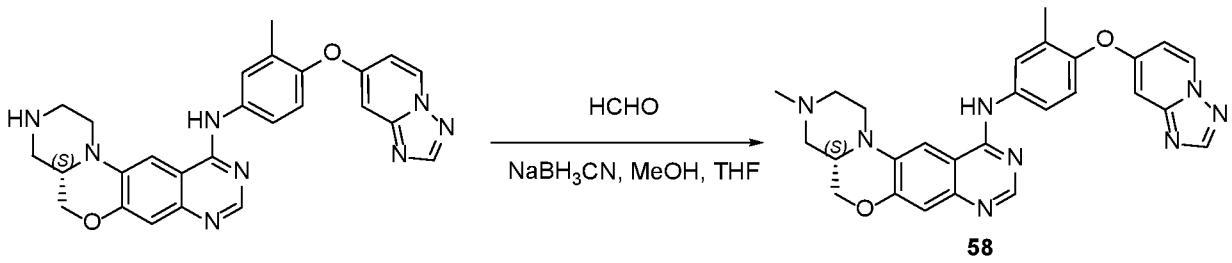
**[0455] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 57)**


**57**

**[0456]** To a solution of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (93.7 mg, 0.16 mmol) in dichloromethane (10.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH value of the mixture was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 41% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 57)** (14.3 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.41 (s, 1H), 8.93 (d, $J$ = 7.2 Hz, 1H), 8.41 - 8.36 (m, 2H), 7.84 - 7.81 (m, 2H), 7.66 (s, 1H), 7.20 (d, $J$ = 8.0 Hz, 1H), 7.04 - 7.00 (m, 2H), 6.80 (s, 1H), 4.38 - 4.32 (m, 1H), 4.04 - 3.92 (m, 2H), 3.14 - 3.07 (m, 2H), 3.01 - 2.98 (m, 1H), 2.87 - 2.80 (m, 1H), 2.75 - 2.68 (m, 1H), 2.37 - 2.32 (m, 1H), 2.20 (s, 3H).

***Example S58: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 58)***

**[0457] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 58)**

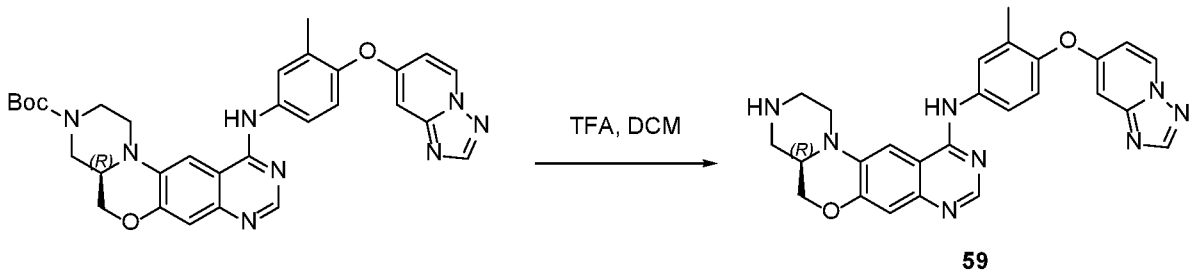



58

**[0458]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (180.0 mg, 0.38 mmol) in THF (10.0 mL) and methanol (2.0 mL) was added formaldehyde (33.7 mg, 30%) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (105.9 mg, 1.69 mmol) was added to the mixture at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 48% B to 63% B in 10 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 58)** (8.7 mg, 5%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.42 (s, 1H), 8.98 - 8.93 (m, 1H), 8.38 - 8.37 (m, 2H), 7.84 - 7.81 (m, 2H), 7.70 (s, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 2H), 6.80 (s, 1H), 4.41 - 4.39 (m, 1H), 4.08 - 4.02 (m, 2H), 3.25 - 3.23 (m, 1H), 3.03 - 3.00 (m, 1H), 2.91 - 2.78 (m, 2H), 2.30 (s, 3H), 2.28 - 2.20 (m, 4H), 1.78 - 1.71 (m, 1H).

***Example S59: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 59)***

**[0459] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 59)**

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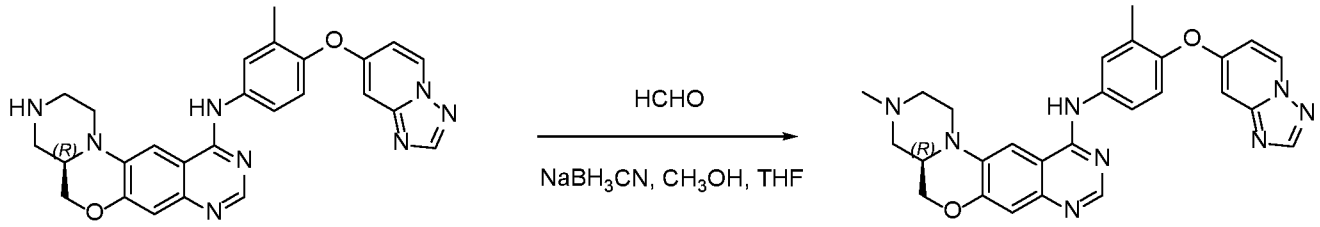
**[0460]** To a stirred mixture of tert-butyl (R)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (300.0 mg, 0.52 mmol) in DCM (6.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture basified to pH=8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (64/36, v/v) and then purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 40% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 59)** (43.1 mg, 17%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 481.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.41 (s, 1H), 8.93 (d, $J$ = 7.2 Hz, 1H), 8.38 - 8.37 (m, 2H), 7.85 - 7.81 (m, 2H), 7.66 (s, 1H), 7.19 (d, $J$ = 8.4 Hz, 1H), 7.04 - 7.00 (m, 2H), 6.80 (d, $J$ = 2.4 Hz, 1H), 4.38 - 4.35 (m, 1H), 4.04 - 3.83 (m, 2H), 3.14 - 3.11 (m, 2H), 3.01 - 2.98 (m, 1H), 2.85 - 2.80 (m, 1H), 2.74 - 2.68 (m, 2H), 2.38 - 2.32 (m, 1H), 2.20 (s, 3H).

***Example S60: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 60)***

**[0461] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 60)**

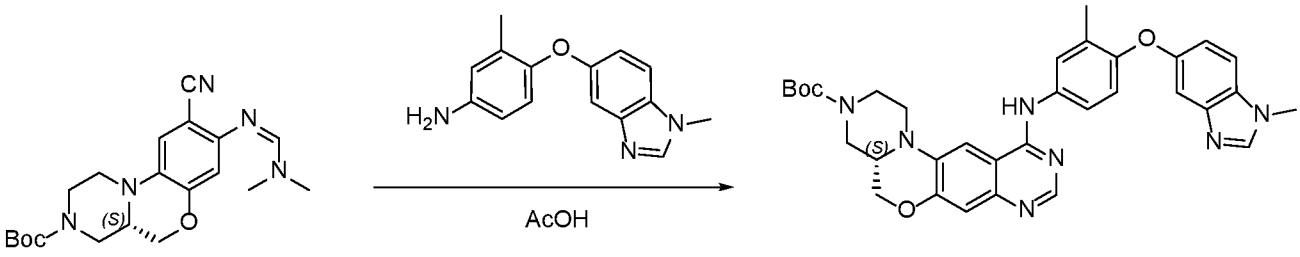



60

**[0462]** A mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (350.0 mg, 0.73 mmol) and HCHO (164.0 mg, 30%) in THF (8.0 mL) and methanol (2.0 mL) was stirred at room temperature for 1.5 h under $N_2$. Then $NaBH_3CN$ (206.0 mg, 3.28 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred room temperature for additional 1 h. After the reaction was completed, the reaction mixture was quenched with water at 0 °C and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (64/36, v/v) and then purified by Prep-HPLC with the following conditions ( Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 38% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 60)** (40.1 mg, 11%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.41 (s, 1H), 8.95 - 8.93 (m, 1H), 8.38 (s, 2H), 7.85 - 7.81 (m, 2H), 7.70 (s, 1H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.04 - 7.02 (m, 2H), 6.80 (d, $J$ = 2.4 Hz, 1H), 4.42 - 4.39 (m, 1H), 4.08 - 4.01 (m, 2H), 3.29 - 3.25 (m, 1H), 3.03 - 3.00 (m, 1H), 2.90 - 2.82 (m, 2H), 2.28 (s, 3H), 2.23 - 2.16 (m, 4H), 1.79 - 1.73 (m, 1H).

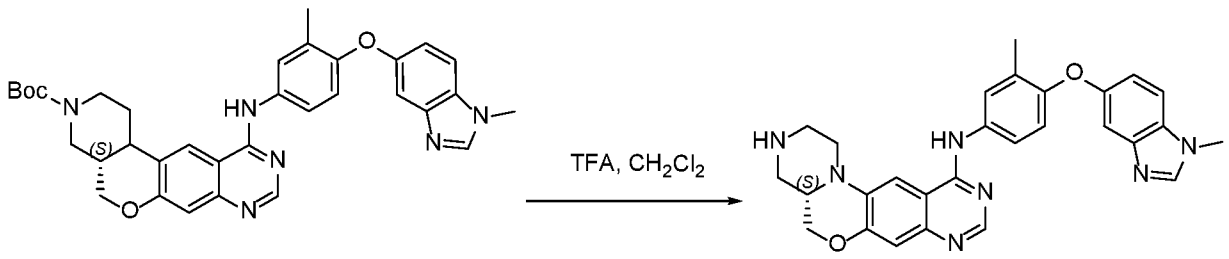
***Example S61: Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 61)***

**[0463] Step 1. Synthesis of tert-butyl (S)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**




**[0464]** To a solution of tert-butyl (S,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (310.0 mg, 0.80 mmol) in AcOH (10.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (203.7 mg, 0.80 mmol) at room temperature. The mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by phase flash chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (S)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (139.0 mg, 29%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

**[0465] Step 2. Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 61)**



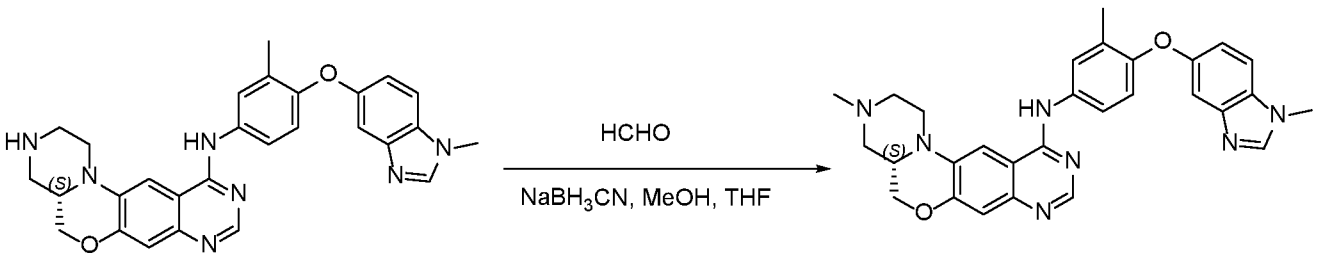

61

**[0466]** To a solution of tert-butyl (4aS)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,4a,5,12b-tetrahydro-2H-pyrido[4',3':4,5]pyrano[3,2-g]quinazoline-3(4H)-carboxylate (139.0 mg, 0.24 mmol) in dichloromethane (10.0 mL) was added TFA (5.0 mL) at room temperature. The mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH value of the mixture was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column:

XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 13.8 mL/min; Gradient: 64% B to 64% B in 15 min; Wave Length: 254 nm) to afford (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 61)** (14.0 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.32 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.69 - 7.56 (m, 4H), 7.09 - 6.86 (m, 4H), 4.38 - 4.35 (m, 1H), 4.03 - 3.98 (m, 1H), 3.94 - 3.91 (m, 1H), 3.84 (s, 3H), 3.14 - 3.07 (m, 2H), 3.00 - 2.98 (m, 1H), 2.85 - 2.79 (m, 1H), 2.68 - 2.65 (m, 1H), 2.37 - 2.34 (m, 2H), 2.25 (s, 3H).

***Example S62: Synthesis of (S)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 62)***

**[0467] Step 1. Synthesis of (S)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 62)**



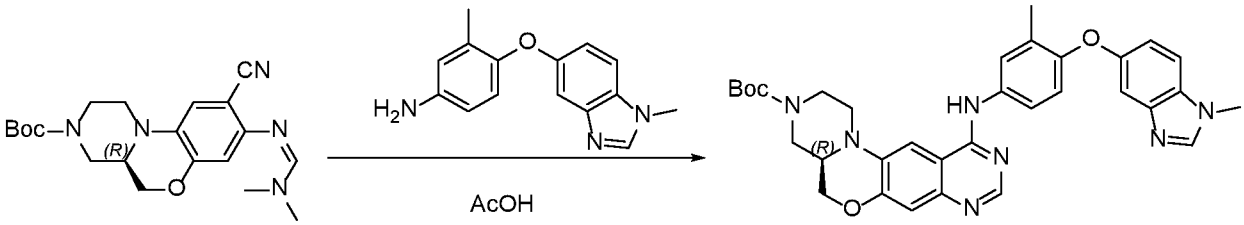

**62**

**[0468]** To a solution of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (456.0 mg, 0.92 mmol) in THF (20.0 mL) was added formaldehyde (83.2 mg, 30%) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (261.2 mg, 4.16mmol) was added to the mixture at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 52% B

to 67% B in 8 min; Wave Length: 254 nm) to afford (S)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 62)** (25.1 mg, 5%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 508.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.32 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.68 (s, 2H), 7.63 - 7.55 (m, 2H), 7.09 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.99 (m, 2H), 6.87 (d, $J$ = 8.8 Hz, 1H), 4.41 - 4.38 (m, 1H), 4.07 - 4.00 (m, 2H), 3.84 (s, 3H), 3.31 - 3.22 (m, 1H), 3.02 - 2.99 (m, 1H), 2.90 - 2.81 (m, 2H), 2.27 - 2.25 (m, 6H), 2.22 - 2.16 (m, 1H), 1.78 - 1.73 (m, 1H).

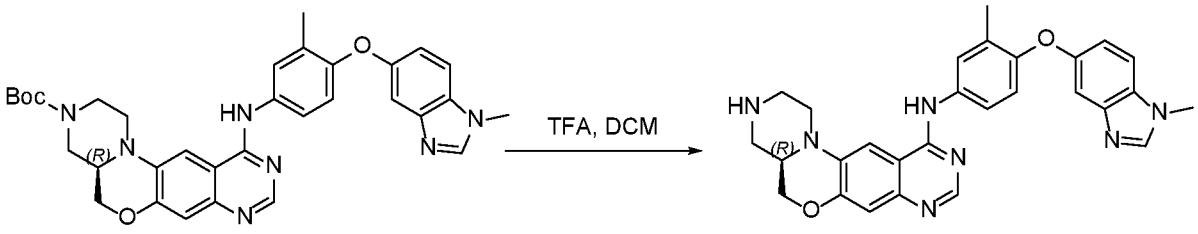
***Example S63: Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 63)***

**[0469] Step 1. Synthesis of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**




**[0470]** To a solution of tert-butyl (R,Z)-9-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (900.0 mg, 2.33 mmol) in acetic acid (10.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (591.4 mg, 2.33 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (1.0 g, 72%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

**[0471] Step 2. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 63)**

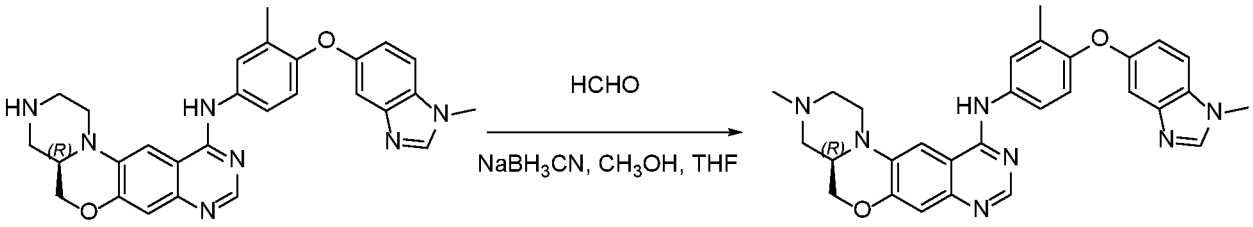



63

**[0472]** To a solution of tert-butyl (R)-11-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (900.0 mg, 1.51 mmol) in DCM (10.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was neutralized to pH = 8 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 63)** (10.1 mg, 1%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 494.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.32 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.68 (d, $J$ = 2.4 Hz, 1H), 7.64 - 7.56 (m, 3H), 7.09 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.97 (m, 2H), 6.87 (d, $J$ = 8.8 Hz, 1H), 4.38 - 4.35 (m, 1H), 4.03 - 3.91 (m, 2H), 3.84 (s, 3H), 3.14 - 3.10 (m, 2H), 3.00 - 2.97 (m, 1H), 2.85 - 2.79 (m, 1H), 2.72 - 2.67 (m, 2H), 2.37 - 2.27 (m, 1H), 2.25 (s, 3H).

***Example S64: Synthesis of (R)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 64)***

**[0473] Step 1. Synthesis of (R)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 64)**

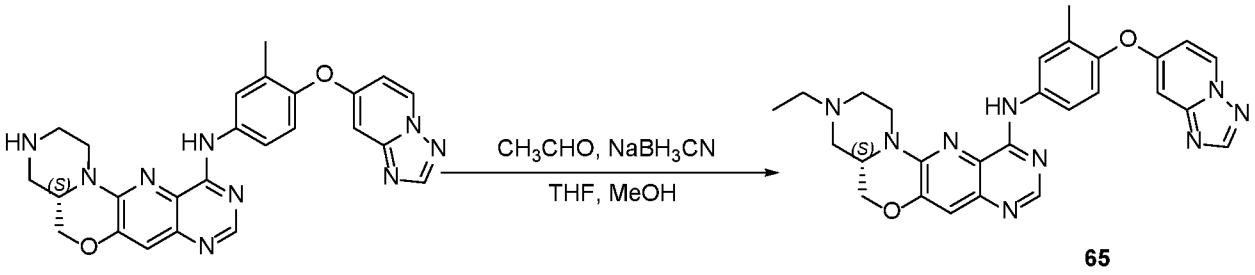



64

**[0474]** A mixture of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (200.0 mg, 0.40 mmol) and HCHO (97.3 mg, 40% in $H_2O$) in THF (4.0 mL) and MeOH (1.0 mL) was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (114.5 mg, 1.82 mmol) was added to the mixture at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was quenched with $H_2O$ at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 37% B in 8 min; Wave Length: 254 nm) to afford (R)-3-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 64)** (13.7 mg, 6%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 508.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.33 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.68 - 7.56 (m, 3H), 7.09 (d, $J$ = 2.4 Hz, 1H), 7.02 - 6.99 (m, 2H), 6.87 (d, $J$ = 8.8 Hz, 1H), 4.41 - 4.37 (m, 1H), 4.07 - 4.00 (m, 2H), 3.84 (s, 3H), 3.24 - 3.20 (m, 1H), 3.02 - 2.99 (m, 1H), 2.90 - 2.83 (m, 2H), 2.28 - 2.25 (m, 6H), 2.23 - 2.18 (m, 1H), 1.80 - 1.70 (m, 1H).

***Example S65: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-ethyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 65)***

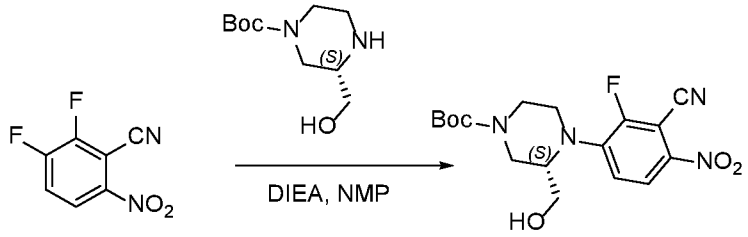
**[0475] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-ethyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 65)**




**[0476]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (200.0 mg, 0.42 mmol) in MeOH/THF (2.0 mL/12.0 mL) was added $CH_3CHO$ (0.1 mL, 5.0 mol/L) at room temperature. The resulting mixture was stirred at 0 °C for 1 h. Then $NaBH_3CN$ (26.1 mg, 0.42 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was diluted with $H_2O$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 44% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3-ethyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 65)** (24.2 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =510.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.30 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.40 - 8.38 (m, 2H), 8.01 - 7.97 (m, 2H), 7.23 - 7.20 (m, 2H), 7.04 - 7.02 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 5.06 - 5.02 (m, 1H), 4.48 - 4.46 (m, 1H), 4.09 - 4.04 (m, 1H), 3.64 - 3.61 (m, 1H), 3.07 - 3.02 (m, 2H), 2.97 - 2.91 (m, 1H), 2.47 - 2.41 (m, 2H), 2.20 (s, 3H), 2.13 - 2.08 (m, 1H), 1.77 - 1.72 (m, 1H), 1.09 - 1.06 (m, 3H).

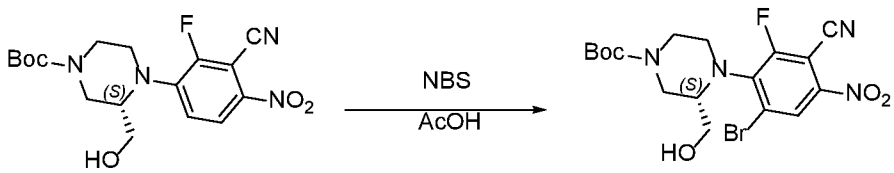
***Example S66: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 66)***

**[0477]** **Step 1. Synthesis of tert-butyl (S)-4-(3-cyano-2-fluoro-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



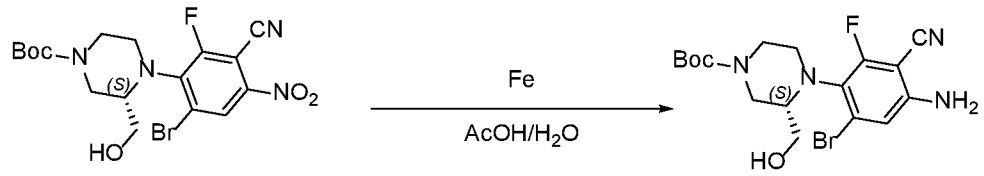

**[0478]** To a solution of 2,3-difluoro-6-nitrobenzonitrile (4.0 g, 21.74 mmol) in NMP (40.0 mL) was added tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (10.3 g, 47.83 mmol) and DIEA (8.4 g, 65.22 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (37/63, v/v) to afford tert-butyl (S)-4-(3-cyano-2-fluoro-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (5.0 g, 60%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =381.2.

**[0479] Step 2. Synthesis of tert-butyl (S)-4-(6-bromo-3-cyano-2-fluoro-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



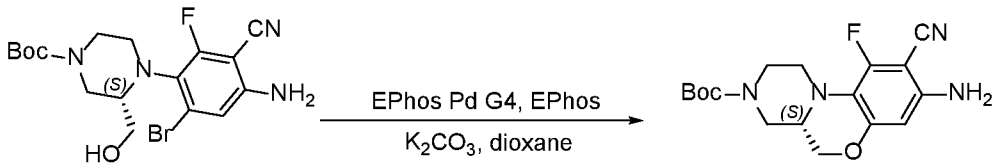

**[0480]** To a solution of tert-butyl (S)-4-(3-cyano-2-fluoro-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.0 g, 10.53 mmol) in AcOH (100.0 mL) was added NBS (19.5 g, 105.30 mmol) at room temperature. The mixture was stirred at room temperature for 16 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (S)-4-(6-bromo-3-cyano-2-fluoro-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.0 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$= 459.1.

**[0481] Step 3. Synthesis of tert-butyl (S)-4-(4-amino-6-bromo-3-cyano-2-fluorophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate**



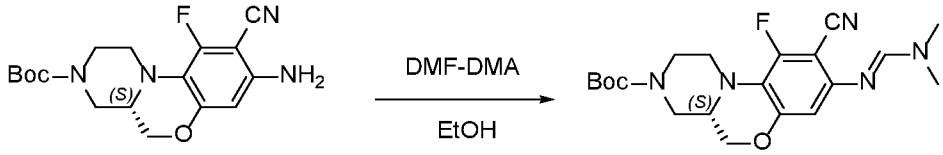

**[0482]** To a solution of tert-butyl (S)-4-(6-bromo-3-cyano-2-fluoro-4-nitrophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.0 g, 8.73 mmol) in AcOH/$H_2O$ (40.0 mL/8.0 mL) was added Fe (2.4 g, 43.65 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (22/78, v/v) to afford tert-butyl (S)-4-(4-amino-6-bromo-3-cyano-2-fluorophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (2.0 g, 53%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 429.1.

**[0483] Step 4. Synthesis of tert-butyl (S)-8-amino-9-cyano-10-fluoro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**



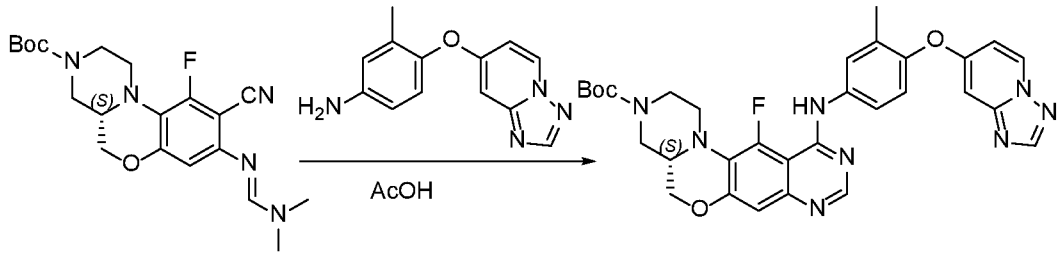

**[0484]** To a solution of tert-butyl (S)-4-(4-amino-6-bromo-3-cyano-2-fluorophenyl)-3-(hydroxymethyl)piperazine-1-carboxylate (800.0 mg, 1.86 mmol) in 1,4-dioxane (10.0 mL) was added $K_2CO_3$ (772.6 mg, 5.59 mmol), EPhos Pd G4 (171.2 mg, 0.19 mmol) and EPhos (199.3 mg, 0.37 mmol) at room temperature under $N_2$. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (15/85, v/v) to afford tert-butyl (S)-8-amino-9-cyano-10-fluoro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (400.0 mg, 61%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 349.2.

**[0485] Step 5. Synthesis of tert-butyl (S,E)-9-cyano-8-(((dimethylamino)methylene)amino)-10-fluoro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate**




**[0486]** To a solution of tert-butyl (S)-8-amino-9-cyano-10-fluoro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (400.0 mg, 1.15 mmol) in EtOH (5.0 mL) was added DMF-DMA (410.4 mg, 3.44 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford tert-butyl (S,E)-9-cyano-8-(((dimethylamino)methylene)amino)-10-fluoro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (400.0 mg, crude) as a brown solid. LCMS (ESI, m/z): [M+H]+ = 404.2.

**[0487] Step 6. Synthesis of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-12-fluoro-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate**

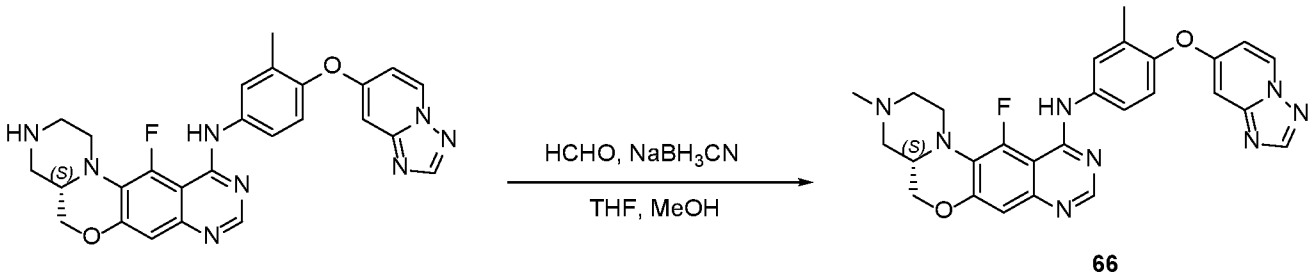



**[0488]** To a solution of tert-butyl (S,E)-9-cyano-8-(((dimethylamino)methylene)amino)-10-fluoro-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (240.0 mg, crude) in AcOH (4.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (171.5 mg, 0.71 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with MeOH/$H_2O$ (66/34, v/v) to afford tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-12-fluoro-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (300.0 mg, 84%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 599.3.

**[0489] Step 7. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine**


**[0490]** To a solution of tert-butyl (S)-11-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-12-fluoro-1,2,4a,5-tetrahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazoline-3(4H)-carboxylate (280.0 mg, 0.47 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was adjusted pH to 8.0 with aq. $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (200.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 499.2.

**[0491] Step 8. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 66)**



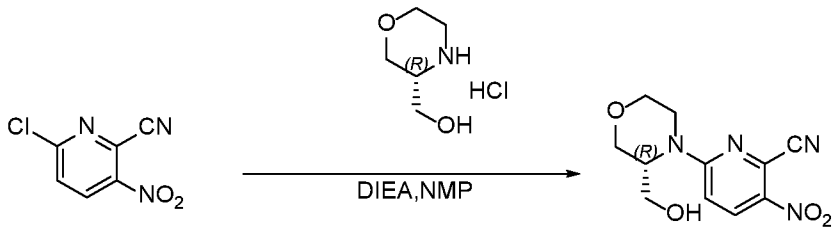

66

**[0492]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (100.0 mg, crude) in THF/MeOH (2.0 mL/0.5 mL) was added HCHO (51.0 mg, 30%) at room temperature. The mixture was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (37.8 mg,

0.60 mmol) was added to the mixture at 0 °C under $N_2$. The mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was diluted with water and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 36% B in 12 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1',2':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 66)** (18.2 mg, 17%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 513.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.98 - 8.93 (m, 2H), 8.39 - 8.37 (m, 2H), 7.79 - 7.77 (m, 2H), 7.19 (d, $J$ = 9.6 Hz, 1H), 7.04 - 7.00 (m, 2H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.37 - 4.34 (m, 1H), 4.22 - 4.17 (m, 1H), 3.87 - 3.84 (m, 1H), 3.37 - 3.29 (m, 1H), 3.21 - 3.16 (m, 1H), 2.74 - 2.64 (m, 2H), 2.40 - 2.29 (m, 1H), 2.21 - 2.19 (m, 7H).

***Example S67: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 67)***

**[0493] Step 1. Synthesis of (R)-6-(3-(hydroxymethyl)morpholino)-3-nitropicolinonitrile**

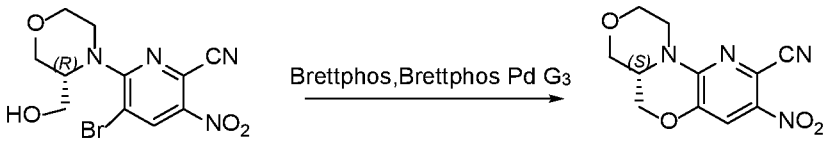



**[0494]** To a solution of 6-chloro-3-nitropicolinonitrile (3.4 g, 18.52 mmol) in NMP (34.0 mL) was added (R)-morpholin-3-ylmethanol hydrochloride (6.3 g, 40.75 mmol) and DIEA (14.4 g, 111.14 mmol) at room temperature. The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (88/12, v/v) to afford (R)-6-(3-(hydroxymethyl)morpholino)-3-nitropicolinonitrile (4.0 g, 81%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 265.1.

**[0495] Step 2. Synthesis of (R)-5-bromo-6-(3-(hydroxymethyl)morpholino)-3-nitropicolinonitrile**

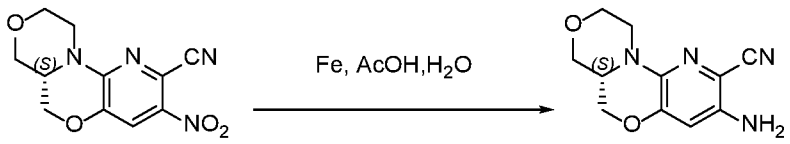

**[0496]** To a solution of (R)-6-(3-(hydroxymethyl)morpholino)-3-nitropicolinonitrile (1.0 g, 3.78 mmol) in DMF (10.0 mL) was added NBS (1.4 g, 7.57 mmol) at room temperature. The mixture was stirred at room temperature for 72 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (48/52, v/v) to afford (R)-5-bromo-6-(3-(hydroxymethyl)morpholino)-3-nitropicolinonitrile (950.0 mg, 73%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+ = 343.0$.

**[0497] Step 3. Synthesis of (S)-3-nitro-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**




**[0498]** To a solution of (R)-5-bromo-6-(3-(hydroxymethyl)morpholino)-3-nitropicolinonitrile (930 mg, 2.71 mmol) in 1,4-dioxane (10.0 mL) was added $Cs_2CO_3$ (2649.2 mg, 8.13 mmol), Brettphos (291.0 mg, 0.54 mmol) and Brettphos Pd G3 (245.7 mg, 0.27 mmol) at room temperature under $N_2$. The mixture was stirred at 100 °C for 2 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (25/75, v/v) to afford (S)-3-nitro-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (470.0 mg, 66%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 263.1$.

**[0499] Step 4. Synthesis of (S)-3-amino-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**

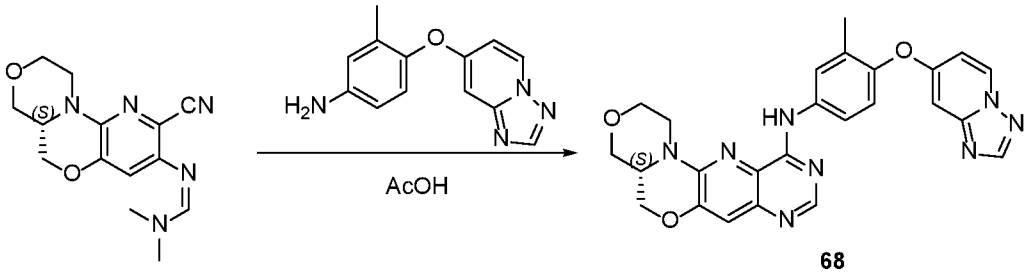



**[0500]** To a solution of (S)-3-nitro-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (460.0 mg, 1.75 mmol) in AcOH/$H_2O$ (5.0 mL/0.1 mL) was added Fe (489.8 mg, 8.77 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (95/5, v/v) to afford (S)-3-amino-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (350.0 mg, 85%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 233.1.

**[0501] Step 5. Synthesis of (S,Z)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**


**[0502]** To a solution of (S)-3-amino-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (340.0 mg, 1.46 mmol) in EtOH (5.0 mL) was added DMF-DMA (523.4 mg, 4.39 mmol) at room temperature. The mixture was stirred at 80 °C for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford (S,Z)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (460.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 288.1.

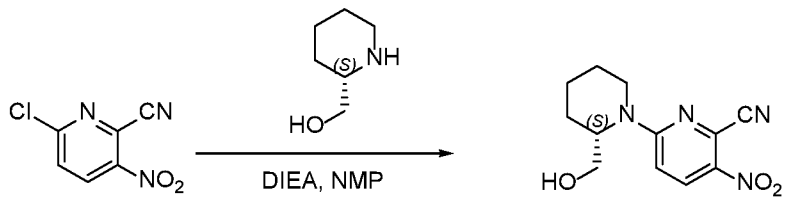
**[0503] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 67)**




**[0504]** To a solution of (S,Z)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (450.0 mg, crude) in AcOH (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (376.3 mg, 1.57 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (97/3, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 50% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 68)** (33.0 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 483.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.33 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.41 - 8.38 (m, 2H), 8.02 - 7.96 (m, 2H), 7.26 - 7.20 (m, 2H), 7.04 - 7.02 (m, 1H), 6.78 (d, $J$ = 2.8 Hz, 1H), 4.97 - 4.94 (m, 1H), 4.46 - 4.42 (m, 1H), 4.09 - 3.95 (m, 3H), 3.77 - 3.61 (m, 2H), 3.33 - 3.22 (m, 1H), 3.04 - 3.01 (m, 1H), 2.20 (s, 3H).

***Example S68: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrido[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 68)***

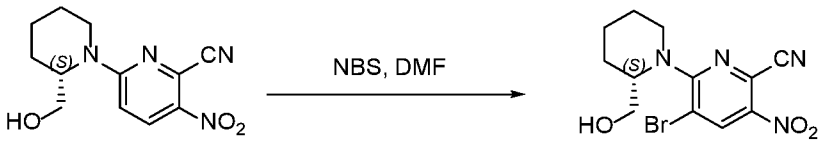
**[0505]** **Step 1. Synthesis of 6-[(2S)-2-(hydroxymethyl)piperidin-1-yl]-3-nitropyridine-2-carbonitrile**




**[0506]** To a solution of 6-chloro-3-nitropyridine-2-carbonitrile (3.0 g, 16.34 mmol) in NMP (30.0 mL) was added (2S)-piperidin-2-ylmethanol (2.5 g, 21.25 mmol) and DIEA (10.6 g, 81.72 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 3 h. After the

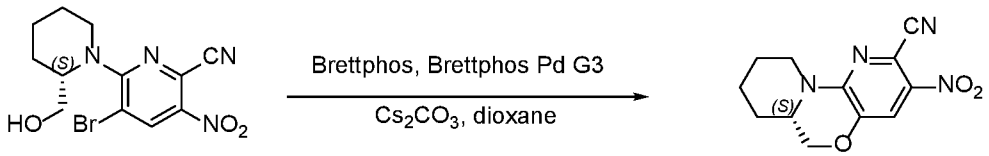
reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ ethyl acetate (47/53, v/v) to afford 6-[(2S)-2-(hydroxymethyl)piperidin-1-yl]-3-nitropyridine-2-carbonitrile (3.3 g, 76%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =263.2.

**[0507] Step 2. Synthesis of 5-bromo-6-[(2S)-2-(hydroxymethyl)piperidin-1-yl]-3-nitropyridine-2-carbonitrile**




**[0508]** To a solution of 6-[(2S)-2-(hydroxymethyl)piperidin-1-yl]-3-nitropyridine-2-carbonitrile (3.0 g, 11.44 mmol) in DMF (30.0 mL) was added NBS (3.1 g, 17.16 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (84/16, v/v) to afford 5-bromo-6-[(2S)-2-(hydroxymethyl)piperidin-1-yl]-3-nitropyridine-2-carbonitrile (420.0 mg, 10%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =341.0.

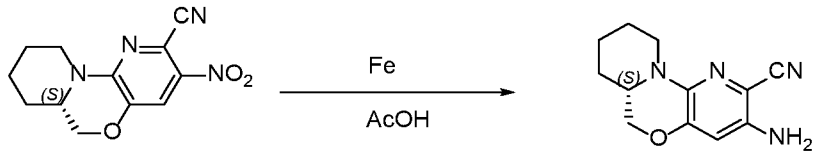
**[0509] Step 3. Synthesis of (S)-3-nitro-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazine-2-carbonitrile**




**[0510]** To a solution of 5-bromo-6-[(2S)-2-(hydroxymethyl)piperidin-1-yl]-3-nitropyridine-2-carbonitrile (183.0 mg, 0.54 mmol) in dioxane (5.0 mL) was added $Cs_2CO_3$ (524.3 mg, 1.61 mmol), BrettPhos (57.6 mg, 0.11 mmol) and BrettPhos Pd G3 (48.6 mg, 0.05 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The

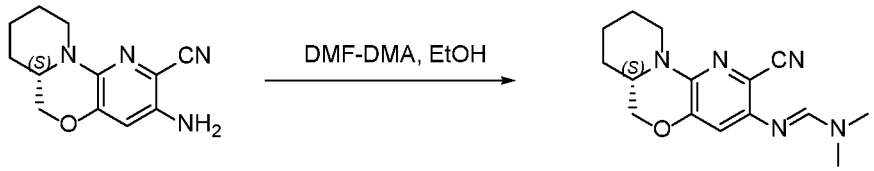
combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ ethyl acetate (64/36, v/v) to afford (S)-3-nitro-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazine-2-carbonitrile (80.0 mg, 57%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =261.1.

**[0511] Step 4. Synthesis of (S)-3-amino-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazine-2-carbonitrile**



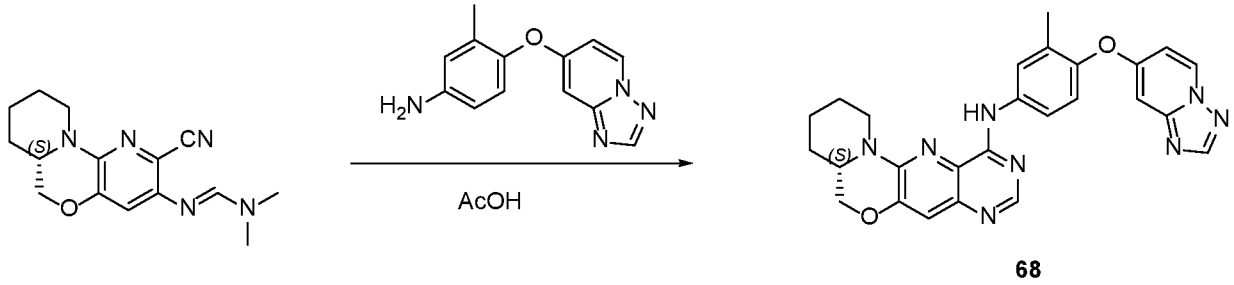

**[0512]** To a stirred solution of (S)-3-nitro-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazine-2-carbonitrile (80.0 mg, 0.31 mmol) in AcOH/$H_2O$ (2.0 mL/0.1 mL) was added Fe (65.3 mg, 1.55 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (1/1, v/v) to afford (S)-3-amino-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazine-2-carbonitrile (70.0 mg, 98%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =231.1.

**[0513] Step 5. Synthesis of (S,E)-N'-(2-cyano-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**




**[0514]** To a solution of (S)-3-amino-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazine-2-carbonitrile (70.0 mg, 0.30 mmol) in EtOH (3.0 mL) was added DMF-DMA (181.1 mg, 1.52 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford (S,E)-N'-(2-cyano-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (60.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =286.2.

**[0515] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrido[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 68)**

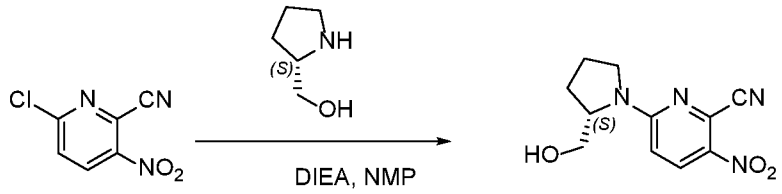



68

**[0516]** To a solution of (S,E)-N'-(2-cyano-6,6a,7,8,9,10-hexahydrodipyrido[3,2-b:1',2'-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (60.0 mg, crude) in AcOH (3.0 mL) was added 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (101.0 mg, 0.42 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (24/ 76, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD $C_{18}$ Column, 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 52% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrido[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 68)** (9.9 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =481.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.25 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.46 - 8.38 (m, 2H), 8.08 - 7.97 (m, 2H), 7.24 - 7.18 (m, 2H), 7.04 - 7.02 (m, 1H), 6.84 (s, 1H), 5.21 - 5.18 (m, 1H), 4.42 - 4.39 (m, 1H), 4.07 - 4.02 (m, 1H), 3.56 - 3.48 (m, 1H), 2.79 - 2.73 (m, 1H), 2.20 (s, 3H), 1.87 - 1.78 (m, 3H), 1.59 - 1.51 (m, 2H), 1.33 - 1.24 (m, 1H).

***Example S69: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,3a,4-tetrahydro-1H-pyrimido[4',5':5,6]pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-10-amine (Compound 69)***

**[0517] Step 1. Synthesis of (S)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-3-nitropicolinonitrile**

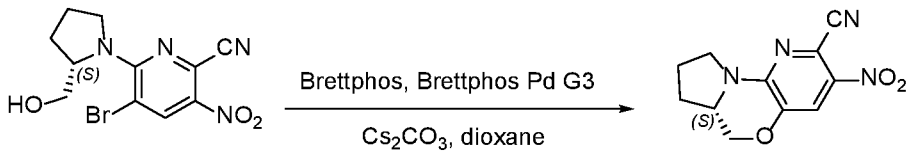



**[0518]** To a solution of 6-chloro-3-nitropicolinonitrile (4.0 g, 21.79 mmol) in NMP (40.0 mL) was added (S)-pyrrolidin-2-ylmethanol (4.4 g, 43.58 mmol) and DIEA (14.1 g, 108.96 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/99, v/v) to afford (S)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-3-nitropicolinonitrile (4.8 g, 89%) as a green solid. LCMS (ESI, m/z): $[M+H]^+$ =249.1.

**[0519] Step 2. Synthesis of (S)-5-bromo-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-3-nitropicolinonitrile**

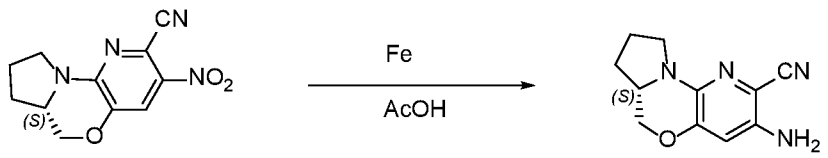

**[0520]** To a solution of (S)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-3-nitropicolinonitrile (4.8 g, 19.34 mmol) in DMF (200.0 mL) was added NBS (5.2 g, 29.00 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/99, v/v) to afford (S)-5-bromo-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-3-nitropicolinonitrile (1.1 g, 17%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =327.0.

**[0521] Step 3. Synthesis of (S)-3-nitro-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-2-carbonitrile**



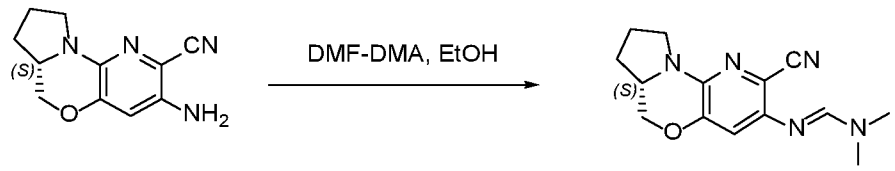

**[0522]** To a solution of (S)-5-bromo-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-3-nitropicolinonitrile (1.1 g, 3.36 mmol) in 1,4-dioxane (50.0 mL) was added $Cs_2CO_3$ (2.1 g, 10.07 mmol), BrettPhos (722.0 mg, 1.35 mmol) and BrettPhos Pd G3 (609.6 mg, 0.67 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (S)-3-nitro-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-2-carbonitrile (270.0 mg, 33%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =247.1.

**[0523] Step 4. Synthesis of (S)-3-amino-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-2-carbonitrile**



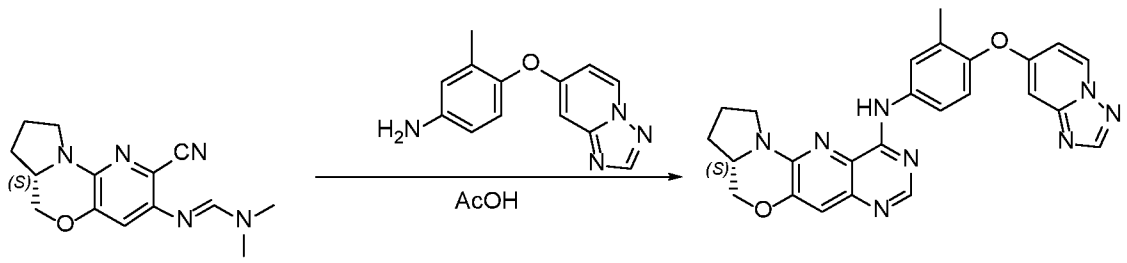

**[0524]** To a solution of (S)-3-nitro-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-2-carbonitrile (350.0 mg, 1.42 mmol) in AcOH (9.0 mL)/$H_2O$ (0.2 mL) was added Fe (396.91 mg, 7.11 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (S)-3-amino-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-2-carbonitrile (105.0 mg, 34%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =217.1

**[0525] Step 5. Synthesis of (S,E)-N'-(2-cyano-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**




**[0526]** To a solution of (S)-3-amino-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazine-2-carbonitrile (205.0 mg, 0.95 mmol) in EtOH (7.0 mL) was added DMF-DMA (338.9 mg, 2.84 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was diluted with water and then filtered. The precipitated solids were collected by filtration and washed with water to afford (S,E)-N'-(2-cyano-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (159.0 mg, 62%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =272.1.

**[0527] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,3a,4-tetrahydro-1H-pyrimido[4',5':5,6]pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-10-amine (Compound 69)**



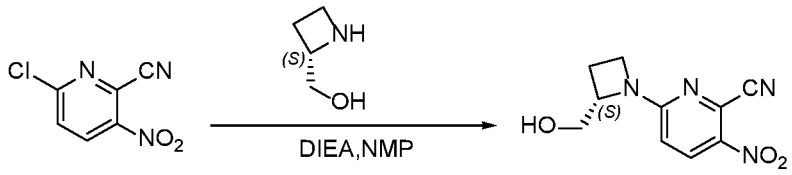

**69**

**[0528]** To a solution of (S,E)-N'-(2-cyano-6a,7,8,9-tetrahydro-6H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (206.0 mg, 0.76 mmol) in AcOH (7.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (200.7 mg, 0.84 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min, 35% B to 55% B in 16 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,3a,4-tetrahydro-1H-pyrimido[4',5':5,6]pyrido[3,2-b]pyrrolo[1,2-d][1,4]oxazin-10-amine **(Compound 69)** (7.0 mg, 2%) as a yellow solid. LCMS (ESI, m/z):

$[M+H]^+$ =467.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.12 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.39 - 8.37 (m, 2H), 8.04 - 7.97 (m, 2H), 7.26 - 7.20 (m, 2H), 7.03 - 7.01 (m, 1H), 6.79 (s, 1H), 4.71 - 4.68 (m, 1H), 3.87 - 3.66 (m, 4H), 2.68 - 2.11 (m, 5H), 2.07 - 1.94 (m, 1H), 1.63 - 1.53 (m, 1H).

***Example S70: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,2a,3-tetrahydroazeto[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-9-amine (Compound 70)***

**[0529] Step 1. Synthesis of (S)-6-(2-(hydroxymethyl)azetidin-1-yl)-3-nitropicolinonitrile**




**[0530]** To a solution of 6-chloro-3-nitropicolinonitrile (0.7 g, 3.68 mmol) in NMP (10.0 mL) was added (S)-azetidin-2-ylmethanol hydrochloride (1.0 g, 8.09 mmol) and DIEA (2.9 g, 22.07 mmol) at room temperature. The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (92/8, v/v) to afford (S)-6-(2-(hydroxymethyl)azetidin-1-yl)-3-nitropicolinonitrile (0.8 g, 92%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 235.1.

**[0531] Step 2. Synthesis of (S)-5-bromo-6-(2-(hydroxymethyl)azetidin-1-yl)-3-nitropicolinonitrile**

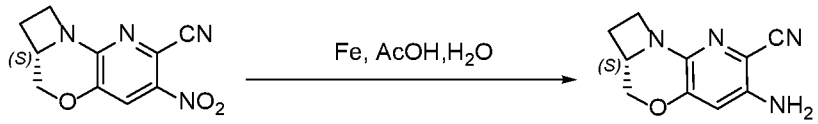

**[0532]** To a solution of (S)-6-(2-(hydroxymethyl)azetidin-1-yl)-3-nitropicolinonitrile (790.0 mg, 3.37 mmol) in DMF (7.0 mL) was added NBS (1.2 g, 6.75 mmol) at room temperature. The mixture was stirred at room temperature for 72 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (49/51, v/v) to afford (S)-5-bromo-6-(2-

(hydroxymethyl)azetidin-1-yl)-3-nitropicolinonitrile (680.0 mg, 64%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 313.0.

**[0533] Step 3. Synthesis of (S)-3-nitro-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**

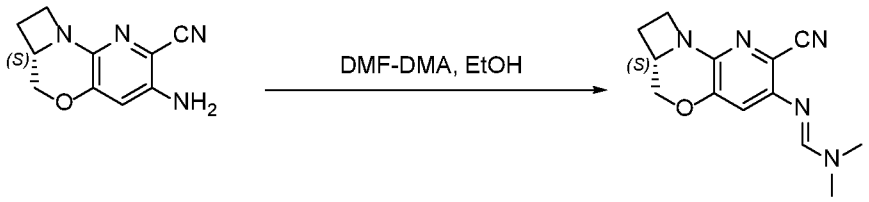

**[0534]** To a solution of (S)-5-bromo-6-(2-(hydroxymethyl)azetidin-1-yl)-3-nitropicolinonitrile (640.0 mg, 2.04 mmol) in 1,4-dioxane (7.0 mL) was added $K_2CO_3$ (847.5 mg, 6.13 mmol), Brettphos (219.4 mg, 0.41 mmol) and Brettphos Pd G3 (185.3 mg, 0.20 mmol) at room temperature under $N_2$. The mixture was stirred at 100 °C for 2 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (15/85, v/v) to afford (S)-3-nitro-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (360.0 mg, 75%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 233.1.

**[0535] Step 4. Synthesis of (S)-3-amino-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile**



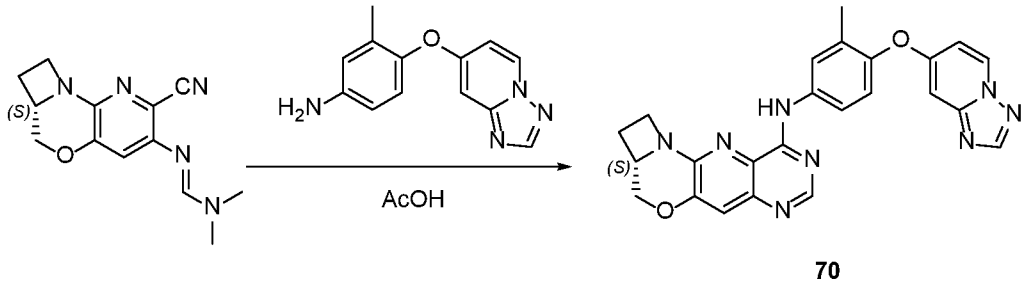

**[0536]** To a solution of (S)-3-nitro-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (350.0 mg, 1.51 mmol) in AcOH/$H_2O$ (5.0 mL/0.1 mL) was added Fe (420.9 mg, 7.54 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (95/5, v/v) to afford (S)-3-amino-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (180.0 mg, 59%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 203.1.

**[0537] Step 5. Synthesis of (S,Z)-N'-(2-cyano-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**




**[0538]** To a solution of (S)-3-amino-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazine-2-carbonitrile (160.0 mg, 0.79 mmol) in EtOH (5.0 mL) was added DMF-DMA (282.9 mg, 2.37 mmol) at room temperature. The mixture was stirred at 80 °C for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford (S,Z)-N'-(2-cyano-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (100.0 mg, crude) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 258.1.

**[0539] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,2a,3-tetrahydroazeto[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-9-amine (Compound 70)**



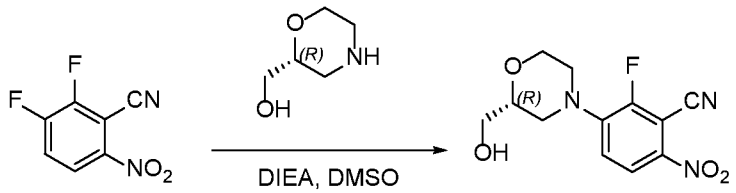

**70**

**[0540]** To a solution of (S,Z)-N'-(2-cyano-6,6a,7,8-tetrahydroazeto[1,2-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (90.0 mg, crude) in AcOH (3.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (84.0 mg, 0.35 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with MeOH/$H_2O$ (55/45, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 20% B to 40% B in 10 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-1,2,2a,3-tetrahydroazeto[1,2-

d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-9-amine **(Compound 70)** (5.0 mg, 3%) as a dark-yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 453.1. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.26 (s, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 8.01 - 7.98 (m, 2H), 7.38 (s, 1H), 7.20 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.01 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 4.77 - 4.73 (m, 1H), 4.59 - 4.48 (m, 2H), 4.45 - 4.39 (m, 1H), 3.86 - 3.81 (m, 1H), 2.71 - 2.63 (m, 1H), 2.51 - 2.42 (m, 1H), 2.19 (s, 3H).

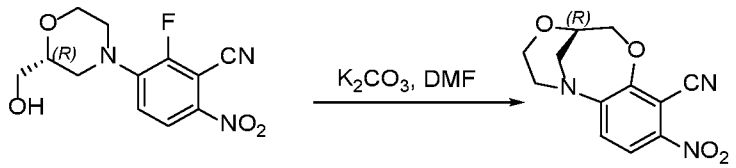
***Example S71: Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,5,6-tetrahydro-3,7-methano[1,4,7]dioxazonino[5,6-f]quinazolin-13-amine (Compound 71)***

**[0541] Step 1. Synthesis of (R)-2-fluoro-3-(2-(hydroxymethyl)morpholino)-6-nitrobenzonitrile**



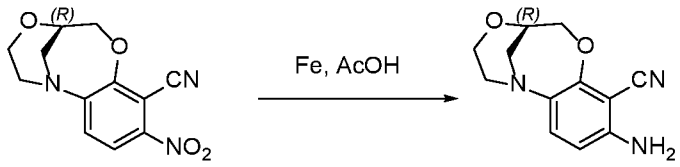

**[0542]** To a solution 2,3-difluoro-6-nitrobenzonitrile (4.0 g, 3.80 mmol) in DMSO (30.0 mL) was added DIEA (14.0 g, 108.63 mmol) and (R)-morpholin-2-ylmethanol hydrochloride (4.7 g, 4.07 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (R)-2-fluoro-3-(2-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (5.0 g, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 282.1.

**[0543] Step 2. Synthesis of (3R)-10-nitro-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile**



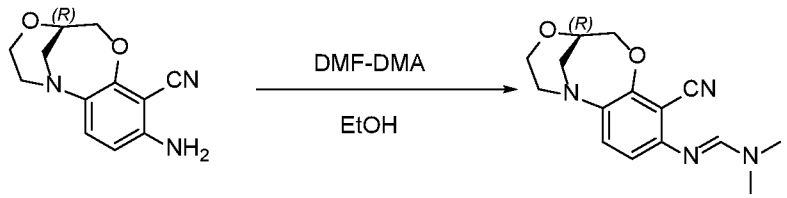
**[0544]** To a solution of (R)-2-fluoro-3-(2-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (2.0 g, 7.11 mmol) in DMF (30.0 mL) was added $K_2CO_3$ (2.9 g, 21.33 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (3R)-10-nitro-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (100.0 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 262.1.

**[0545] Step 3. Synthesis of (3R)-10-amino-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile**




**[0546]** To a solution of (3R)-10-nitro-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (100.0 mg, 0.38) in AcOH (5.0 mL) and $H_2O$ (1.0 mL) was added Fe (106.8 mg, 1.91 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (3R)-10-amino-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (100.0 mg, 90%) as a yellow solid LCMS (ESI, m/z): $[M+H]^+$ = 232.1.

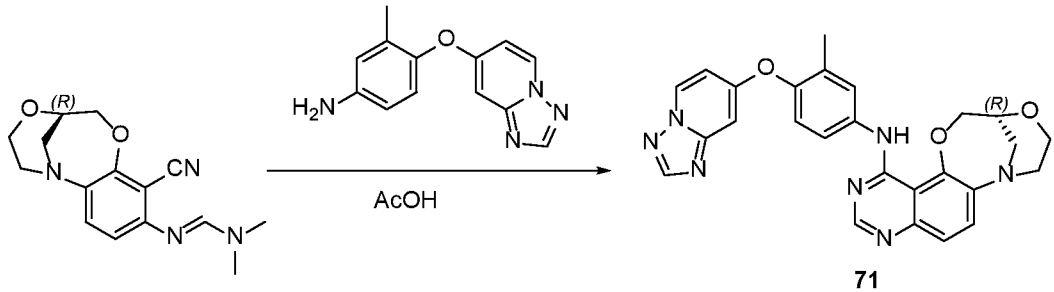
**[0547] Step 4. Synthesis of (E)-N'-((3R)-11-cyano-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonin-10-yl)-N,N-dimethylformimidamide**




**[0548]** To a solution of (3R)-10-amino-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (100.0 mg, 0.43 mmol) in EtOH (5.0 mL)

was added DMF-DMA (154.5 mg, 1.29 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford (E)-N'-((3R)-11-cyano-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonin-10-yl)-N,N-dimethylformimidamide (150.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 287.1.

**[0549] Step 5. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,5,6-tetrahydro-3,7-methano[1,4,7]dioxazonino[5,6-f]quinazolin-13-amine (Compound 71)**

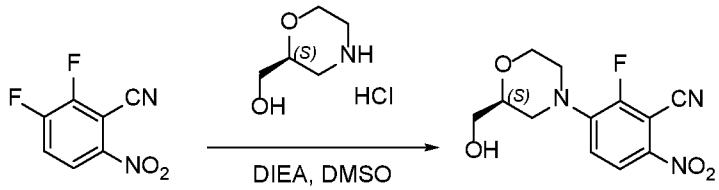



71

**[0550]** A mixture of (E)-N'-((3R)-11-cyano-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonin-10-yl)-N,N-dimethylformimidamide (150.0 mg, 0.52 mmol) and 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (125.8 mg, 0.52 mmol) in HOAc (5.0 mL) was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC with the following conditions: Column: Xselect CSH C18 OBD Column 30x150 mm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 35% B in 12 min; Wave Length: 254 nm) to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,5,6-tetrahydro-3,7-methano[1,4,7]dioxazonino[5,6-f]quinazolin-13-amine **(Compound 71)** (26.1 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.13 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 7.95 - 7.92 (m, 1H), 7.84 (s, 1H), 7.55 (d, $J$ = 8.8 Hz, 1H), 7.40 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 5.04 - 4.99 (m, 1H), 4.67 - 4.65 (m, 1H), 4.34 - 4.32 (s, 1H), 4.19 - 4.12 (m, 1H), 4.00 - 3.96 (m, 1H), 3.59 - 3.52 (m, 2H), 3.48 - 3.42 (m, 1H), 3.38 - 3.35 (m, 1H), 2.20 (s, 3H).

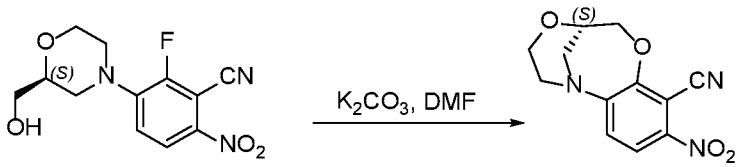
***Example S72: Synthesis of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,5,6-tetrahydro-3,7-methano[1,4,7]dioxazonino[5,6-f]quinazolin-13-amine (Compound 72)***

**[0551] Step 1. Synthesis of (S)-2-fluoro-3-(2-(hydroxymethyl)morpholino)-6-nitrobenzonitrile**




**[0552]** To a solution of 2,3-difluoro-6-nitrobenzonitrile (4.0 g, 21.727 mmol) in DMSO (40.0 mL) was added DIEA (14.1 g, 108.63 mmol) and (S)-morpholin-2-ylmethanol hydrochloride (5.0 g, 32.59 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (S)-2-fluoro-3-(2-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (4.0 g, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 282.1.

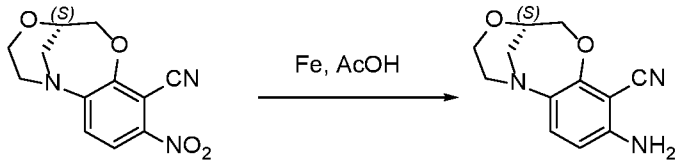
**[0553] Step 2. Synthesis of (3S)-10-nitro-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile**




**[0554]** To a solution of (S)-2-fluoro-3-(2-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (4.0 g, 14.22 mmol) in DMF (50.0 mL) was added $K_2CO_3$ (5.9 g, 42.66 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (3S)-10-nitro-

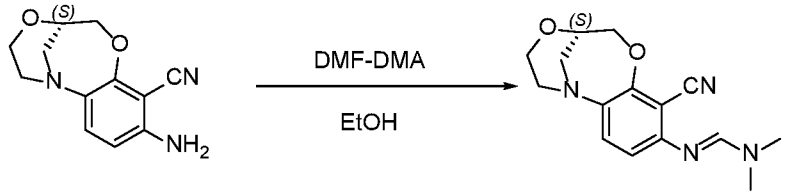
2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (380.0 mg, 9%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 262.1.

**[0555] Step 3. Synthesis of (3S)-10-amino-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile**



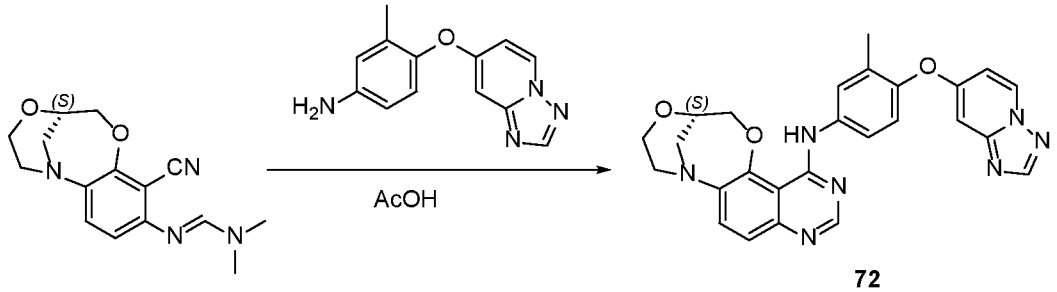

**[0556]** To a solution of (3S)-10-nitro-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (380.0 mg, 1.45 mmol) in AcOH (5.0 mL) and $H_2O$ (0.5 mL) was added Fe (406.1 mg, 7.27 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) to afford (3S)-10-amino-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (300.0 mg, 75%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 232.1.

**[0557] Step 4. Synthesis of (E)-N'-((3S)-11-cyano-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonin-10-yl)-N,N-dimethylformimidamide**




**[0558]** To a solution of (3S)-10-amino-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonine-11-carbonitrile (300.0 mg, 1.29 mmol) in EtOH (5.0 mL,) was added DMF-DMA (772.5 mg, 6.48 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford (E)-N'-((3S)-11-cyano-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonin-10-yl)-N,N-dimethylformimidamide (200.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 287.1.

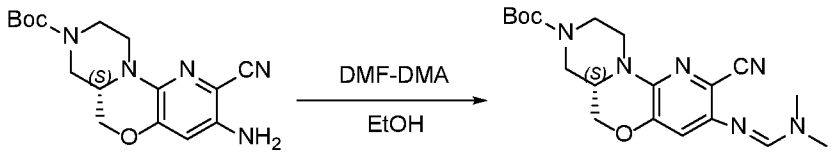
**[0559] Step 5. Synthesis of (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,5,6-tetrahydro-3,7-methano[1,4,7]dioxazonino[5,6-f]quinazolin-13-amine (Compound 72)**




**[0560]** To a solution of (E)-N'-((3S)-11-cyano-2,3,5,6-tetrahydro-3,7-methanobenzo[e][1,4,7]dioxazonin-10-yl)-N,N-dimethylformimidamide (200.0 mg, crude) in HOAc (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (237.0 mg, 1.04 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (3/1, v/v) to afford (3S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-2,3,5,6-tetrahydro-3,7-methano[1,4,7]dioxazonino[5,6-f]quinazolin-13-amine **(Compound 72)** (21.4 mg, 6%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.13 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 7.94 - 7.91 (m, 1H), 7.83 (d, $J$ = 2.0 Hz, 1H), 7.55 (d, $J$ = 8.8 Hz, 1H), 7.40 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.4 Hz, 1H), 7.04 - 7.01 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 5.04 - 4.99 (m, 1H), 4.70 - 4.66 (m, 1H), 4.36 - 4.32 (m, 1H), 4.18 - 4.07 (m, 1H), 4.00 - 3.96 (m, 1H), 3.59 - 3.42 (m, 3H), 3.17 (d, $J$ = 4.8 Hz, 1H), 2.20 (s, 3H).

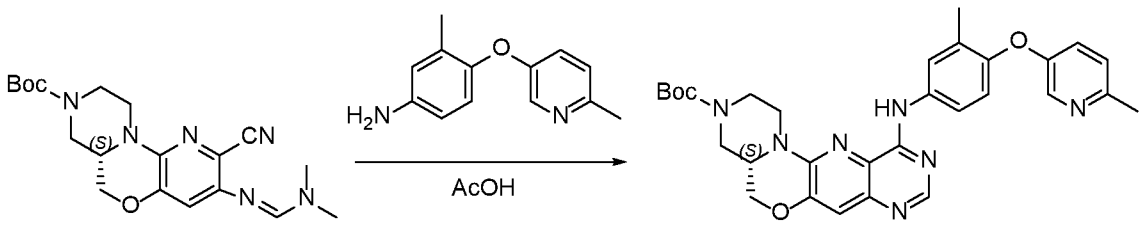
***Example S73: Synthesis of (S)-3-methyl-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 73)***

**[0561] Step 1. Synthesis of tert-butyl (S,E)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



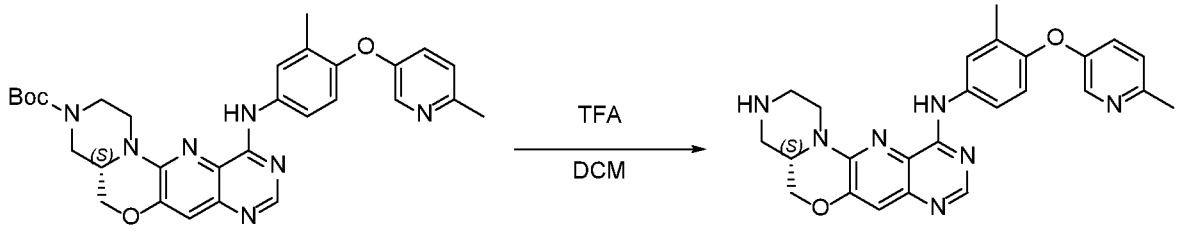

**[0562]** To a solution of tert-butyl (S)-3-amino-2-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (500.0 mg, 1.51 mmol) in EtOH (5.0 mL) was added DMF-DMA (899.0 mg, 7.55 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (45/55, v/v) to afford tert-butyl (S,E)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (470.0 mg, 81%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =387.2.

**[0563] Step 2. Synthesis of tert-butyl (S)-11-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**



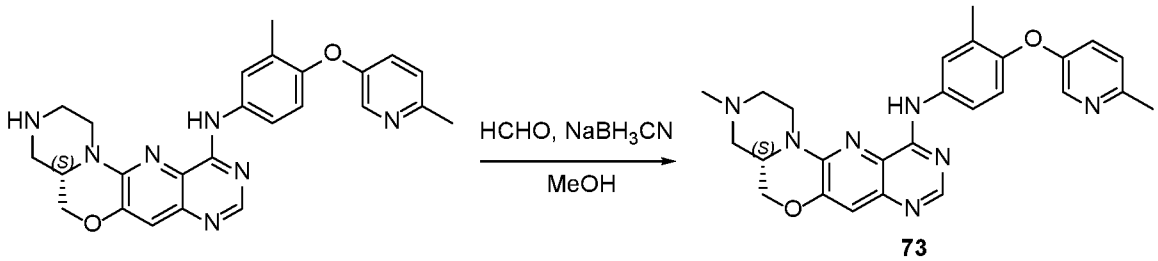

**[0564]** To a solution of tert-butyl (S,E)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (410.0 mg, 1.06 mmol) in AcOH (5.0 mL) was added 3-methyl-4-((6-methylpyridin-3-yl)oxy)aniline (454.6 mg, 2.12 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/H2O (50/50, v/v) to afford tert-butyl (S)-11-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (266.0 mg, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =556.3.

**[0565] Step 3. Synthesis of (S)-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**




**[0566]** To a solution of tert-butyl (S)-11-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (266.0 mg, 0.48 mmol) in DCM (5.0 mL) was added TFA (2.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH of resulting mixture was adjusted to 8 with $NaHCO_3$ (aq) and then extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (180.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =456.2.

**[0567] Step 4. Synthesis of (S)-3-methyl-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 73)**



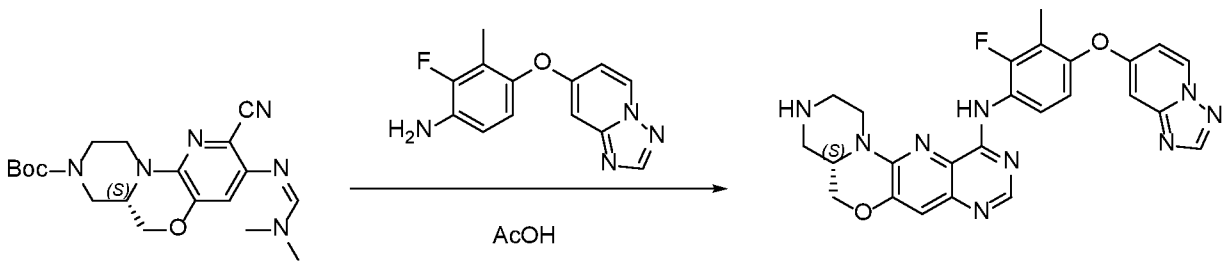

73

**[0568]** To a solution of (S)-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (180.0 mg, crude) in MeOH (5.0 mL) was added HCHO (296.0 mg, 30%) at room temperature. The mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (111.7 mg, 1.78 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for

additional 3 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19 x 250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN -----Preparative; Flow rate: 25 mL/min; Gradient: 45% B to 50% B in 10 min; Wave Length: 254 nm) to afford (S)-3-methyl-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 73)** (15.3 mg, 8%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =470.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.22 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 7.88 - 7.86 (m, 2H), 7.24 - 7.17 (m, 3H), 6.99 - 6.96 (m, 1H), 5.02 - 4.99 (m, 1H), 4.46 - 4.42 (m, 1H), 4.07 - 4.02 (m, 1H), 3.64 - 3.59 (m, 1H), 2.96 - 2.90 (m, 3H), 2.51 (d, $J$ = 1.6 Hz, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 2.14 - 2.09 (m, 1H), 1.84 - 1.71 (m, 1H).

***Example S74: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 74)***

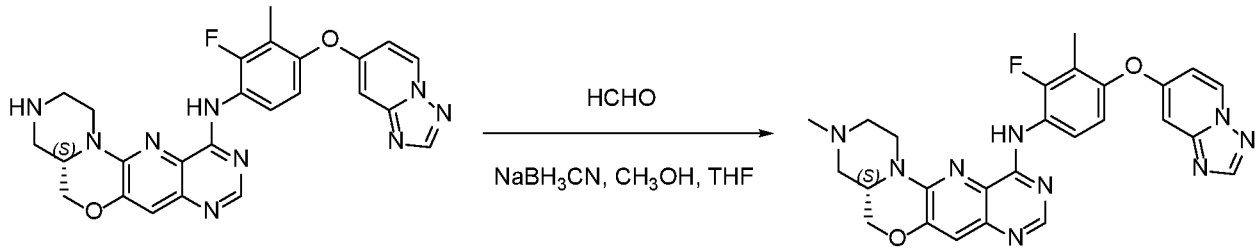
**[0569] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**




**[0570]** To a stirred mixture of tert-butyl (S,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (520.0 mg, 1.35 mmol) and 2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (347.5 mg, 1.35 mmol) in acetic acid (6.0 mL) was added HCl (6.4 mg, 0.18 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (61/39, v/v) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-

fluoro-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (180.0 mg, 26%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.1.

**[0571] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 74)**

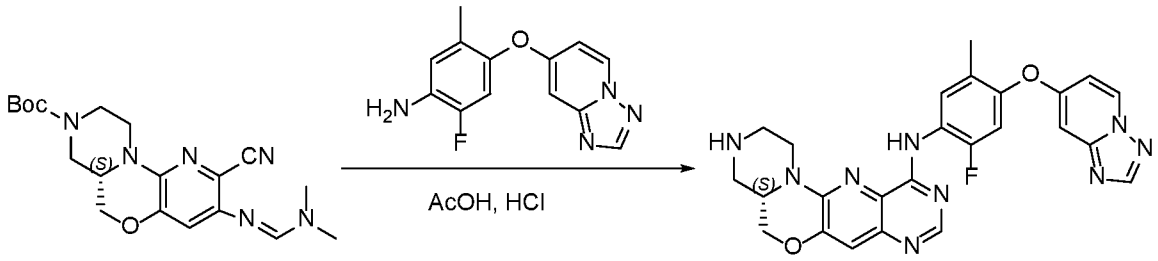



**74**

**[0572]** The mixture of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (170.0 mg, 0.34 mmol) and HCHO (81.8 mg, 40% in $H_2O$) in THF (6.0 mL) and $CH_3OH$ (1.5 mL) was stirred at room temperature for 1 h under $N_2$. Then $NaBH_3CN$ (96.2 mg, 1.53 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (67/33, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 45% B to 60% B in 10 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 74)** (6.8 mg, 3%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 514.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.18 (d, $J$ = 3.6 Hz, 1H), 8.98 - 8.96 (m, 1H), 8.41 - 8.38 (m, 2H), 8.13 - 8.08 (m, 1H), 7.25 (d, $J$ = 2.4 Hz, 1H), 7.13 (d, $J$ = 8.8 Hz, 1H), 7.08 - 7.06 (m, 1H), 6.92 (d, $J$ = 2.4 Hz, 1H), 4.81 - 4.78 (m, 1H), 4.49 - 4.45 (m, 1H), 4.09 - 4.04 (m, 1H), 3.68 - 3.62 (m, 1H), 3.02 - 2.91 (m, 3H), 2.31 - 2.28 (m, 3H), 2.17 (s, 3H), 2.14 - 2.10 (m, 1H), 1.81 - 1.72 (m, 1H).

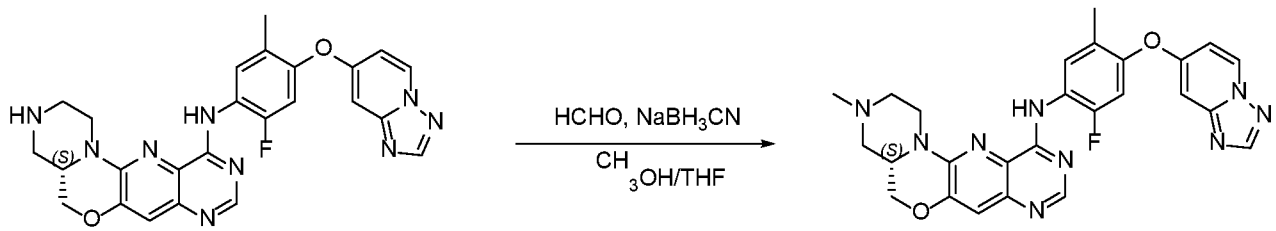
***Example S75: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 75)***

**[0573] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**




**[0574]** To a solution of tert-butyl (S, E)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (350.0 mg, 0.90 mmol) in AcOH (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylaniline (467.7 mg,, 1.81mmol) and HCl (0.025 mL, 6 mol/L) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the reaction mixture was f basified to pH=8 with saturated $NaHCO_3$(aq.). The resulting mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (200.0 mg, 36%) LCMS (ESI, m/z): $[M+H]^+$ =500.2.

**[0575] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 75)**

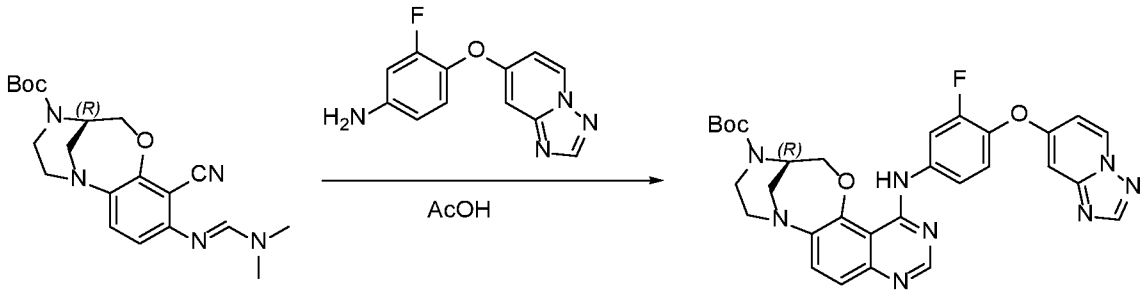



**75**

**[0576]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (150.0 mg, 0.30 mmol) in $CH_3OH$ (3.0 mL) and THF (3.0 mL) was added HCHO (85.5 mg, 37% ~ 40% in $H_2O$) at 0 °C under $N_2$. The resulting mixture was stirred at 0 °C for 2 h. Then $NaBH_3CN$ (84.9 mg, 1.35 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 41% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 75)** (14.7 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 514.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.19 (s, 1H), 8.96 (d, $J$ = 7.6 Hz, 1H), 8.41 (s, 1H), 8.37 (s, 1H), 8.05 (d, $J$ = 8.8 Hz, 1H), 7.30 (d, $J$ = 10.8 Hz, 1H), 7.24 (s, 1H), 7.07 - 7.04 (m, 1H), 6.91 (d, $J$ = 2.4 Hz, 1H), 4.85 - 4.82 (m, 1H), 4.48 - 4.44 (m, 1H), 4.09 - 4.04 (m, 1H), 3.67 - 3.62 (m, 1H), 3.10 - 2.91 (m, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 2.13 - 2.07 (m, 1H), 1.80 - 1.74 (m, 1H).

***Example S76: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 76)***

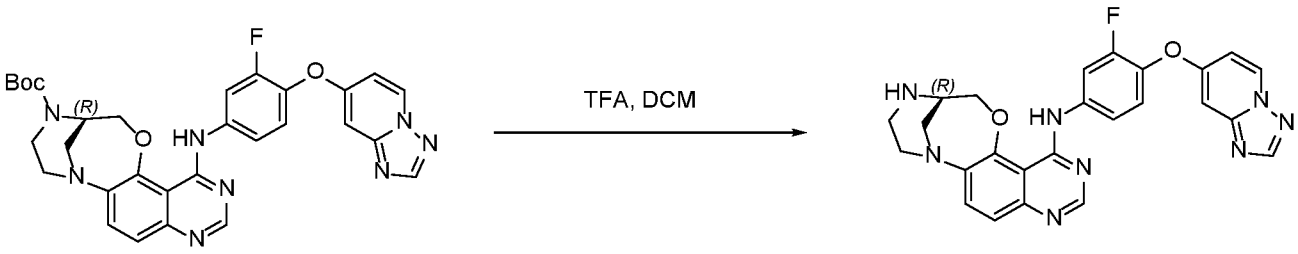
**[0577]** **Step 1. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0578]** To a solution of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-

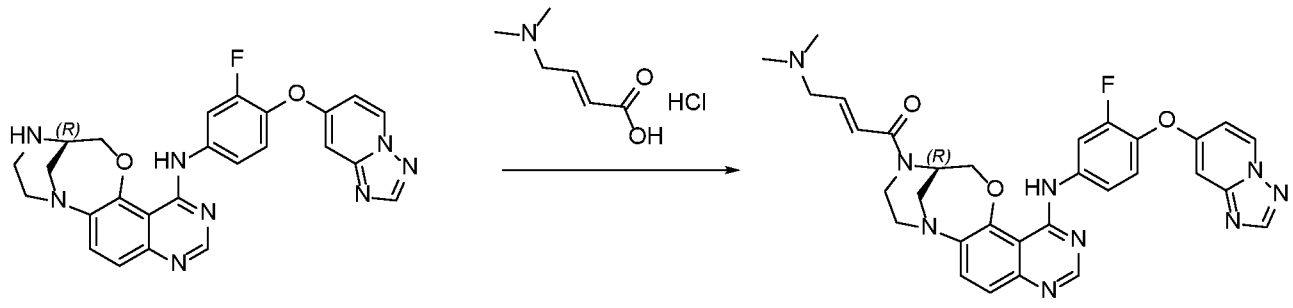
methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (300.0 mg, 0.77mmol) in acetic acid (10.0 mL) was added 3-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (190.0 mg, 0.77 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (147.5 mg, 49%) as a grey solid. LCMS (ESI, m/z): $[M+H]^+$ =585.2.

**[0579] Step 2. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-3,4,5,6-tetrahydro-2H-3,7 methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**




**[0580]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (147.5 mg, 0.25 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8 with $NaHCO_3$(aq). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-3,4,5,6-tetrahydro-2H-3,7 methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (140.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =485.2.

**[0581] Step 3. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 76)**

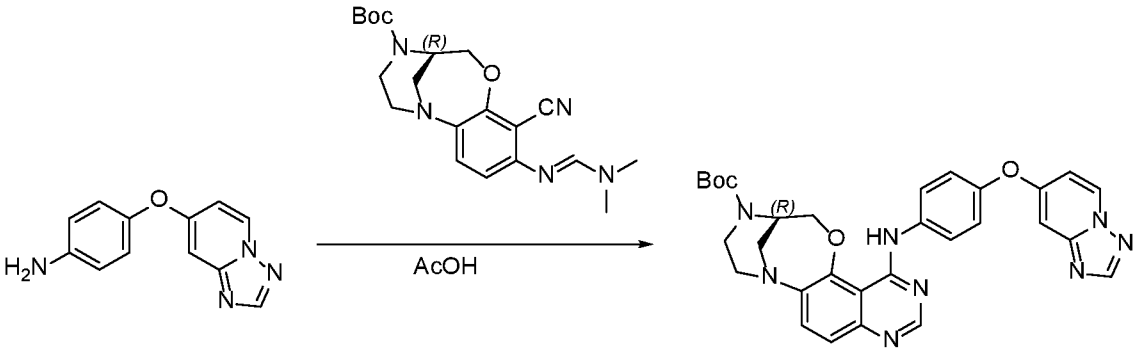


76

**[0582]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-3,4,5,6-tetrahydro-2H-3,7 methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (140.0 mg, crude) in DMF (5.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (74.6 mg, 0.57 mmol), DIEA (224.1 mg, 1.73 mmol) and HATU (241.7 mg, 0.63 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 76)** (6.0 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =596.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.26 - 10.23 (m, 1H), 8.96 (d, $J$ = 7.2 Hz, 1H), 8.53 (s, 1H), 8.41 (s, 1H), 8.33 - 8.27 (m, 1H), 7.82 - 7.73 (m, 1H), 7.62 (d, $J$ = 9.2 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.11 - 7.08 (m, 1H), 7.02 (s, 1H), 6.68 - 6.57 (m, 2H), 5.13 - 4.67 (m, 2H), 4.39 - 4.07 (m, 3H), 3.78 - 3.67 (m, 2H), 3.30 - 3.15 (m, 2H), 3.03 (d, $J$ = 5.2 Hz, 2H), 2.17 - 2.15 (m, 6H).

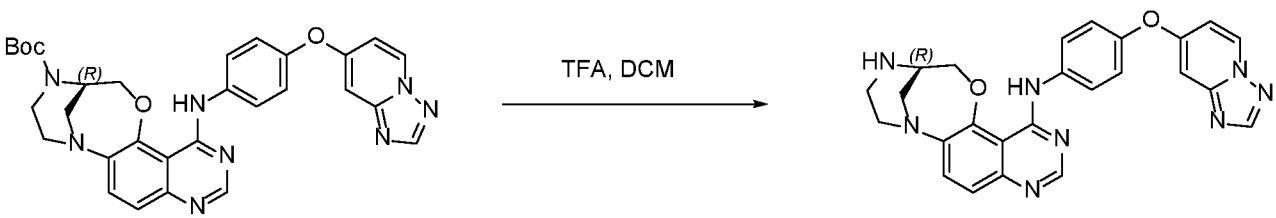
***Example S77: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 77)***

**[0583] Step 1. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0584]** To a solution of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)aniline (200.0 mg, 0.88 mmol) in AcOH (10.0 mL) was added tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (340.8 mg, 0.88 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (200.0 mg, 39%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 567.2.

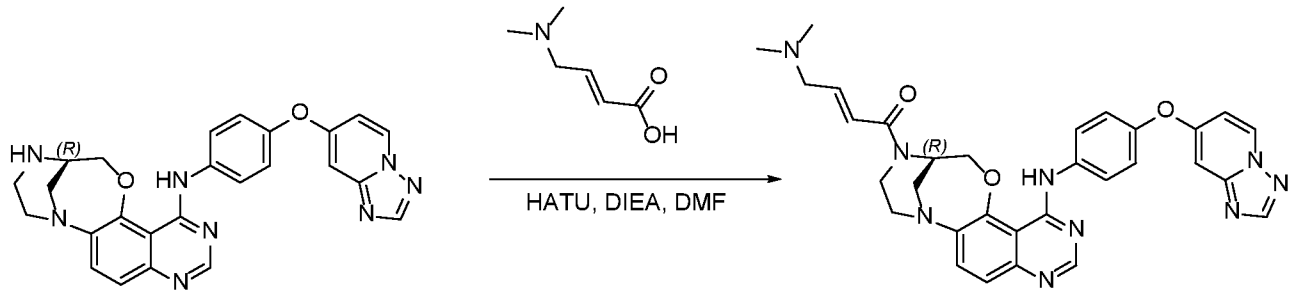
**[0585] Step 2. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**




**[0586]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (180.0 mg, 0.32 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-

methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (90.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 467.2.

**[0587] Step 3. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 77)**

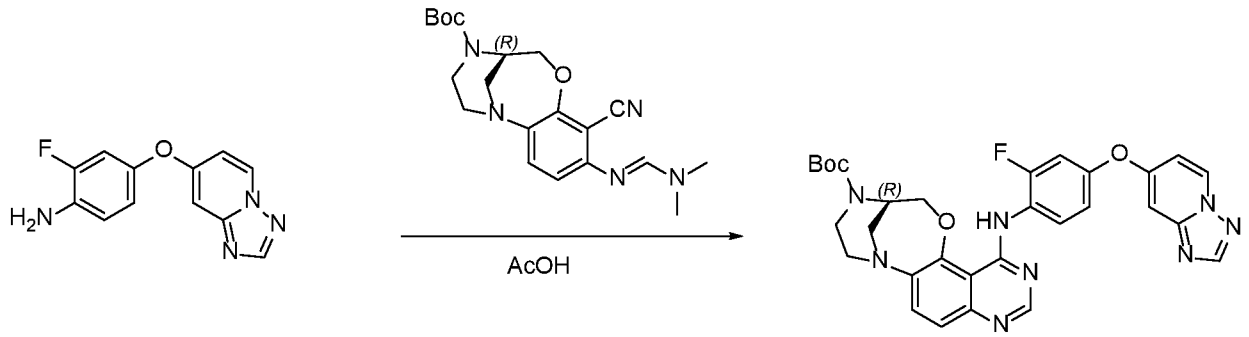



**77**

**[0588]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (80.0 mg, crude) in DMF (2.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (34.1 mg, 0.21 mmol), DIEA (110.8 mg, 0.86 mmol) and HATU (97.8 mg, 0.26 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (4/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% to 32% in 8 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 77)** (16.7 mg, 16%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =578.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.13 (s, 1H), 8.95 (d, $J$ = 7.6 Hz, 1H), 8.46 (s, 1H), 8.40 (s, 1H), 8.04 - 7.98 (m, 2H), 7.60 (d, $J$ = 8.8 Hz, 1H), 7.43 (d, $J$ = 9.2 Hz, 1H), 7.31 - 7.27 (m, 2H), 7.05 - 7.00 (m, 2H), 6.68 - 6.56 (m, 2H), 5.08 - 4.68 (m, 2H), 4.44 - 4.39 (m, 1H), 4.21 - 4.06 (m, 2H), 3.79 - 3.67 (m, 2H), 3.40 - 3.32 (m, 1H), 3.23 - 3.16 (m, 1H), 3.05 - 3.03 (m, 2H), 2.17 - 2.15 (m, 6H).

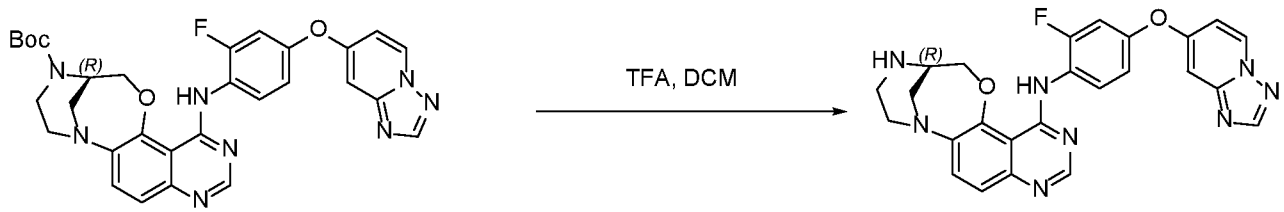
***Example S78: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 78)***

**[0589] Step 1. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**



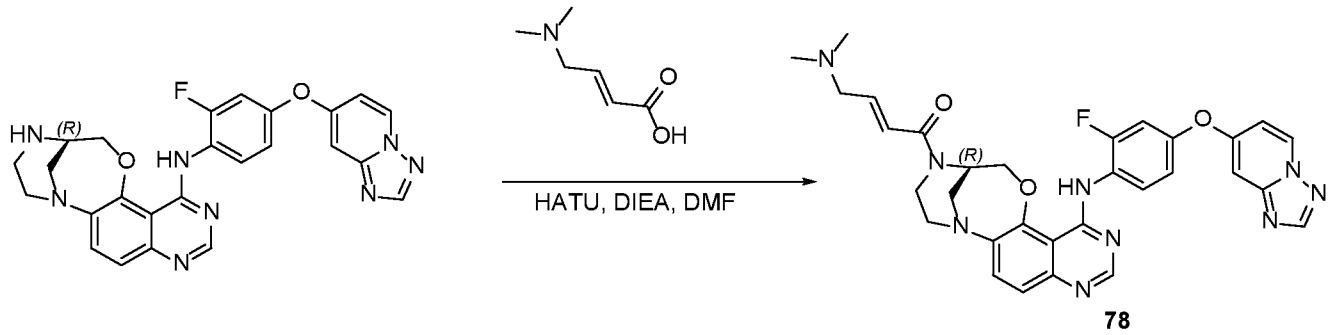

**[0590]** To a solution of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoroaniline (202.0 mg, 0.82 mmol) in acetic acid (6.0 mL) was added tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (320.0 mg, 0.82 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (185.0 mg, 91%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =585.2.

**[0591] Step 2. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**



**[0592]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (147.0 mg, 0.25mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (135.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =485.2.

**[0593] Step 3. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 78)**



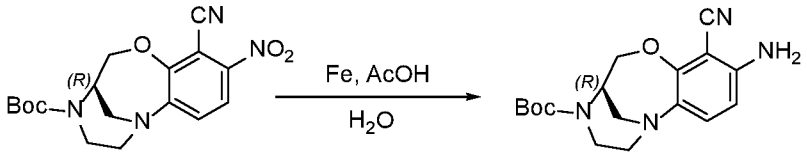

78

**[0594]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (115.0 mg, crude) in DMF (5.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (78.4 mg, 0.47 mmol), DIEA (183.9 mg, 1.42 mmol) and HATU (198.7 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 65% B to 65% B in 12 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-2,3,5,6-tetrahydro-

4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 78)** (15.8 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =596.4. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.21 (s, 1H), 8.98 (d, $J$ = 7.6 Hz, 1H), 8.57 - 8.43 (m, 3H), 7.62 (d, $J$ = 8.8 Hz, 1H), 7.47 - 7.39 (m, 2H), 7.19 - 7.15 (m, 2H), 7.08 - 7.05 (m, 1H), 6.65 - 6.60 (m, 2H), 5.04 - 4.77 (m, 2H), 4.47 - 4.43 (m, 1H), 4.17 - 4.07 (m, 2H), 3.84 - 3.64 (m, 2H), 3.39 - 3.29 (m, 1H), 3.23 - 3.17 (m, 1H), 3.03 (d, $J$ = 6.0 Hz, 2H), 2.16 - 2.14 (m, 6H).

***Example S79: Synthesis of (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 79)***

**[0595] Step 1. Synthesis of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**



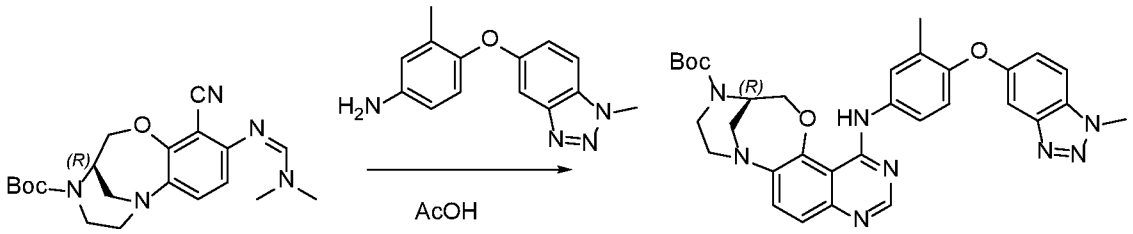

**[0596]** To a solution of tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (1.2 g, 3.33 mmol) in AcOH/$H_2O$ (20.0 mL/0.5 mL) was added Fe (930.0 mg, 16.65 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) to afford tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (757.0 mg, 68%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =331.2.

**[0597] Step 2. Synthesis of tert-butyl (3R)-11-cyano-10-(((Z)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate**


**[0598]** To a solution of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (750.0 mg, 2.27 mmol) in EtOH (10.0 mL) was added DMF-DMA (1.3 g, 11.3 mmol) at room temperature. The resulting mixture was

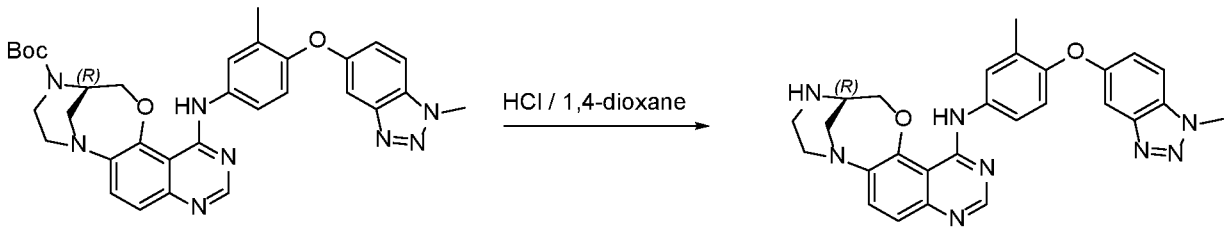
stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (3R)-11-cyano-10-(((Z)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (721.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =386.2.

**[0599] Step 3. Synthesis of tert-butyl (3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**



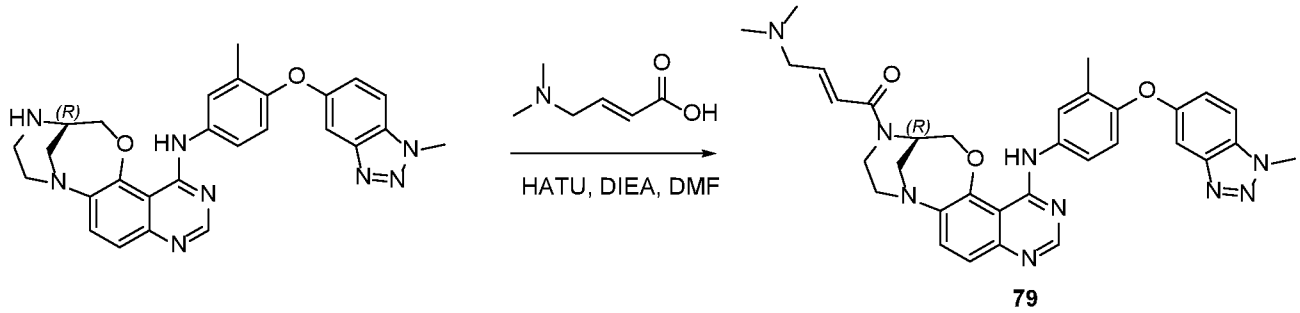

**[0600]** To a solution of tert-butyl (3R)-11-cyano-10-(((Z)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (500.0 mg, crude) in AcOH (5.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)aniline (659.7 mg, 2.59 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (75/25, v/v) to afford tert-butyl (3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (280.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =595.3.

**[0601] Step 4. Synthesis of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**



**[0602]** The solution of tert-butyl (3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (280.0 mg, 0.47 mmol) in HCl/1,4-dioxane (5.0 mL, 4 mol/L) was stirred at room temperature for 1 h. After the reaction was completed, The pH value of the mixture was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure to afford (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (166.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2

**[0603] Step 5. Synthesis of (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 79)**



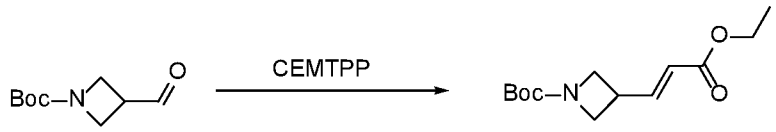

79

**[0604]** To a solution of (3R)-N-(3-methyl-4-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (160.0 mg, crude) in DMF (10.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (83.5 mg, 0.64 mmol), DIEA (250.8 mg, 1.94 mmol) and HATU (147.6 mg, 0.39 mmol) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 19 x 250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$+0.1% $NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 45% B to 55% B in 10 min; Wave Length: 254 nm) to afford (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((1-methyl-1H-

benzo[d][1,2,3]triazol-5-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one **(Compound 79)** (29.3 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 606.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.07 - 10.03 (m, 1H), 8.44 (s, 1H), 7.89 - 7.87 (m, 2H), 7.81 - 7.78 (m, 1H), 7.59 (d, $J$ = 9.2 Hz, 1H), 7.41 (d, $J$ = 8.8 Hz, 1H), 7.36 - 7.33 (m, 1H), 7.25 (d, $J$ = 2.0 Hz, 1H), 7.02 - 6.99 (m, 1H), 6.68 - 6.62 (m, 2H), 5.07 - 4.72 ( m, 2H), 4.42 - 4.40 (m, 1H), 4.31 (s, 3H), 4.11 - 4.06 (m, 1.5 H), 3.84 - 3.67 (m, 2H), 3.39 - 3.33 (m, 1H), 3.23 - 3.15 (m, 1H), 3.09 - 3.07 (m, 2H), 2.23 (s, 3H), 2.19 - 2.17 (m, 6H).

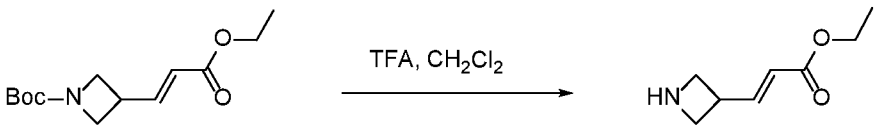
***Example S80: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-3-(1-methylazetidin-3-yl)prop-2-en-1-one (Compound 80)***

**[0605] Step 1. Synthesis of tert-butyl (E)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate**




**[0606]** To a solution of tert-butyl 3-formylazetidine-1-carboxylate (10.0 g, 53.98 mmol) in DCM (150.0 mL) was added CEMTPP (28.2 g, 80.97 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (E)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate (11.0 g, 79%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 256.1.

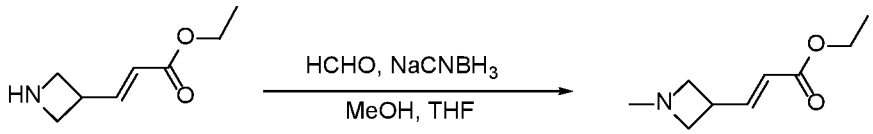
**[0607] Step 2. Synthesis of ethyl (E)-3-(azetidin-3-yl)acrylate 2,2,2-trifluoroacetate**




**[0608]** To a solution of tert-butyl (E)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate (11.0 g, 43.08 mmol) in $CH_2Cl_2$ (150.0 mL) was added TFA (30.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under vacuum to afford ethyl (E)-3-(azetidin-3-

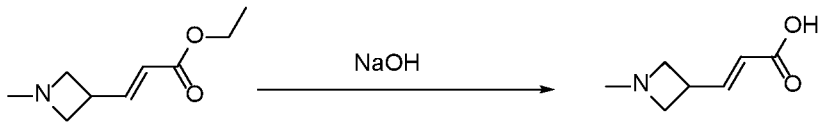
yl)acrylate 2,2,2-trifluoroacetate (24.0 g, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 156.1.

**[0609] Step 3. Synthesis of ethyl (E)-3-(1-methylazetidin-3-yl)acrylate**



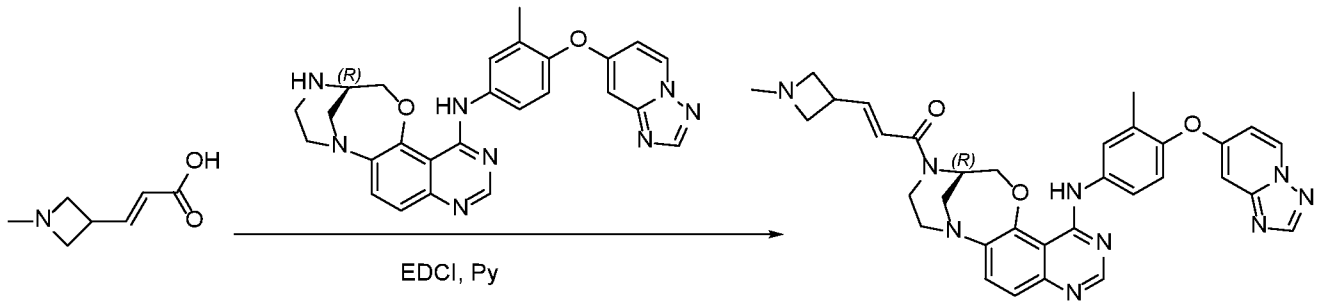

**[0610]** To a solution of ethyl (E)-3-(azetidin-3-yl)acrylate 2,2,2-trifluoroacetate (24.0 g, crude) in THF (60.0 mL)/MeOH (300.0 mL) was added HCHO (32.5 g, 30%) at 0 °C under $N_2$. The mixture was stirred at 0 °C for 1 h under $N_2$. Then $NaCNBH_3$ (43.7 g, 142.16 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$ (10 mmol/L $NH_4HCO_3$)/MeOH (95/5, v/v) to afford ethyl (E)-3-(1-methylazetidin-3-yl)acrylate (12.0 g, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 170.1.

**[0611] Step 4. Synthesis of (E)-3-(1-methylazetidin-3-yl)acrylic acid**




**[0612]** To a solution of ethyl (E)-3-(1-methylazetidin-3-yl)acrylate (5.0 g, 0.79 mmol) in THF (60.0 mL)/$H_2O$ (12.0 mL) was added NaOH (7.0 g, 177.28 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction mixture was acidified to pH=6 with saturated HCl (aq.). The resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/ACN (95/5, v/v) to afford (E)-3-(1-methylazetidin-3-yl)acrylic acid (135.0 mg, 3%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 142.1.

**[0613] Step 5. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-3-(1-methylazetidin-3-yl)prop-2-en-1-one (Compound 80)**

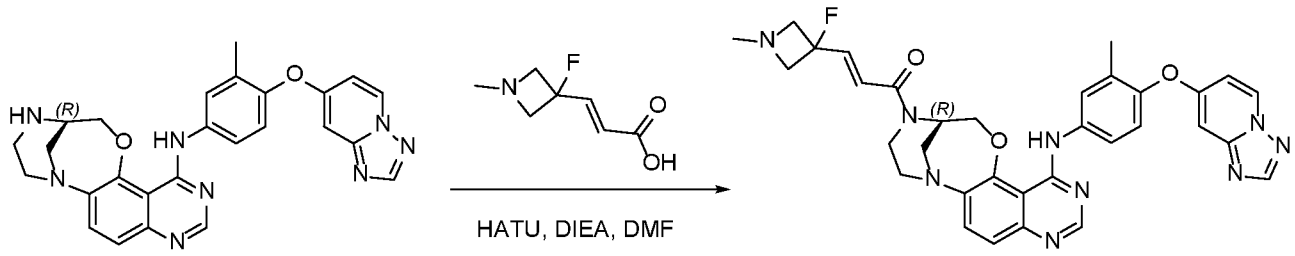



80

**[0614]** To a solution of (E)-3-(1-methylazetidin-3-yl)acrylic acid (80.0 mg, 0.30 mmol) in Pyridine (5.0 mL) was added (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (132.1 mg, 0.28 mmol) and EDCI (135.7 mg, 0.70 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 32% B in 8 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-3-(1-methylazetidin-3-yl)prop-2-en-1-one **(Compound 80)** (22.7 mg, 13%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 604.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.14 - 10.09 (m, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.00 - 7.89 (m, 1H), 7.84 (d, $J$ = 6.0 Hz, 1H), 7.60 (d, $J$ = 9.2 Hz, 1H), 7.42 (d, $J$ = 9.2 Hz, 1H), 7.23 - 7.19 (m, 1H), 7.04 - 7.02 (m, 1H), 6.90 - 6.84 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 6.51 - 6.46 (m, 1H), 5.10 - 4.72 (m, 2H), 4.43 - 4.35 (m, 1H), 4.19 - 4.06 (m, 1H), 3.85 - 3.62 (m, 2H), 3.41 - 3.35 (m, 3H), 3.22 - 3.14 (m, 3H), 2.96 - 2.88 (m, 2H), 2.20 - 2.18 (m, 6H).

***Example S81: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-3-(3-fluoro-1-methylazetidin-3-yl)prop-2-en-1-one (Compound 81)***

**[0615] Step 1. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-3-(3-fluoro-1-methylazetidin-3-yl)prop-2-en-1-one (Compound 81)**

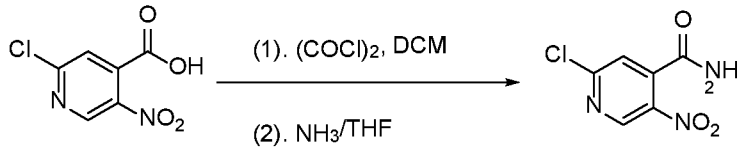



81

**[0616]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (200.0 mg, 0.41 mmol) in DMF (8.0 mL) was added (2E)-3-(3-fluoro-1-methylazetidin-3-yl)prop-2-enoic acid (79.5 mg, 0.49 mmol), DIEA (537.9 mg, 4.10 mmol) and HATU (253.2 mg, 0.66 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (60/40, v/v) and then purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 12 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-3-(3-fluoro-1-methylazetidin-3-yl)prop-2-en-1-one **(Compound 81)** (5.8 mg, 2%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 622.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.14 - 10.09 (m, 1H), 8.93 (d, $J$ = 7.2 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 7.94 - 7.85 (m, 1H), 7.84 - 7.82 (m, 1H), 7.62 - 7.58 (m, 1H), 7.42 (d, $J$ = 9.2 Hz, 1H), 7.21 - 7.19 (m, 1H), 7.04 - 7.01 (m, 1H), 6.89 - 6.84 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 6.50 - 6.45 (m, 1H), 5.15 - 4.75 (m, 2H), 4.42 - 4.32 (m, 1H), 4.15 - 4.06 (m, 1H), 3.85 - 3.62 (m, 2H), 3.38 - 3.32 (m, 3H), 3.20 - 3.16 (m, 2H), 2.93 - 2.90 (m, 2H), 2.19 - 2.18 (m, 6H).

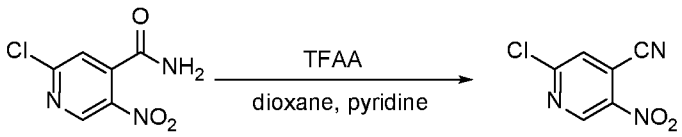
***Example S82: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 82)***

**[0617]** **Step 1. Synthesis of 2-chloro-5-nitropyridine-4-carboxamide**



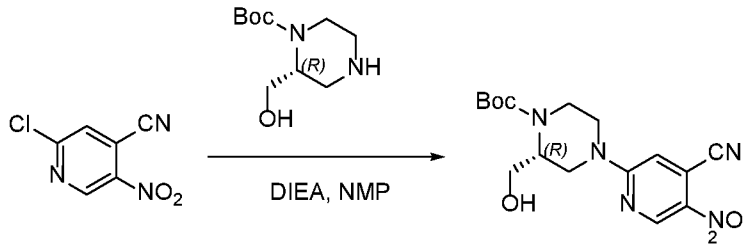

**[0618]** To a solution of 2-chloro-5-nitropyridine-4-carboxylic acid (10.0 g, 49.37 mmol) in DCM (200.0 mL) and DMF (1.0 mL) was added $(COCl)_2$ (15.6 g, 123.42 mmol) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure. A solution of $NH_3.H_2O$ (9.6 mL) in THF (200.0 mL) was added to the residue. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford 2-chloro-5-nitropyridine-4-carboxamide (4.0 g, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 202.0.

**[0619] Step 2. Synthesis of 2-chloro-5-nitropyridine-4-carbonitrile**



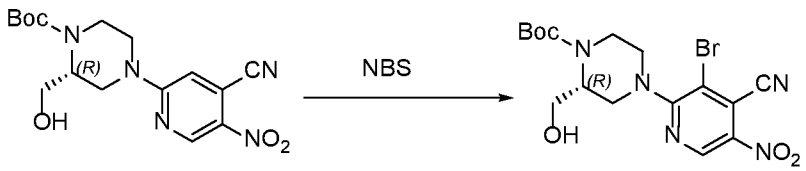

**[0620]** To a solution of 2-chloro-5-nitropyridine-4-carboxamide (4.0 g, 19.84 mmol) in dioxane (50.0 mL) and pyridine (20.0 mL) was added TFAA (14.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 2-chloro-5-nitropyridine-4-carbonitrile (2.0 g, 49%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 184.0.

**[0621] Step 3. Synthesis of tert-butyl (2R)-4-(4-cyano-5-nitropyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate**



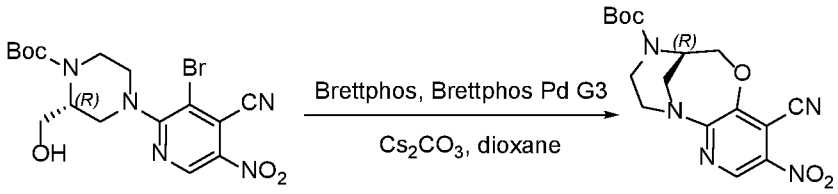

**[0622]** To a solution of 2-chloro-5-nitropyridine-4-carbonitrile (2.0 g, 10.89 mmol) and tert-butyl (R)-2-(hydroxymethyl)piperazine-1-carboxylate (3.5 g, 16.34 mmol) in NMP (20.0 mL) was added DIEA (4.2 g, 32.68 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford tert-butyl (2R)-4-(4-cyano-5-nitropyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (2.0 g, 48%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 364.2.

**[0623] Step 4. Synthesis of tert-butyl (2R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate**



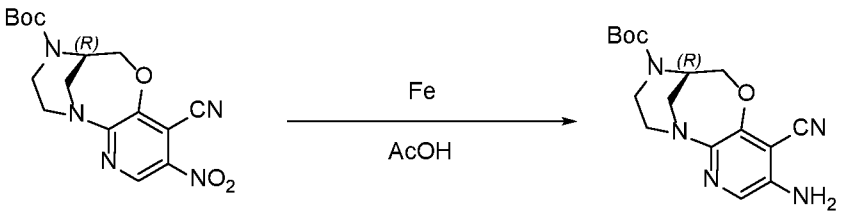

**[0624]** To a solution of tert-butyl (2R)-4-(4-cyano-5-nitropyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (2.0 g, 5.50 mmol) in AcOH (20.0 mL) was added NBS (2.9 g, 16.51 mmol) at room temperature. The resulting mixture was stirred at room temperature for 48 h. After the reaction was completed, The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (60/40, v/v) to afford tert-butyl (2R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (1.0 g, 37%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 442.1.

**[0625] Step 5. Synthesis of tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate**



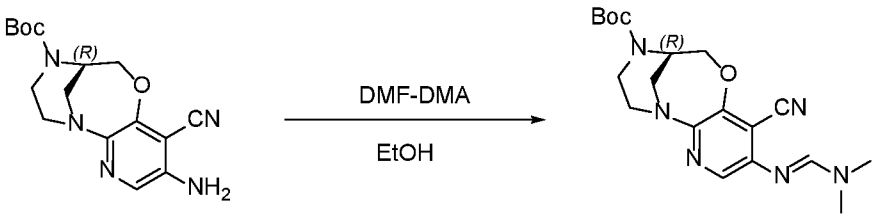

**[0626]** To a solution of tert-butyl (2R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxylate (1.0 g, 2.26 mmol) in dioxane (10.0 mL) was added $Cs_2CO_3$ (2.2 g, 6.78 mmol), Brettphos (0.5 g, 0.90 mmol) and Brettphos Pd G3 (0.4 g, 0.45 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (500.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 362.1.

**[0627] Step 6. Synthesis of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate**



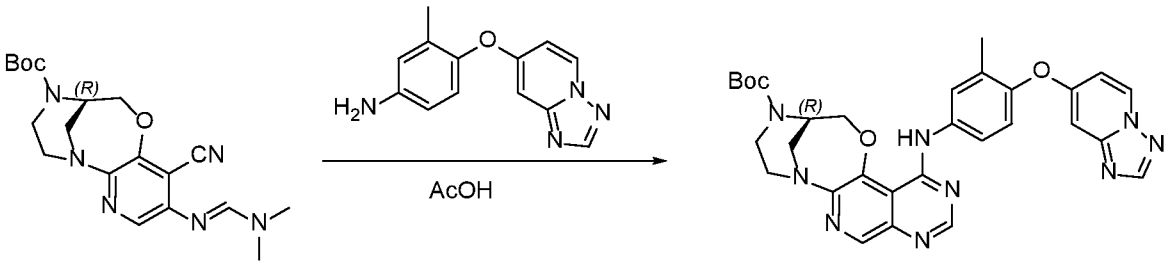

**[0628]** To a solution tert-butyl (3R)-11-cyano-10-nitro-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (500.0 mg, 1.38 mmol) in HOAc (5.0 mL) and $H_2O$ (1.0 mL) was added Fe (386.3 mg, 6.92 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) to afford tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (200.0 mg, 39%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 332.2.

**[0629] Step 7. Synthesis of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate**




**[0630]** To a solution of tert-butyl (3R)-10-amino-11-cyano-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (200.0 mg, 0.60 mmol) in EtOH (5.0 mL) was added DMF-DMA (215.7 mg, 1.81 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (200.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 387.2.

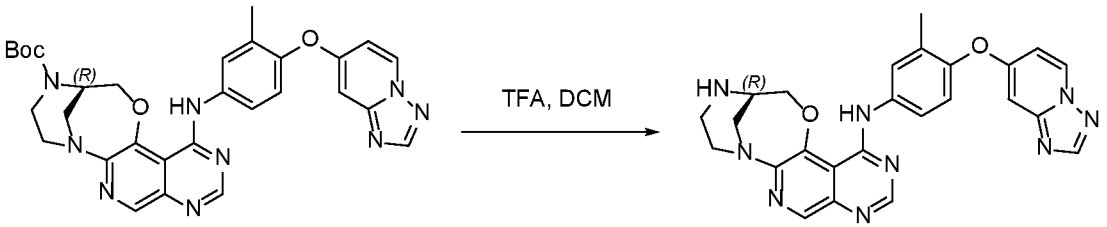
**[0631] Step 8. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate**




**[0632]** To a solution of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (200.0 mg, crude) in AcOH (3.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (117.1 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-

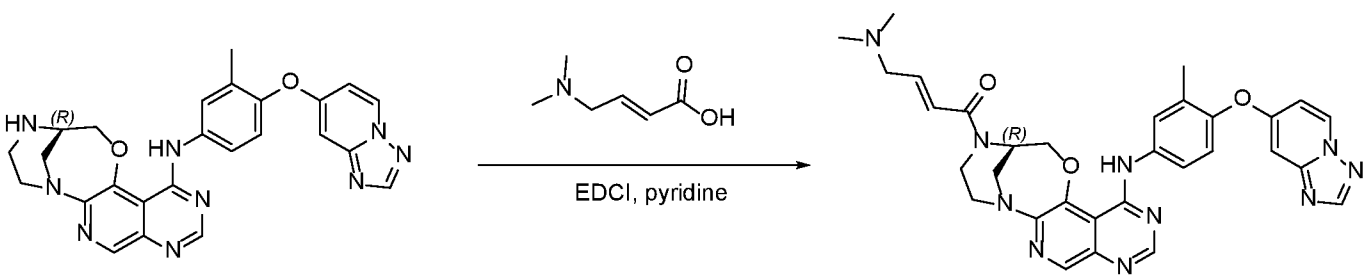
3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (150.0 mg, 44%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 582.2.

**[0633] Step 9. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-13-amine**




**[0634]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (150.0 mg, 0.26 mmol) in DCM (2.0 mL) was added TFA (0.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was neutralized to pH = 8 with $NaHCO_3$(aq.). The resulting mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-13-amine (150.0 mg, 72%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.2.

**[0635] Step 10. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 82)**

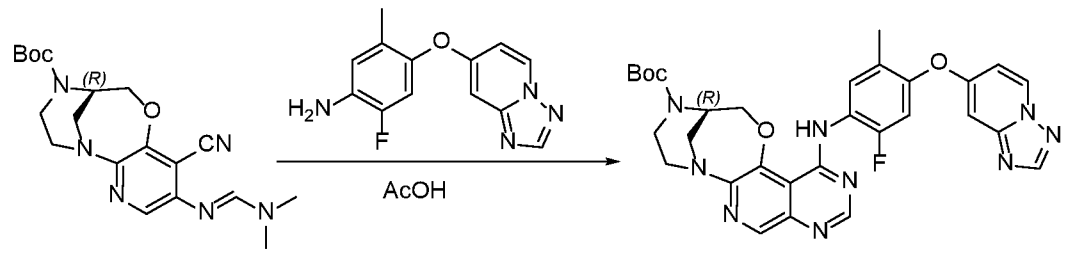



**82**

**[0636]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-13-amine (150.0 mg, 0.31 mmol) in pyridine (5.0 mL) was added (2E)-4-(dimethylamino)but-2-enoic acid (60.3 mg, 0.46 mmol) and EDCI (119.4 mg, 0.62 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 29% B in 12 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 82)** (3.4 mg, 2%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 593.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.97 - 9.92 (m, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 8.38 (s, 1H), 8.00 - 7.85 (m, 2H), 7.24 (d, $J$ = 9.2 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.80 (d, $J$ = 2.4 Hz, 1H), 6.68 - 6.58 (m, 2H), 5.15 - 4.72 (m, 2H), 4.42 - 4.13 (m, 3H), 3.87 - 3.63 (m, 1H), 3.28 - 3.17 (m, 2H), 3.06 - 3.02 (m, 2H), 2.21- 2.16 (m, 9H).

***Example S83: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 83)***

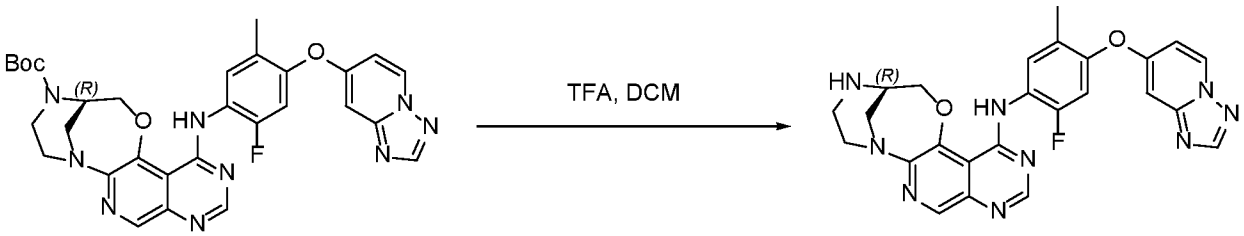
**[0637] Step 1. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate**




**[0638]** To a solution of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (100.0 mg, 0.26 mmol) in AcOH (2.0 mL) was added 2-fluoro-5-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (100.2 mg, 0.39 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 3 h. After the reaction was

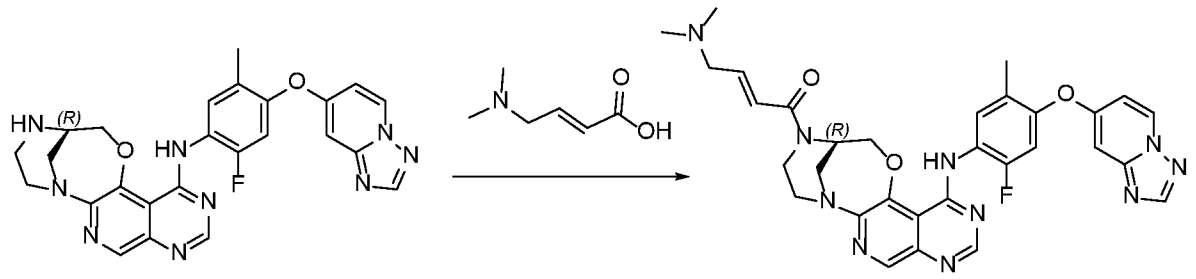
completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (40.0 mg, 24%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 600.2.

**[0639] Step 2. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-13-amine**




**[0640]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonine-4-carboxylate (40.0 mg, 0.06 mmol) in DCM (2.0 mL) was added TFA (0.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was neutralized to pH = 8 with $NaHCO_3$(aq.). The resulting mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-13-amine (40.0 mg, 96%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.2.

**[0641] Step 3. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 83)**

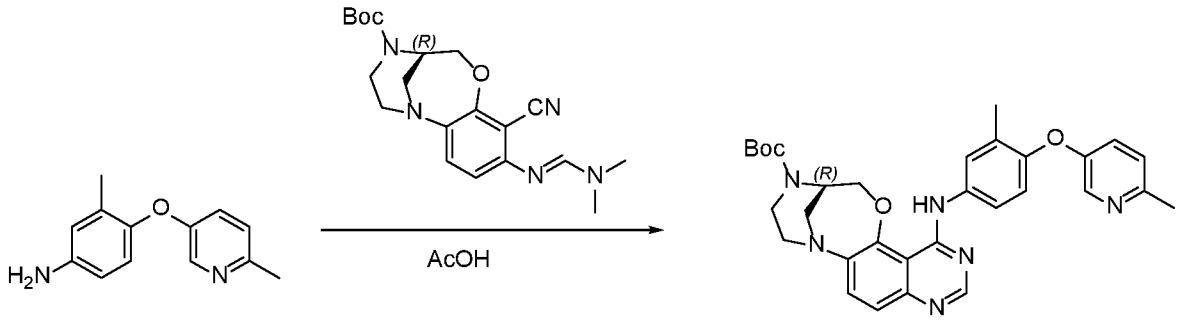


83

**[0642]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-13-amine (40.0 mg, 0.08 mmol) in DMF (2.0 mL) was added HATU (91.3 mg, 0.24 mmol), DIEA (31.0 mg, 0.24 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (31.3 mg, 0.24 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 12 min; Wave Length: 254 nm) to afford (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methanopyrimido[5',4':4,5]pyrido[3,2-b][1,4,7]oxadiazonin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 83)** (7.1 mg, 14%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 611.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.01 - 9.96 (m, 1H), 8.97 (d, $J$ = 7.2 Hz, 1H), 8.70 (s, 1H), 8.55 (d, $J$ = 8.0 Hz, 1H), 8.43 - 8.30 (m, 2H), 7.36 (d, $J$ = 11.2 Hz, 1H), 7.07 - 7.04 (m, 1H), 6.93 (d, $J$ = 2.4 Hz, 1H), 6.68 - 6.56 (m, 2H), 5.11 - 4.81 (m, 2H), 4.46 - 4.36 (m, 1H), 4.27 - 4.17 (m, 2H), 3.87 - 3.68 (m, 1H), 3.38 - 3.33 (m, 1H), 3.28 - 3.20 (m, 2H), 3.06 - 3.02 (m, 2H), 2.20 (s, 3H), 2.16 - 2.14 (m, 6H).

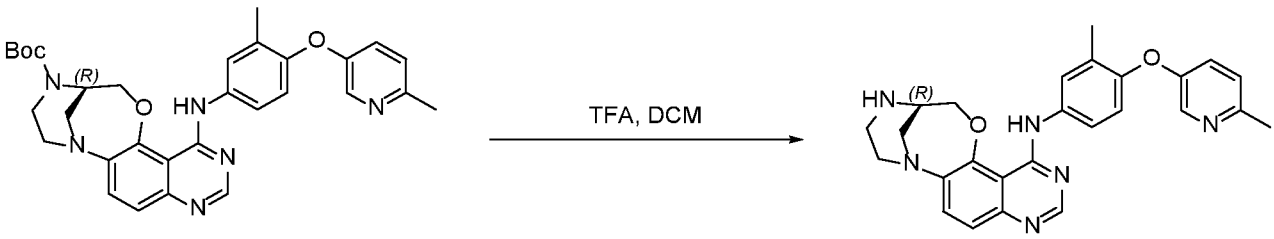
***Example S84: Synthesis of (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 84)***

**[0643] Step 1. Synthesis of tert-butyl (3R)-13-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**




**[0644]** To a solution of 3-methyl-4-((6-methylpyridin-3-yl)oxy)aniline (355.0 mg, 1.65 mmol) in acetic acid (5.0 mL) was added tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (638.6 mg, 1.65 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-13-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (300.0 mg, 32%) as a brown yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 555.3.

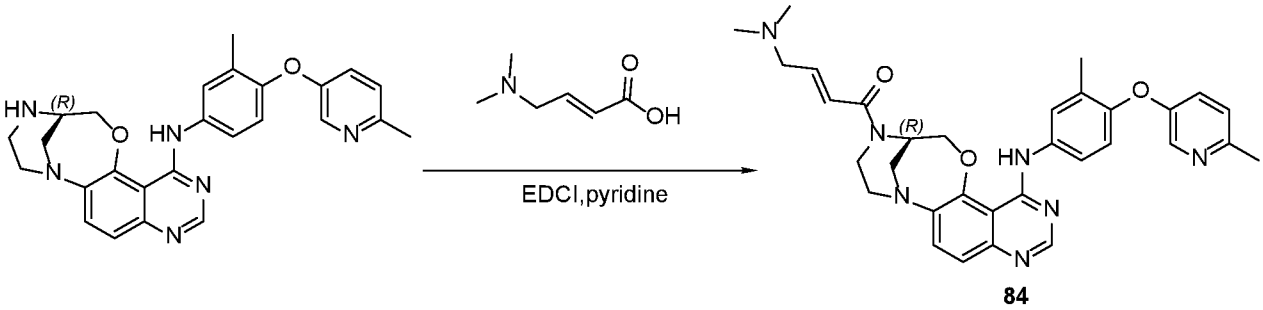
**[0645] Step 2. Synthesis of (3R)-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**




**[0646]** To a solution of tert-butyl (3R)-13-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (250.0 mg, 0.45 mmol) in DCM (4.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was neutralized to pH = 8 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with

$CH_2Cl_2$/MeOH (10/1, v/v) to afford (3R)-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (200.0 mg, 97%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 455.2.

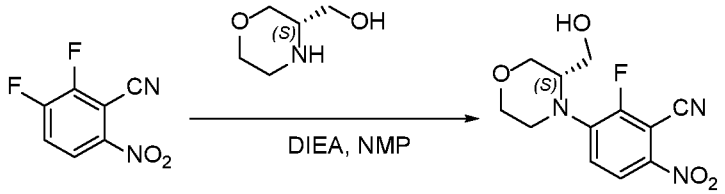
**[0647] Step 3. Synthesis of (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one (Compound 84)**




**[0648]** To a solution of (3R)-N-(3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (150.0 mg, 0.33 mmol) in pyridine (2.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid (85.2 mg, 0.66 mmol) and EDCI (126.5 mg, 0.66 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 37% B in 8 min; Wave Length: 254 nm) to afford (E)-4-(dimethylamino)-1-((3R)-13-((3-methyl-4-((6-methylpyridin-3-yl)oxy)phenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)but-2-en-1-one **(Compound 84)** (36.7 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 566.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.04 - 10.01 (m, 1H), 8.44 (s, 1H), 8.17 (d, $J$ = 2.8 Hz, 1H), 7.87 - 7.76 (m, 2H), 7.58 (d, $J$ = 9.2 Hz, 1H), 7.41 (d, $J$ = 8.8 Hz, 1H), 7.25 - 7.18 (m, 2H), 6.99 - 6.96 (m, 1H), 6.68 - 6.61 (m, 2H), 5.11 - 4.71 (m, 2H), 4.45 - 4.35 (m, 1H), 4.20 - 4.05 (m, 2H), 3.82 - 3.66 (m, 2H), 3.43 - 3.35 (m, 1H), 3.22 - 3.15 (m, 1H), 3.05 - 3.03 (m, 2H), 2.44 (s, 3H), 2.22 (s, 3H), 2.17 - 2.15 (m, 6H).

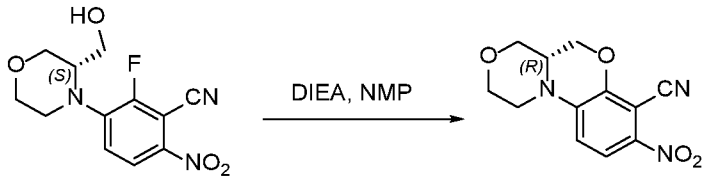
***Example S85: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 85)***

**[0649] Step 1. Synthesis of (S)-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile**




**[0650]** To a solution of 2,3-difluoro-6-nitrobenzonitrile (1.0 g, 5.43 mmol) in NMP (10.0 mL) was added (S)-morpholin-3-ylmethanol hydrochloride (1.8 g, 11.95 mmol) and DIEA (4.2 g, 32.59 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (17/83, v/v) to afford (S)-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (1.4 g, 92%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 282.1.

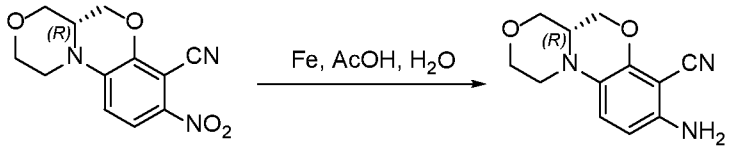
**[0651] Step 2. Synthesis of (R)-8-nitro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-7-carbonitrile**




**[0652]** To a solution of (S)-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (1.4 g, 4.98 mmol) in NMP (15.0 mL) was added DIEA (1.9 g, 14.93 mmol) at room temperature. The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford (R)-8-nitro-1,2,4a,5-tetrahydro-4H-

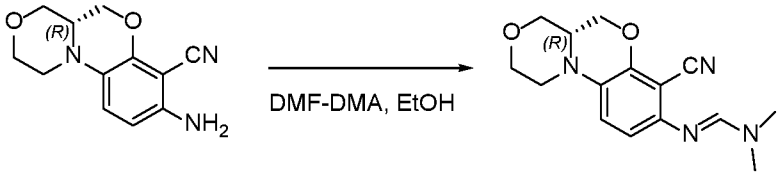
benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-7-carbonitrile (1.0 g, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 262.1.

**[0653] Step 3. Synthesis of (R)-8-amino-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-7-carbonitrile**



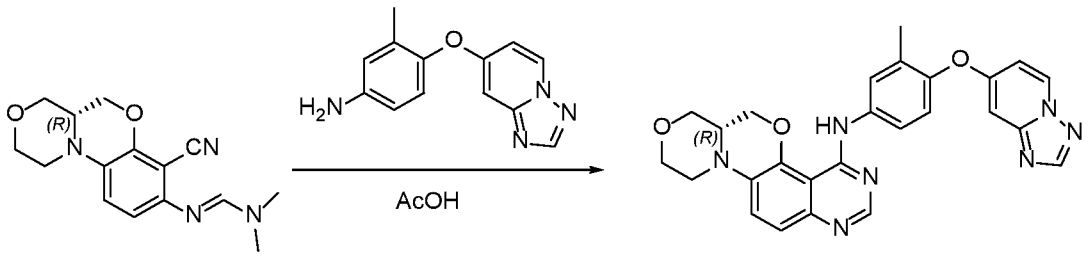

**[0654]** To a solution of (R)-8-nitro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-7-carbonitrile (1.0 g, 3.83 mmol) in AcOH/$H_2O$ (10.0 mL/0.2 mL) was added Fe (1.1 g, 19.14 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (42/58, v/v) to afford (R)-8-amino-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-7-carbonitrile (510.0 mg, 57%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 232.1.

**[0655] Step 4. Synthesis of (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide**




**[0656]** To a solution of (R)-8-amino-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-7-carbonitrile (490.0 mg, 2.12 mmol) in EtOH (5.0 mL) was added DMF-DMA (757.5 mg, 6.36 mmol) at room temperature. The mixture was stirred at 80 °C for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (500.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 287.1.

**[0657] Step 5. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 85)**

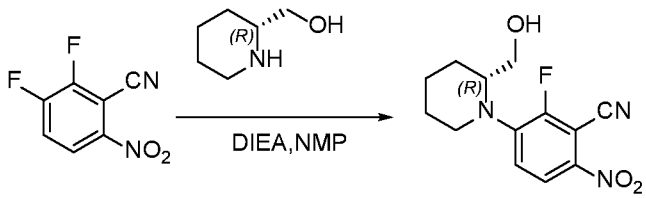



85

**[0658]** To a solution of (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (150.0 mg, 0.52 mmol) in AcOH (2.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (188.8 mg, 0.79 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (44/56, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 45% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 85)** (21.5 mg, 8%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.93 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.38 (s, 2H), 7.90 - 7.82 (m, 2H), 7.60 (d, $J$ = 9.2 Hz, 1H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.71 - 4.68 (m, 1H), 4.21 - 4.16 (m, 1H), 4.02 - 3.95 (m, 2H), 3.84 - 3.81 (m, 1H), 3.69 - 3.63 (m, 1H), 3.32 - 3.27 (m, 2H), 2.89 - 2.82 (m, 1H), 2.20 (s, 3H).

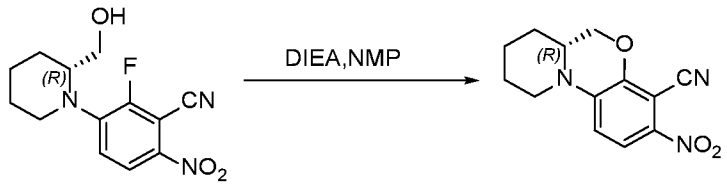
***Example S86: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrido[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 86)***

**[0659]** **Step 1. Synthesis of (R)-2-fluoro-3-(2-(hydroxymethyl)piperidin-1-yl)-6-nitrobenzonitrile**



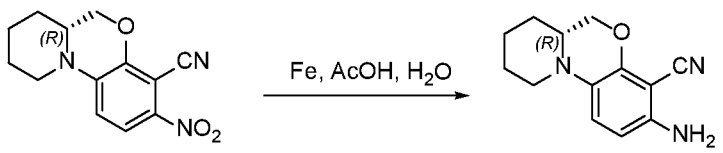
**[0660]** To a solution of 2,3-difluoro-6-nitrobenzonitrile (1.0 g, 5.43 mmol) in NMP (10.0 mL) was added (2R)-piperidin-2-ylmethanol (625.6 mg, 5.43 mmol) and DIEA (2.1 g, 16.30 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (R)-2-fluoro-3-(2-(hydroxymethyl)piperidin-1-yl)-6-nitrobenzonitrile (1.0 g, 84%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 280.1.

**[0661] Step 2. Synthesis of (R)-3-nitro-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazine-4-carbonitrile**




**[0662]** To a solution of (R)-2-fluoro-3-(2-(hydroxymethyl)piperidin-1-yl)-6-nitrobenzonitrile (900.0 mg, 3.22 mmol) in NMP (10.0 mL) was added DIEA (1.3 g, 9.67 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (R)-3-nitro-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazine-4-carbonitrile (800.0 mg, 86%) as a yellow solid. (ESI, m/z): $[M+H]^+$ = 260.1.

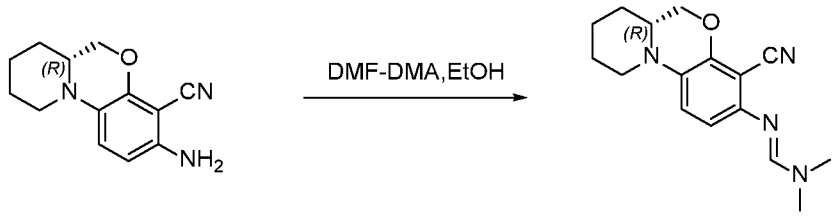
**[0663] Step 3. Synthesis of (R)-3-amino-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazine-4-carbonitrile**




**[0664]** To a solution of (R)-3-nitro-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazine-4-carbonitrile (780.0 mg, 3.01 mmol) in AcOH/$H_2O$ (10.0 mL/1.0 mL) were

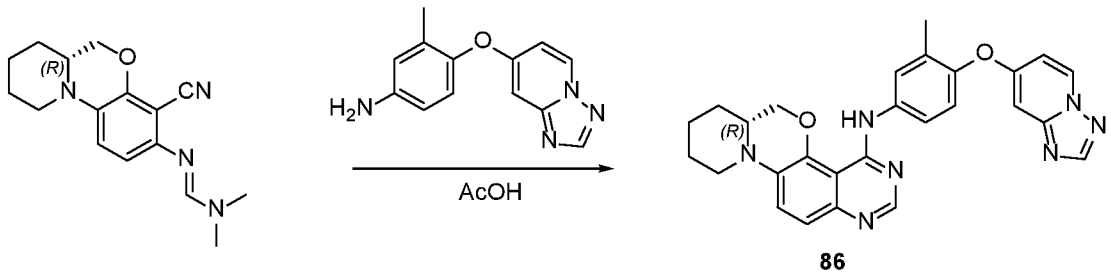
added Fe (840.1 mg, 15.05 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (R)-3-amino-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazine-4-carbonitrile (500.0 mg, 65%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 230.1.

**[0665] Step 4. Synthesis of (R,E)-N'-(4-cyano-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**




**[0666]** To a solution of (R)-3-amino-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazine-4-carbonitrile (480.0 mg, 2.10 mmol) in EtOH (5.0 mL) was added DMF-DMA (499.0 mg, 4.20 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford (R,E)-N'-(4-cyano-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (400.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 285.2.

**[0667] Step 5. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrido[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 86)**



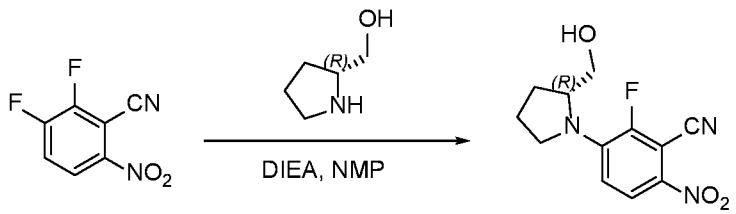

86

**[0668]** To a solution of (R,E)-N'-(4-cyano-6,6a,7,8,9,10-hexahydrobenzo[b]pyrido[1,2-d][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (150.0 mg, crude) in AcOH (3.0 mL) was added 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (126.7 mg, 0.53 mmol) at room

temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (1/1, v/v) and then purified by Prep-HPLC with the following conditions: (Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: ACN, Mobile Phase B: Water (0.1% FA); Flow rate: 60 mL/min; Gradient: 3% B to 18% B in 10 min; Wave Length: 254/220 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrido[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 86)** (34.9 mg, 13%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 480.1. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.03 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.38 - 8.35 (m, 2H), 7.92 - 7.89 (m, 1H), 7.83 (d, $J$ = 2.4 Hz, 1H), 7.63 (d, $J$ = 9.6 Hz, 1H), 7.29 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.01 (m, 1H), 6.78 (d, $J$ = 2.4 Hz, 1H), 4.67 - 4.64 (m, 1H), 4.24 - 4.19 (m, 1H), 4.06 - 4.03 (m, 1H), 3.17 - 3.12 (m, 1H), 2.68 - 2.51 (m, 1H), 2.19 (s, 3H), 1.86 - 1.73 (m, 3H), 1.54 - 1.41(m, 2H), 1.31 - 1.21 (m, 1H).

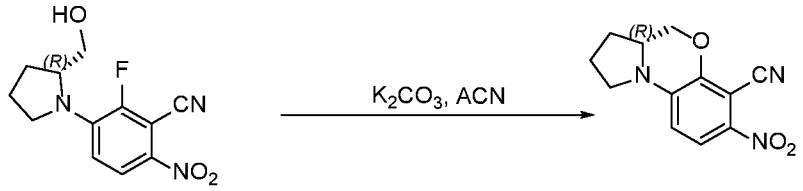
***Example S87: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,8,9-tetrahydro-6H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 87)***

**[0669] Step 1. Synthesis of (R)-2-fluoro-3-(2-(hydroxymethyl)pyrrolidin-1-yl)-6-nitrobenzonitrile**



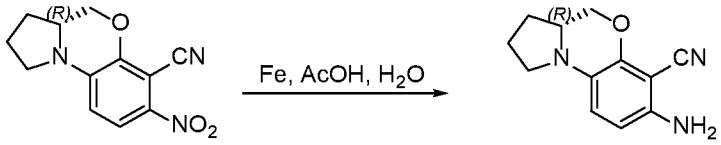

**[0670]** To a solution of 2,3-difluoro-6-nitrobenzonitrile (1.0 g, 5.43 mmol) in NMP (10.0 mL) was added (R)-pyrrolidin-2-ylmethanol (1.1 g, 10.86 mmol) and DIEA (2.8 g, 21.73 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (10/1, v/v) to afford (R)-2-fluoro-3-(2-(hydroxymethyl)pyrrolidin-1-yl)-6-nitrobenzonitrile (1.1 g, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 266.1.

**[0671] Step 2. Synthesis of (R)-7-nitro-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazine-6-carbonitrile**



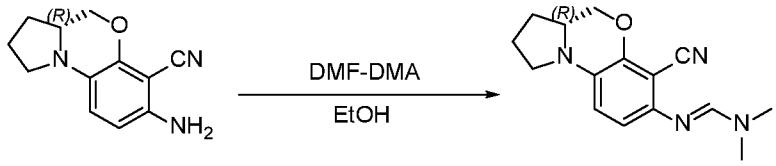

**[0672]** To a solution of (R)-2-fluoro-3-(2-(hydroxymethyl)pyrrolidin-1-yl)-6-nitrobenzonitrile (1.0 g, 3.77 mmol) in ACN (15.0 mL) was added $K_2CO_3$ (1.6 g, 11.31 mmol) at room temperature. The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/3, v/v) to afford (R)-7-nitro-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazine-6-carbonitrile (900.0 mg, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 246.1.

**[0673] Step 3. Synthesis of (R)-7-amino-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazine-6-carbonitrile**



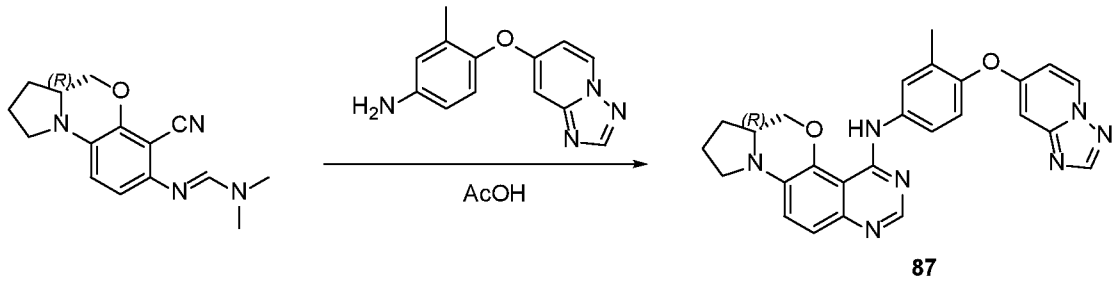

**[0674]** To a solution of (R)-7-nitro-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazine-6-carbonitrile (600.0 mg, 2.45 mmol) in AcOH/$H_2O$ (5.0 mL/0.1 mL) was added Fe (683.2 mg, 12.24 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (R)-7-amino-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazine-6-carbonitrile (300.0 mg, 56%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 216.1.

**[0675] Step 4. Synthesis of (R,E)-N'-(6-cyano-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-7-yl)-N,N-dimethylformimidamide**




**[0676]** To a solution of (R)-7-amino-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazine-6-carbonitrile (280.0 mg, 1.30 mmol) in EtOH (5.0 mL) was added DMF-DMA (465.0 mg, 3.90 mmol) at room temperature. The mixture was stirred at 80 °C for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford (R,E)-N'-(6-cyano-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-7-yl)-N,N-dimethylformimidamide (200.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 271.1.

**[0677] Step 5. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,8,9-tetrahydro-6H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 87)**



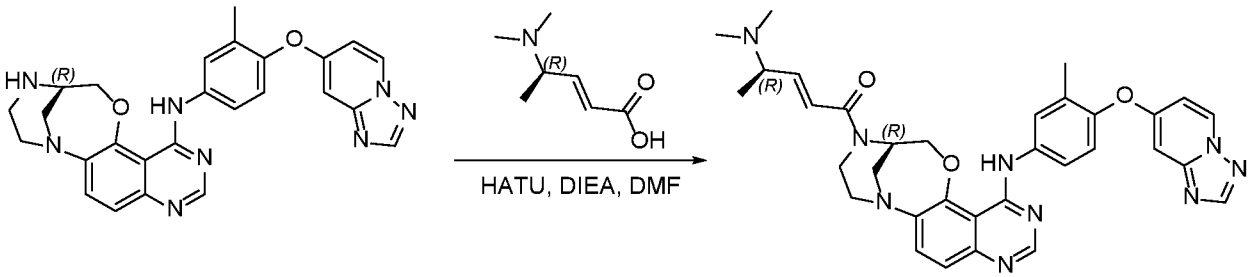

87

**[0678]** To a solution of (R,E)-N'-(6-cyano-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-7-yl)-N,N-dimethylformimidamide (150.0 mg, 0.56 mmol) in AcOH (3.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (132.3 mg, 0.56 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (7/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 52% B in 8 min, Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,8,9-tetrahydro-6H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 87)** (42.5 mg, 16%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 466.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.08 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 7.95 - 7.92 (m, 1H), 7.87 (d, $J$ = 2.4 Hz,

1H), 7.36 (s, 2H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.96 - 4.92 (m, 1H), 3.73 - 3.68 (m, 1H), 3.65 - 3.61 (m, 1H), 3.55 - 3.51 (m, 1H), 3.26 - 3.19 (m, 1H), 2.20 - 2.17 (m, 4H), 2.08 - 1.97 (m, 2H), 1.58 - 1.54 (m, 1H).

***Example S88: Synthesis of (4R,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one formic acid (Compound 88)***

**[0679] Step 1. Synthesis of (4R,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one formic acid (Compound 88)**



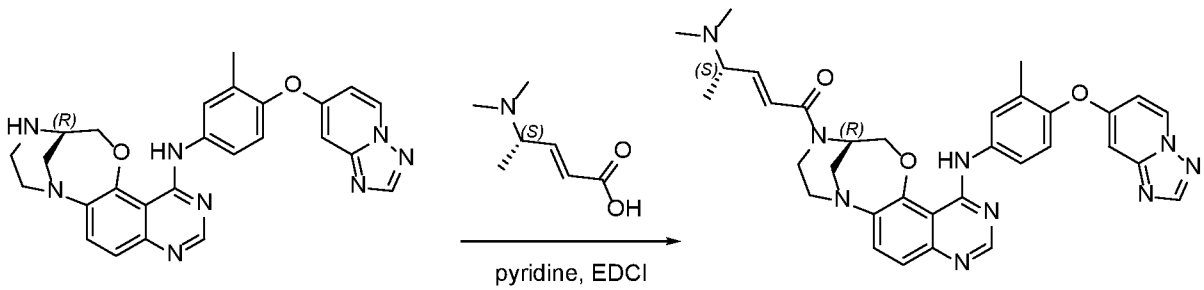

88

**[0680]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (60.0 mg, 0.12 mmol) in pyridine (5.0 mL) was added (R,E)-4-(dimethylamino)pent-2-enoic acid (178.7 mg, 1.25 mmol) and EDCI (47.8 mg, 0.25 mmol) at room temperature.The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30x150 mm, 5 μm; Mobile Phase A: ACN, Mobile Phase B: Water (0.1% FA); Flow rate: 60 mL/min; Gradient: 3% B to 10% B in 10 min; Wave Length: 254/220 nm) to afford (4R,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one formic acid **(Compound 88)** (3.6 mg, 4%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 606.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.14 - 10.08 (m, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 8.00 - 7.84 (m, 2H), 7.60 (d, $J$ = 9.2 Hz, 1H), 7.43 (d, $J$ = 8.8 Hz, 1H), 7.23 - 7.19 (m, 1H), 7.04 - 7.02 (m, 1H), 6.79 (s, 1H), 6.70 - 6.61 (m, 1H), 6.56 - 6.46 (m, 1H),

5.07 - 4.75 (m, 2H), 4.47 - 4.35 (m, 1H), 4.20 - 4.05 (m, 2H), 3.84 - 3.65 (m, 3H), 3.21 - 3.06 (m, 2H), 2.20 (s, 3H), 2.16 (s, 6H), 1.14 - 1.09 (m, 3H).

***Example S89: Synthesis of (4S,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one (Compound 89)***

**[0681] Step 1. Synthesis of (4S,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one (Compound 89)**

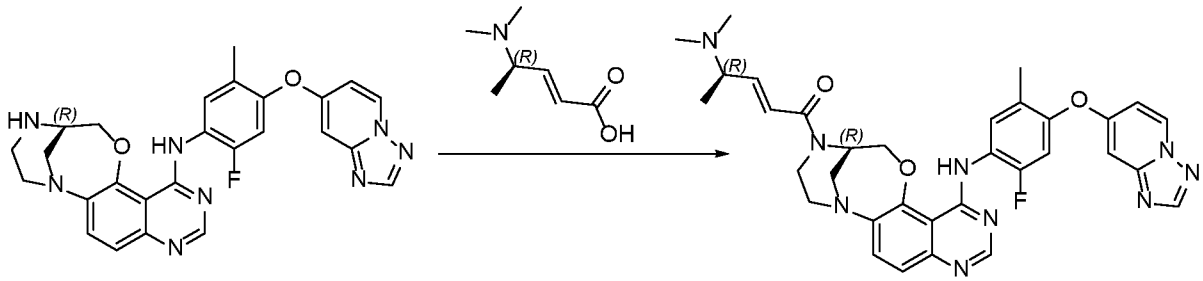



**[0682]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (40.0 mg, 0.08 mmol) in pyridine (2.0 mL) was added (2E,4S)-4-(dimethylamino)pent-2-enoic acid (119.2 mg, 0.83 mmol) and EDCI (47.9 mg, 0.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 31% B in 12 min; Wave Length: 254 nm) to afford (4S,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one **(Compound 89)** (7.3 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 606.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.13 - 10.08 (m, 1H), 8.93 (d, $J$ = 7.6 Hz, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.00 - 7.88 (m, 1H), 7.84 (s, 1H), 7.59 (d, $J$ = 9.2 Hz, 1H), 7.42 (d, $J$ = 8.8 Hz, 1H), 7.23 - 7.19 (m, 1H), 7.04 - 7.01 (m, 1H), 6.79 (d, $J$ = 1.6 Hz, 1H), 6.68 - 6.63 (m, 1H), 6.55 - 6.49 (m, 1H), 5.08 - 4.72 (m, 2H), 4.43 - 4.40 (m, 1H),

4.19 - 4.06 (m, 1H), 3.83 - 3.66 (m, 2H), 3.39 - 3.33 (m, 1H), 3.24 - 3.20 (m, 1H), 3.11 - 3.08 (m, 1H), 2.20 - 2.14 (m, 9H), 1.13 - 1.10 (m, 3H).

***Example S90: Synthesis of (4R,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one (Compound 90)***

**[0683] Step 1. Synthesis of (4R,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one (Compound 90)**



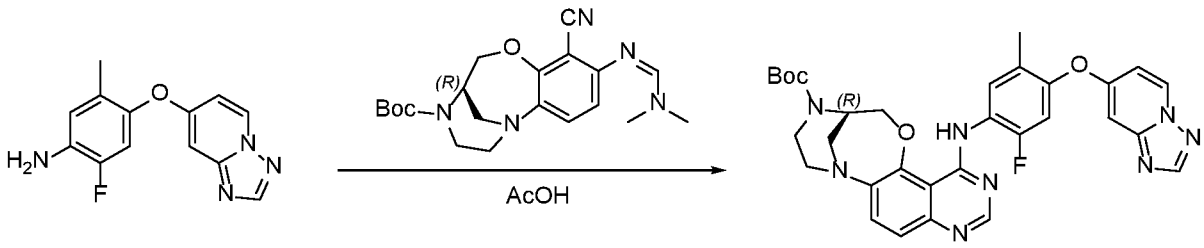
**90**

**[0684]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (90.0 mg, 0.18 mmol) in pyridine (2.0 mL) was added (R,E)-4-(dimethylamino)pent-2-enoic acid (258.5 mg, 1.81 mmol) and EDCI (69.2 mg, 0.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 41% B in 10 min; Wave Length: 254 nm) to afford (4R,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one **(Compound 90)** (4.8 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 624.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.17 (s, 1H), 8.96 (d, $J$ = 7.2 Hz, 1H), 8.50 - 8.41 (m, 3H), 7.63 (d, $J$ = 9.2 Hz, 1H), 7.46 (d, $J$ = 9.2 Hz, 1H), 7.34 (d, $J$ = 11.6 Hz, 1H), 7.07 - 7.04 (m, 1H), 6.91 (d, $J$ = 2.8 Hz, 1H), 6.68 - 6.51 (m, 2H), 5.04 - 4.85 (m, 1H), 4.82 - 4.76 (m, 1H), 4.49 - 4.42 (m, 1H),

4.20 - 4.02 (m, 1H), 3.85 - 3.64 (m, 2H), 3.44 - 3.37 (m, 1H), 3.26 - 3.21 (m, 1H), 3.20 - 3.14 (m, 1H), 3.12 - 3.06 (m, 1H), 2.19 (s, 3H), 2.14 (s, 6H), 1.12 - 1.08 (m, 3H).

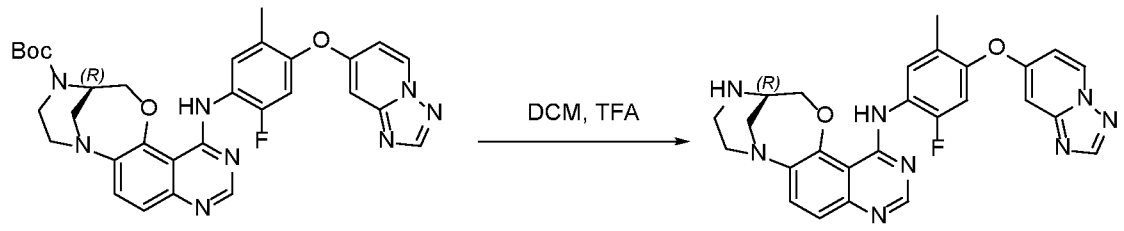
***Example S91: Synthesis of (4S,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one triformate (Compound 91)***

**[0685] Step 1. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**



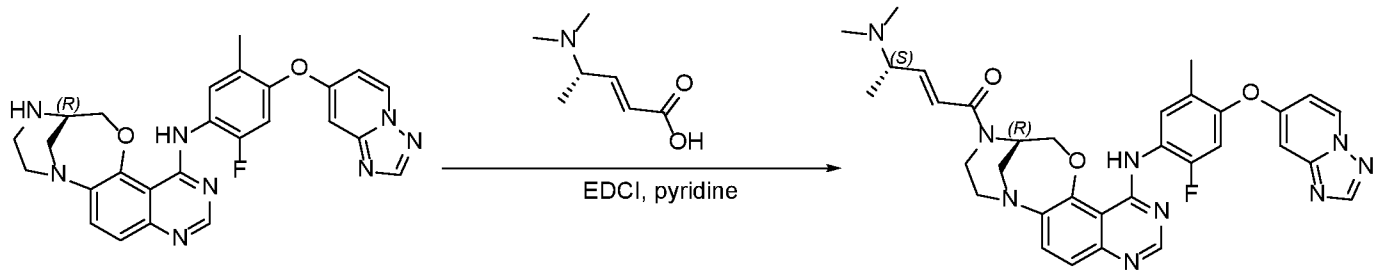

**[0686]** To a solution of 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylaniline (500.0 mg, 2.01mmol) in AcOH (10.0 mL) was added tert-butyl (3R)-11-cyano-10-(((Z)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (730.4 mg, 1.89 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography with dichloromethane/methanol (85/15, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (600.0 mg, 49%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 599.3.

**[0687] Step 2. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**



**[0688]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (500.0 mg, 0.80 mmol) in $CH_2Cl_2$ (9.0 mL) was added TFA (3.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH value of the mixture was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (300.0 MG, CRUDE) AS A YELLOW SOLID. LCMS (ESI, m/z): $[M+H]^+$ = 499.2.

**[0689] Step 3. Synthesis of (4S,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one triformate (Compound 91)**



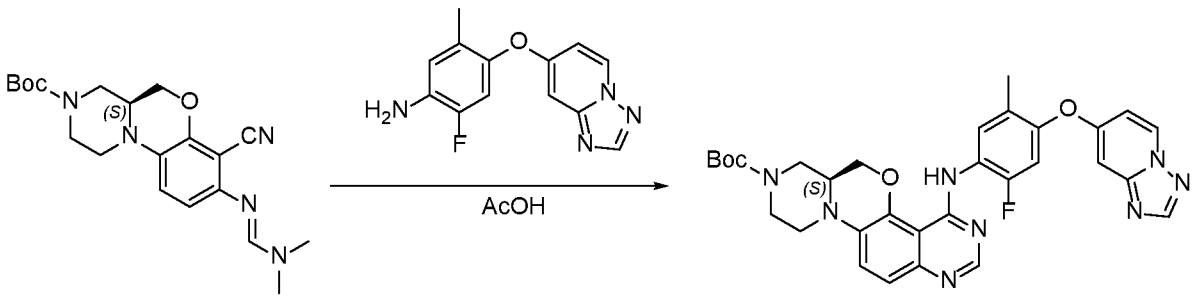

91

**[0690]** To a solution of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (40.0 mg, 0.08 mmol) in Pyridine (5.0 mL) was added (2E,4S)-4-(dimethylamino)pent-2-enoic acid (119.2 mg, 0.83 mmol) and EDCI (47.9 mg, 0.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 10% B to 30% B in 10 min; Wave Length: 254 nm) to afford (4S,E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-

methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)pent-2-en-1-one triformate **(Compound 91)** (4.1 mg, 12%) as an orange solid. LCMS (ESI, m/z): $[M+H]^+$ = 624.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.17 (s, 1H), 8.96 (d, $J$ = 7.2 Hz, 1H), 8.50 - 8.41 (m, 3H), 8.22 (s, 3H), 7.63 (d, $J$ = 9.2 Hz, 1H), 7.46 (d, $J$ = 9.2 Hz, 1H), 7.36 - 7.33 (m, 1H), 7.07 - 7.04 (m, 1H), 6.91 (d, $J$ = 2.0 Hz, 1H), 6.67 - 6.50 (m, 2H), 5.07 - 4.77 (m, 2H), 4.48 - 4.43 (m, 1H), 4.19 - 4.02 (m, 2H), 3.84 - 3.65 (m, 3H), 3.30 - 3.05 (m, 2H), 2.20 (s, 3H), 2.16 - 2.14 (m, 6H), 1.11 (d, $J$ = 3.2 Hz, 3H).

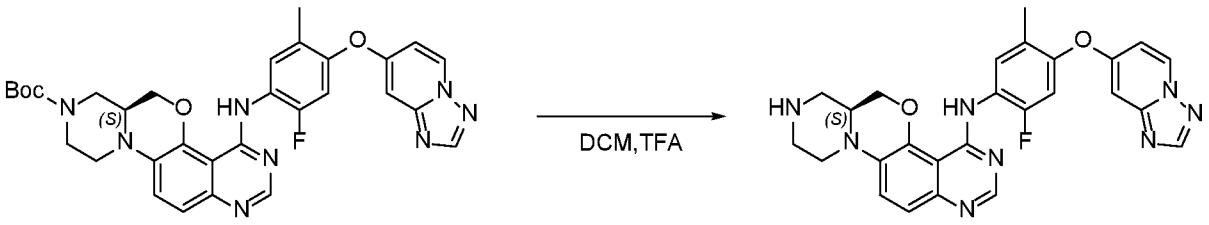
***Example S92: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 92)***

**[0691] Step 1. Synthesis of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**



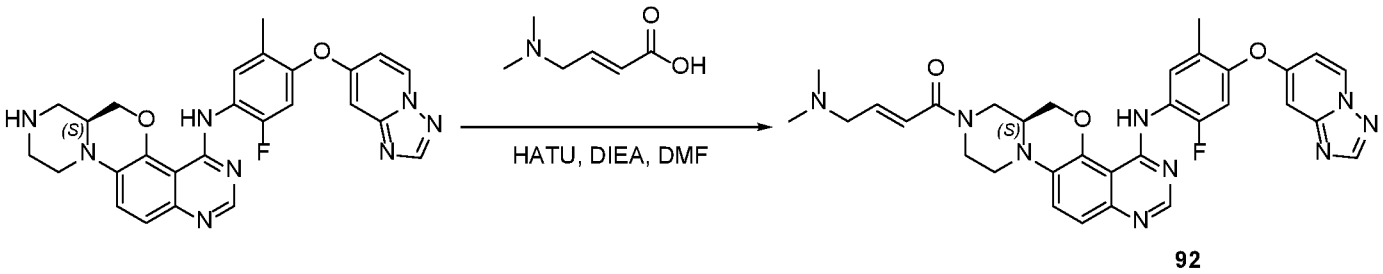

**[0692]** To a solution of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (230.0 mg, 0.60 mmol) in AcOH (2.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylaniline (124.1 mg, 0.60 mmol) at room temperature. The resulting mixture was stirred 85 °C for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/$CH_3CN$ (3/7, v/v) to afford tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (160.0 mg, 44%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 599.3.

**[0693] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0694]** To a solution of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (140.0 mg, 0.23 mmol) in $CH_2Cl_2$ (2.0 mL) was added TFA (2.4 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure, The pH value of the residue was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (110.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 499.2.

**[0695] Step 3. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 92)**



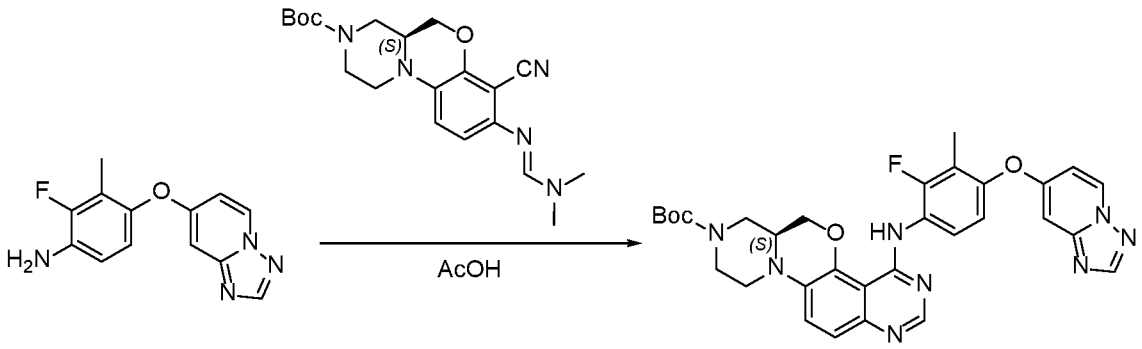

92

**[0696]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (90.0 mg, crude) in DMF (2.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (59.8 mg, 0.36 mmol), DIEA (116.7 mg, 0.91 mmol) and HATU (164.8 mg, 0.43 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was

purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30×150 mm, 5 um; Mobile Phase A: ACN, Mobile Phase B: Water (0.1% FA); Flow rate: 60 mL/min; Gradient: 8% to 18% in 10 min, 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 92)** (22.4 mg, 20%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 610.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.98 (s, 1H), 8.96 (d, $J$ = 7.2 Hz, 1H), 8.42 - 8.35 (m, 3H), 7.67 (d, $J$ = 9.2 Hz, 1H), 7.37 - 7.31 (m, 2H), 7.05 (d, $J$ = 7.2 Hz, 1H), 6.92 (s, 1H), 6.75 - 6.65 (m, 2H), 4.74 - 4.71 (m, 1H), 4.57 - 4.53 (m, 1H), 4.29 - 4.17 (m, 2H), 4.07 - 4.04 (m, 1H), 3.11 (d, $J$ = 4.0 Hz, 2H), 3.05 - 2.91 (m, 1H), 2.85 - 2.74 (m, 1H), 2.63 - 2.54 (m, 1H), 2.20 (s, 9H).

***Example S93: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 93)***

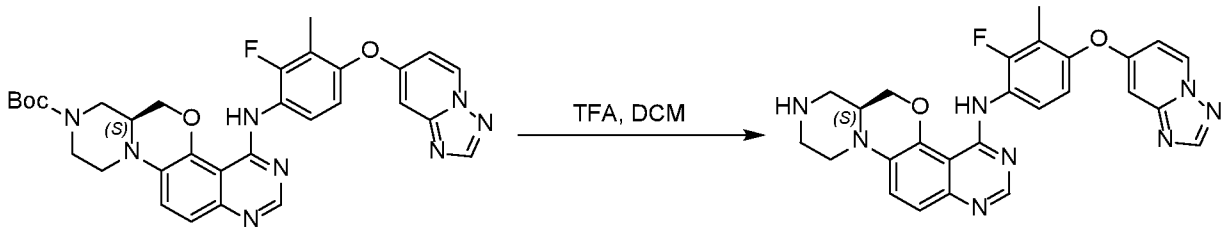
**[0697] Step 1. Synthesis of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**




**[0698]** To a solution of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (447.8 mg, 1.16 mmol) in acetic acid (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylaniline (200.0 mg, 0.77 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash column chromatography with $H_2O$/ACN (40/60, v/v) to afford tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-

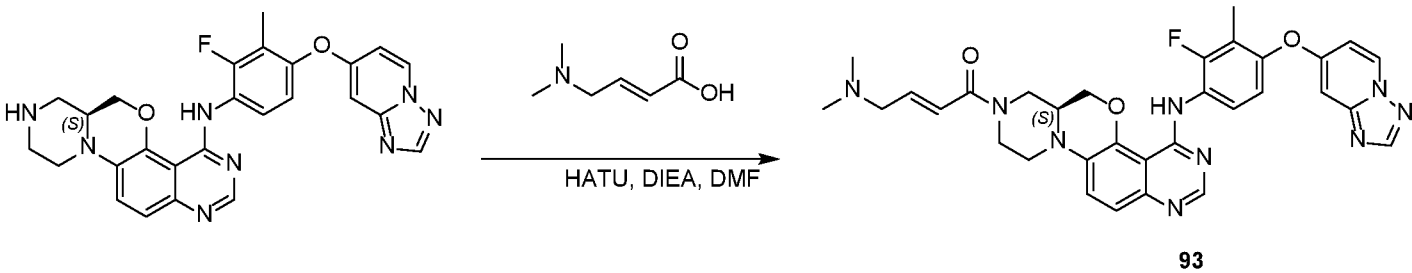
f]quinazoline-8(6H)-carboxylate (270.0 mg, 58%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =599.2.

**[0699] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0700]** To a solution of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (250.0 mg, 0.42 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 7 with $NaHCO_3$ (aq.). The resulting mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (150.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =499.2.

**[0701] Step 3. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 93)**

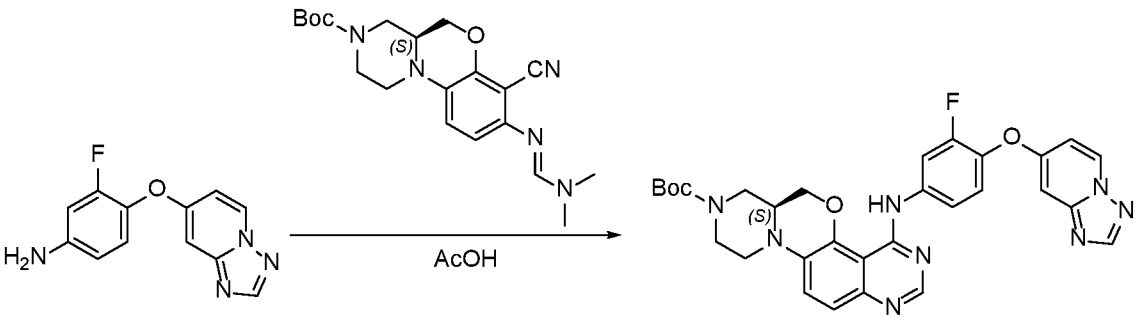



**93**

**[0702]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, crude) in DMF (5.0 mL) was added (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (66.4 mg, 0.40 mmol), DIEA (155.6 mg, 1.21 mmol) and HATU (167.8 mg, 0.44 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 30 min. After the reaction was completed, the resulting mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 45% B to 50% B in 8 min; Wave Length: 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 93)** (16.7 mg, 13%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 610.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.12 - 10.07 (m, 1H), 8.96 (d, $J$ = 7.6 Hz, 1H), 8.51 - 8.37 (m, 3H), 7.68 (d, $J$ = 9.2 Hz, 1H), 7.37 (d, $J$ = 9.2 Hz, 1H), 7.14 - 7.05 (m, 2H), 6.92 (d, $J$ = 2.4 Hz, 1H), 6.74 - 6.65 (m, 2H), 4.77 - 4.74 (m, 1H), 4.59 - 4.52 (m, 1H), 4.32 - 4.27 (m, 2H), 4.07 - 4.04 (m, 1H), 3.07 (d, $J$ = 4.4 Hz, 2H), 2.97 - 2.79 (m, 2H), 2.17 (s, 9H).

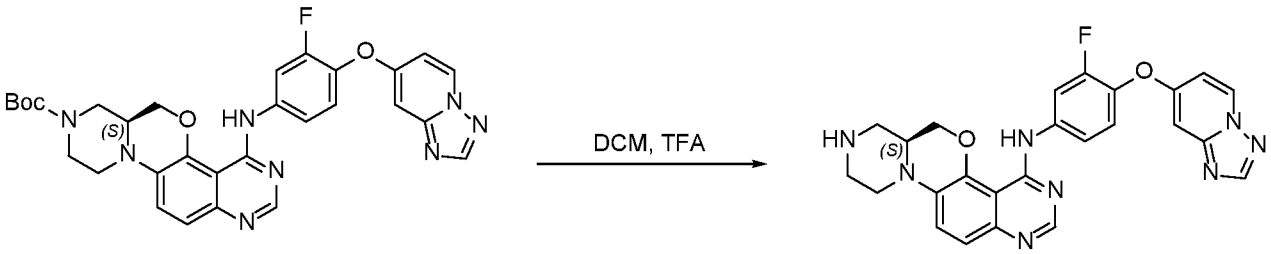
***Example S94: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 94)***

**[0703]** **Step 1. Synthesis of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**



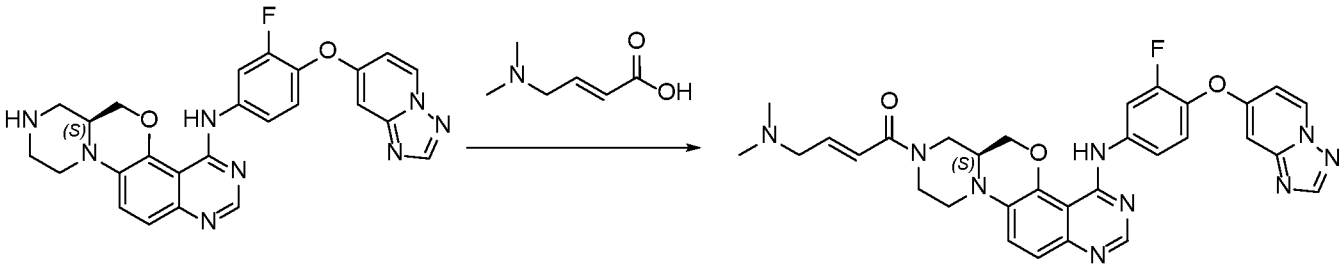
**[0704]** To a solution of 3-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (150.0 mg, 0.61 mmol) in AcOH (2.0 mL) was added tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (236.8 mg, 0.61 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (34/66, v/v) to afford tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (113.0 mg, 31%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =585.2.

**[0705] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0706]** To a solution of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (100.0 mg, 0.17 mmol) in $CH_2Cl_2$ (1.5 mL) was added TFA (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (76.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =485.2.

**[0707] Step 3. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 94)**

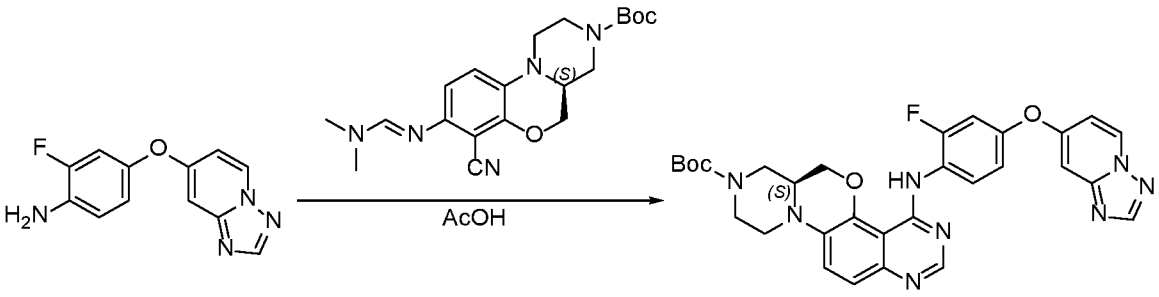


94

**[0708]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (67.0 mg, crude) in DMF (2.0 mL) was added (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (45.8 mg, 0.28 mmol) and EDCI (53.0 mg, 0.28 mmol ) at room temperature. The resulting mixture was stirred at room temperature for 30 min. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH $C_{18}$ OBD Column 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 35% B in 10 min; Wave Length: 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 94)** (5.6 mg, 6%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =596.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.11 (s, 1H), 8.96 (d, $J$ = 7.6 Hz, 1H), 8.44 - 8.41 (m, 2H), 8.27 (d, $J$ = 11.6 Hz, 1H), 7.75 - 7.67 (m, 2H), 7.52 - 7.47 (m, 1H), 7.38 - 7.35 (m, 1H), 7.09 (d, $J$ = 6.0 Hz, 1H), 7.02 (s, 1H), 6.78 - 6.69 (m, 2H), 4.80 - 4.78 (m, 1H), 4.51 - 4.43 (m, 1H), 4.30 - 4.15 (m, 2H), 4.12 - 4.05 (m, 1H), 3.11 - 3.04 (m, 3H), 2.91 - 2.79 (m, 2H), 2.17 (s, 6H).

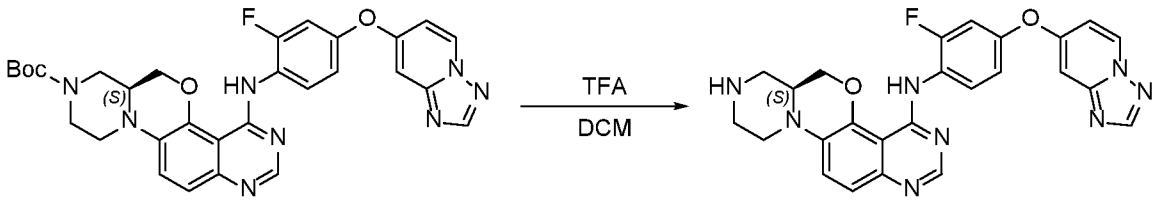
***Example S95: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 95)***

**[0709]** **Step 1. Synthesis of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**




**[0710]** To a solution of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (200.0 mg, 0.52 mmol) in AcOH (2.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoroaniline (126.7 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred 85 °C for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (3/7, v/v) to afford tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (100.0 mg, 32%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 585.2.

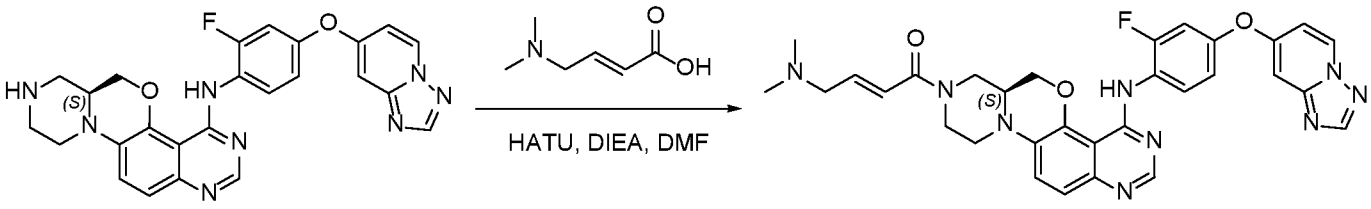
**[0711] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0712]** To a solution of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (100.0 mg, 0.17 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure, The pH value of the residue was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6,6a,7,8,9,10-

hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (80.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 485.2.

**[0713] Step 3. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 95)**

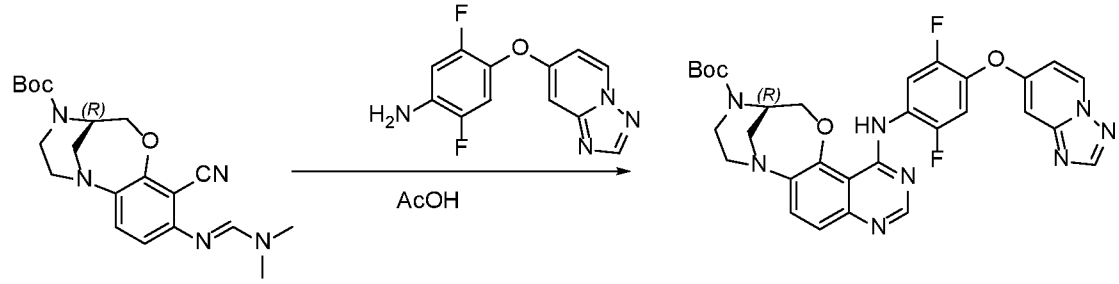



95

**[0714]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, crude) in DMF (2.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid (53.3 mg, 0.41 mmol), DIEA (133.4 mg, 1.03mmol) and HATU (188.4 mg, 0.49 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% to 42% in 8 min, 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 95)** (42.9 mg, 34%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 596.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.00 (s, 1H), 8.97 (d, $J$ = 7.6 Hz, 1H), 8.47 - 8.38 (m, 3H), 7.67 (d, $J$ = 9.2 Hz, 1H), 7.41 - 7.35 (m, 2H), 7.18 - 7.15 (m, 2H), 7.07 - 7.05 (m, 1H), 6.73 - 6.65 (m, 2H), 4.75 - 4.71 (m, 1H), 4.56 - 4.54 (m, 1H), 4.29 - 4.15 (m, 2H), 4.07 - 4.03 (m, 1H), 3.06 - 3.02 (m, 3H), 2.90 - 2.51 (m, 3H), 2.15 (s, 6H).

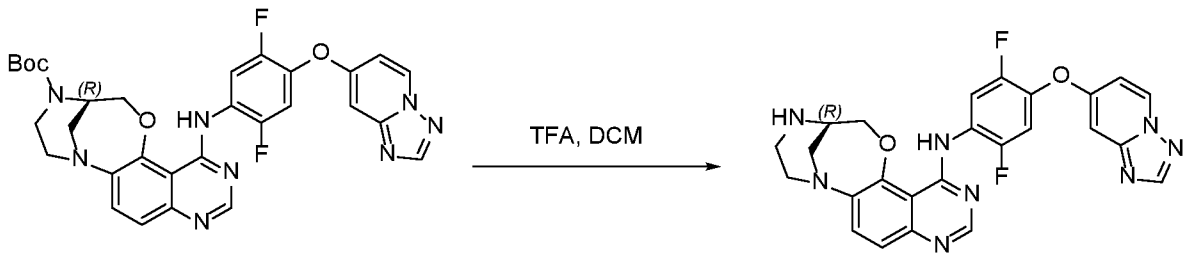
***Example S96: Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 96)***

**[0715] Step 1. Synthesis of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate**



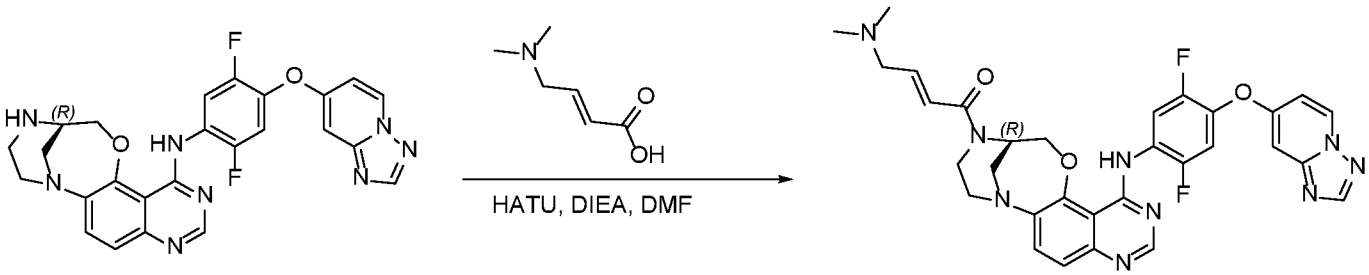

**[0716]** To a solution of tert-butyl (3R)-11-cyano-10-(((E)-(dimethylamino)methylene)amino)-2,3,5,6-tetrahydro-4H-3,7-methanobenzo[b][1,4,7]oxadiazonine-4-carboxylate (900.0 mg, 2.33 mmol) in acetic acid (10.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluoroaniline (489.7 mg, 1.86 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (500.0 mg, 26%) as a dark red solid. LCMS (ESI, m/z): $[M+H]^+$ = 603.2.

**[0717] Step 2. Synthesis of (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine**



**[0718]** To a solution of tert-butyl (3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazoline-4-carboxylate (490.0 mg, 0.81 mmol) in DCM (6.0 mL) was added TFA (3.0 mL) at room temperature.The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was neutralized to pH = 8 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (110.0 mg, 26%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 503.2.

**[0719] Step 3. Synthesis of (E)-1-((3R)-13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one (Compound 96)**



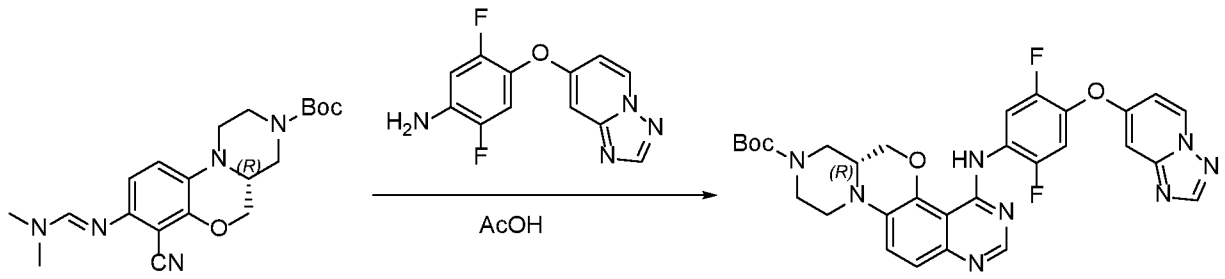

96

**[0720]** To a solution of (E)-4-(dimethylamino)but-2-enoic acid (23.1 mg, 0.18 mmol) in DMF (3.0 mL) was added DIEA (28.9 mg, 0.22 mmol), (3R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-3,4,5,6-tetrahydro-2H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-13-amine (90.0 mg, 0.09 mmol) and HATU (34.0 mg, 0.09 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 37% B in 8 min; Wave Length: 254 nm) to afford (E)-1-((3R)-

13-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-2,3,5,6-tetrahydro-4H-3,7-methano[1,4,7]oxadiazonino[2,3-f]quinazolin-4-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 96)** (14.0 mg, 25%) as a white solid. $[M+H]^+$ = 614.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.43 (s, 1H), 8.98 (d, $J$ = 7.2 Hz, 1H), 8.89 - 8.79 (m, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 7.71 - 7.65 (m, 2H), 7.50 (d, $J$ = 9.2 Hz, 1H), 7.17 - 7.12 (m, 2H), 6.70 - 6.60 (m, 2H), 5.07 - 4.78 (m, 2H), 4.48 - 4.44 (m, 1H), 4.21 - 4.06 (m, 2H), 3.83 - 3.62 (m, 2H), 3.44 - 3.34 (m, 1H), 3.23 - 3.18 (m, 1H), 3.06 - 3.02 (m, 2H), 2.16 - 2.15 (m, 6H).

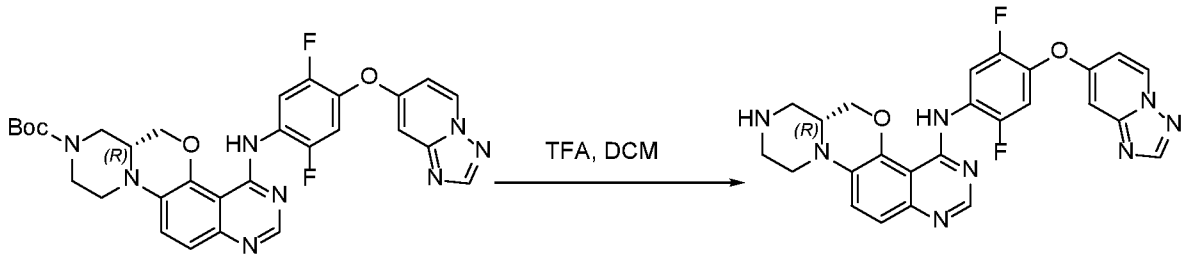
***Example S97: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 97)***

**[0721] Step 1. Synthesis of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**



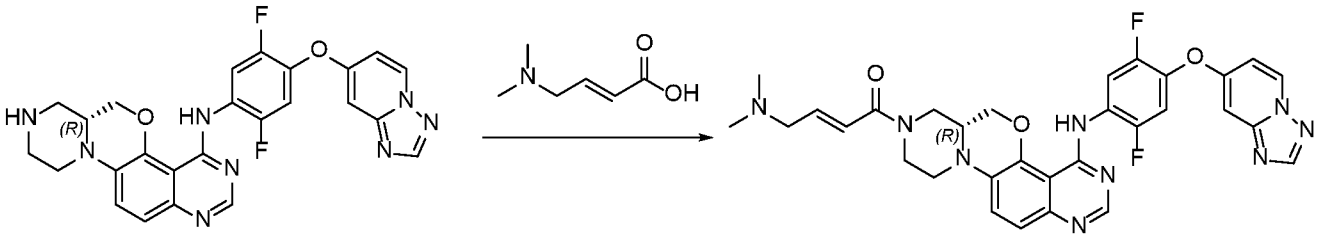

**[0722]** To a stirred mixture of tert-butyl (R,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (200.0 mg, 0.52 mmol) in acetic acid (6.0 mL) was added 2,5-difluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (136.1 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at 85 °C under $N_2$ for 2 days. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (6/1, v/v) to afford tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (150.0 mg, 47%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 603.2.

**[0723] Step 2. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0724]** To a stirred mixture of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (140.0 mg, 0.23 mmol) in DCM (4.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH value of the mixture was adjusted to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (7/1, v/v) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, 85%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 503.2

**[0725] Step 3. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 97)**



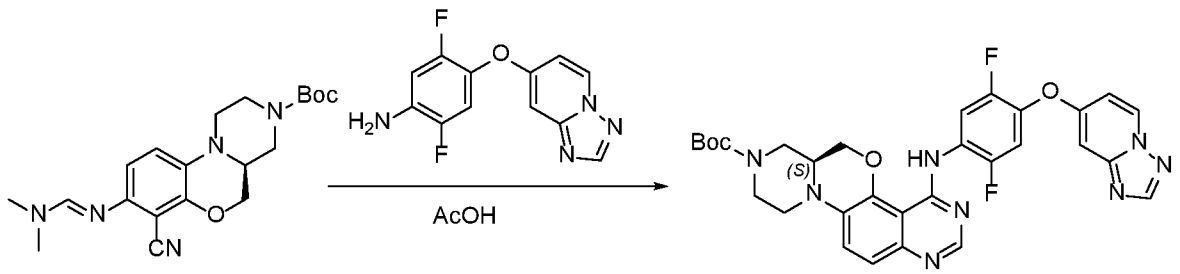

**97**

**[0726]** To a stirred mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (90.0 mg, 0.18 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (46.3 mg, 0.36 mmol) in pyridine (2.0 mL) were added EDCI (68.7 mg, 0.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction mixture was evaporated in vacuo, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (27/73, v/v) and then

purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 35% B in 8 min; Wave Length: 254 nm) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 97)** (18.4 mg, 16%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 614.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.22 (s, 1H), 8.98 (d, $J$ = 7.6 Hz, 1H), 8.81 (s, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 7.72 - 7.65 (m, 2H), 7.40 (d, $J$ = 8.8 Hz, 1H), 7.17 - 7.12 (m, 2H), 6.73 - 6.70 (m, 2H), 4.76 - 4.74 (m, 1H), 4.64 - 4.49 (m, 1H), 4.32 - 4.23 (m, 2H), 4.08 - 4.06 (m, 1H), 3.30 - 3.21 (m, 1H), 3.06 (d, $J$ = 4.4 Hz, 2H), 2.93 - 2.74 (m, 2H), 2.68 - 2.51 (m, 1H), 2.17 (s, 6H).

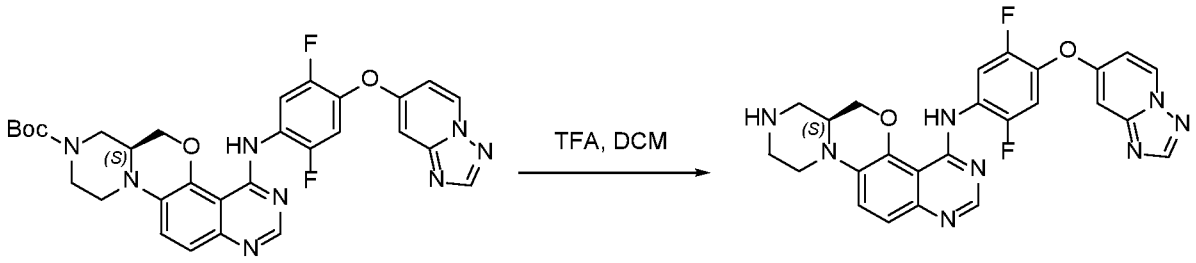
***Example S98: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 98)***

**[0727] Step 1. Synthesis of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**



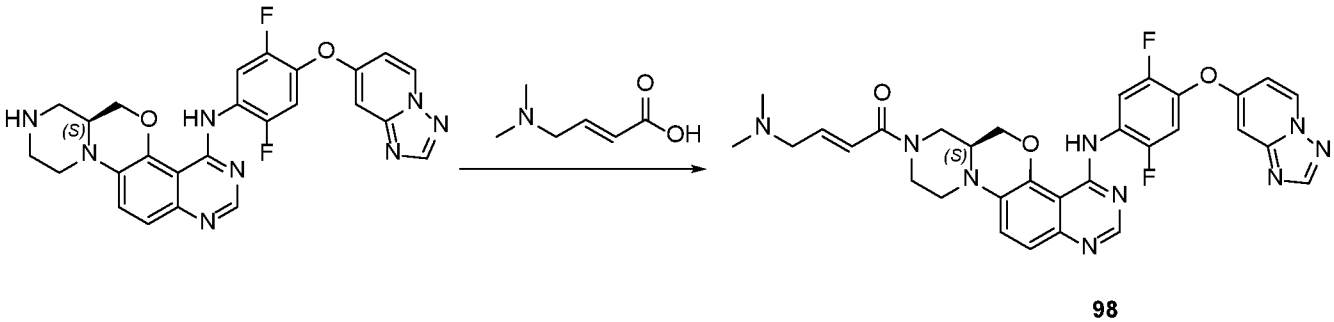

**[0728]** A mixture of tert-butyl (S,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (360.0 mg, 0.93 mmol) and 2,5-difluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (244.9 mg, 0.93 mmol) in acetic acid (8.0 mL) was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (120.0 mg, 21%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 603.2.

**[0729] Step 2. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0730]** A mixture of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (100.0 mg, 0.16 mmol) in DCM (5.0 mL) and TFA (5.0 mL) was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was neutralized to pH=7 with saturated $NaHCO_3$ (aq). The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (60/40, v/v) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (80.0 mg, 95%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 503.2.

**[0731] Step 3. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 98)**



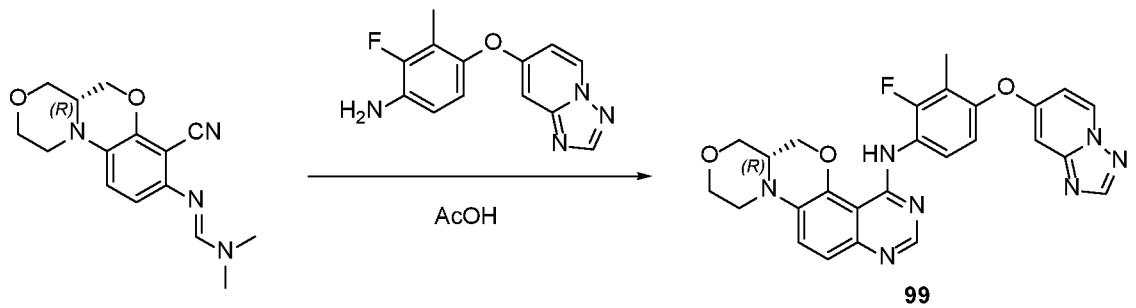

98

**[0732]** To a stirred mixture of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (70.0 mg, 0.15 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (20.5 mg, 0.16 mmol)

in pyridine (5.0 mL) was added EDCI (61.0 mg, 0.31 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (60/40, v/v) and then purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 44% B in 12 min; Wave Length: 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 98)** (10.6 mg, 10%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ = 614.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.22 (s, 1H), 8.98 (d, $J$ = 7.6 Hz, 1H), 8.86 - 8.78 (m, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 7.72 - 7.64 (m, 2H), 7.39 (d, $J$ = 8.8 Hz, 1H), 7.18 - 7.11 (m, 2H), 6.74 - 6.65 (m, 2H), 4.76 - 4.73 (m, 1H), 4.65 - 4.48 (m, 1H), 4.33 - 4.19 (m, 2H), 4.08 - 4.04 (m, 1H), 3.07 - 2.60 (m, 6H), 2.16 (s, 6H).

***Example S99: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 99)***

**[0733] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 99)**



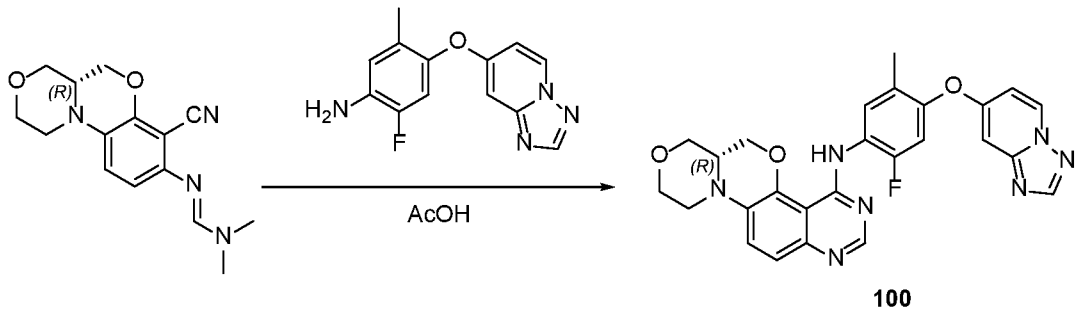

99

**[0734]** To a solution of (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (150.0 mg, 0.52 mmol) in AcOH (4.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylaniline (270.6 mg, 1.05 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (49/51, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge

Shield RP18 OBD Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 48% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 99)** (2.6 mg, 1%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.1.$^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.09 (s, 1H), 8.96 (d, $J$ = 7.2 Hz, 1H), 8.46 - 8.40 (m, 3H), 7.62 (d, $J$ = 8.8 Hz, 1H), 7.36 (d, $J$ = 9.2 Hz, 1H), 7.14 - 7.05 (m, 2H), 6.92 (s, 1H), 4.66 - 4.63 (m, 1H), 4.23 - 4.19 (m, 1H), 4.02 - 3.90 (m, 2H), 3.84 - 3.81 (m, 1H), 3.68 - 3.51 (m, 1H), 3.27 - 3.12 (m, 1H), 2.89 - 2.83 (m, 1H), 2.16 (s, 3H).

***Example S100: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 100)***

**[0735] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 100)**

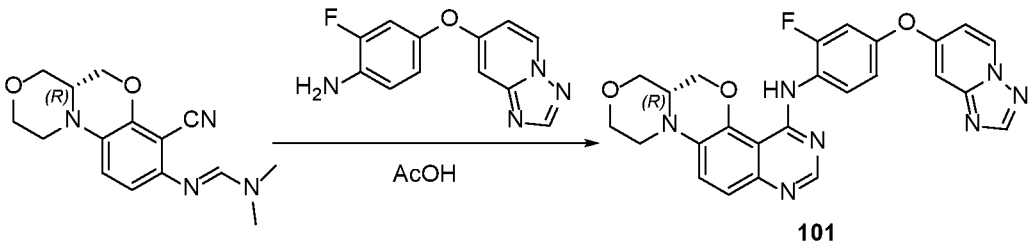



**[0736]** To a solution of (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (150.0 mg, 0.52 mmol) in acetic acid (3.0 mL) was added 2-fluoro-5-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (135.2 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with DCM/MeOH (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine

**(Compound 100)** (30.4 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.97 (s, 1H), 8.96 (d, $J$ = 7.2 Hz, 1H), 8.41 - 8.36 (m, 3H), 7.62 (d, $J$ = 9.2 Hz, 1H), 7.36 - 7.31 (m, 2H), 7.07 - 7.04 (m, 1H), 6.91 (d, $J$ = 2.0 Hz, 1H), 4.63 - 4.60 (m, 1H), 4.21 - 4.17 (m, 1H), 4.02 - 3.96 (m, 2H), 3.84 - 3.81 (m, 1H), 3.65 - 3.63 (m, 1H), 3.32 - 3.25 (m, 2H), 2.91 - 2.79 (m, 1H), 2.19 (s, 3H).

***Example S101: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 101)***

**[0737] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 101)**

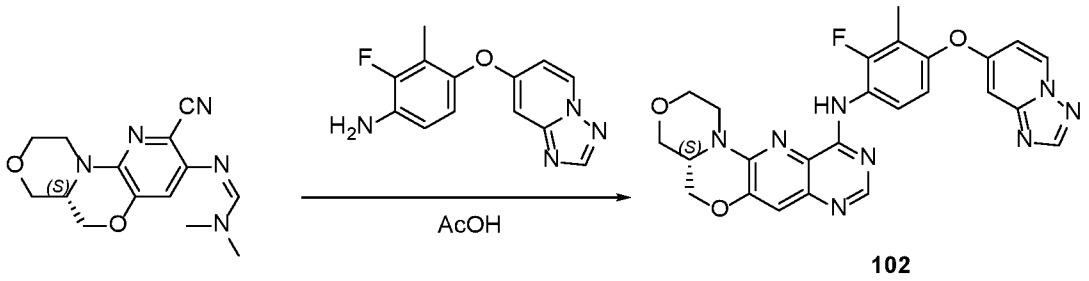



101

**[0738]** To a solution of (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (150.0 mg, 0.52 mmol) in AcOH (2.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoroaniline (256.4 mg, 1.05 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $CH_3CN/H_2O$ (49/51, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 73% B to 75% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 101)** (8.6 mg, 3%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 486.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.99 (s, 1H), 8.97 (d, $J$ = 7.6 Hz, 1H), 8.49 - 8.38 (m, 3H), 7.62 (d, $J$ = 9.2 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.18 - 7.05 (m, 3H), 4.64 - 4.60 (m, 1H), 4.22 - 4.17 (m, 1H), 4.02 - 3.96 (m, 2H), 3.84 - 3.81 (m, 1H), 3.69 - 3.63 (m, 1H), 3.31 - 3.25 (m, 1H), 2.89 - 2.83 (m, 1H).

***Example S102: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 102)***

**[0739] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 102)**

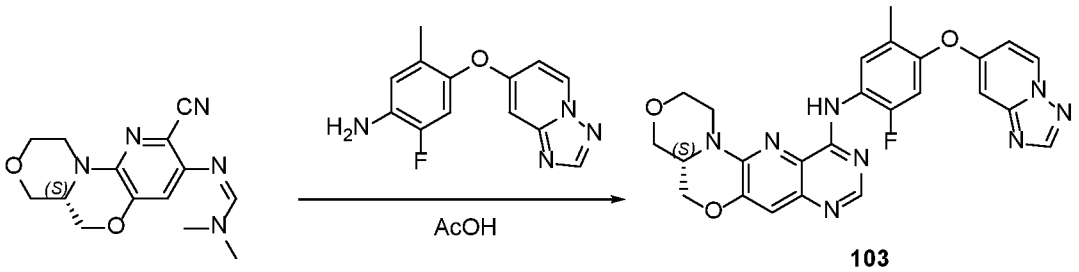



102

**[0740]** To a solution of (S,Z)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (200.0 mg, 0.70 mmol) in AcOH (5.0 mL) was added 2-fluoro-3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (197.7 mg, 0.77 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (1/ 1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD $C_{18}$ Column, 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-3-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 102)** (17.6 mg, 4%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =501.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.20 (s, 1H), 8.97 (d, $J$ = 7.2 Hz, 1H), 8.41 - 8.39 (m, 2H), 8.14 - 8.10 (m, 1H), 7.27 (s, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H), 7.08 - 7.05 (m, 1H), 6.92 (d, $J$ = 2.4 Hz, 1H), 4.69 - 4.66 (m, 1H), 4.47 - 4.43 (m, 1H), 4.11 - 3.96 (m, 3H), 3.75 - 3.70 (m, 1H), 3.66 - 3.59 (m, 1H), 3.27 - 3.21 (m, 1H), 3.09 - 3.01 (m, 1H), 2.16 (s, 3H).

***Example S103: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 103)***

**[0741] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 103)**

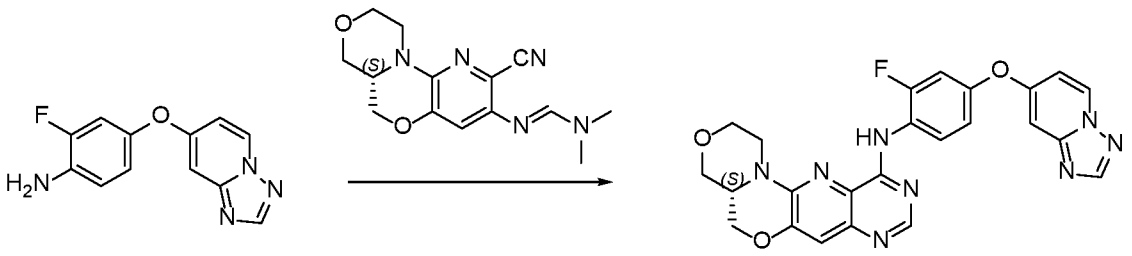



103

**[0742]** To a solution of (S,Z)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (150.0 mg, 0.51 mmol) in HOAc (3.0 mL) was added 2-fluoro-5-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (134.7 mg, 0.51 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (1/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD $C_{18}$ Column, 30×150 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 103)** (6.6 mg, 2%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =501.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.22 (s, 1H), 8.97 (d, $J$ = 7.6 Hz, 1H), 8.41 - 8.37 (m, 2H), 8.04 (d, $J$ = 8.8 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.07 - 7.04 (m, 1H), 6.91 (d, $J$ = 2.4 Hz, 1H), 4.76 - 4.73 (m, 1H), 4.47 - 4.43 (m, 1H), 4.10 - 3.95 (m, 3H), 3.75 - 3.60 (m, 2H), 3.29 - 3.21 (m, 1H), 3.08 - 3.01 (m, 1H), 2.20 (s, 3H).

***Example S104: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 104)***

**[0743] Step 1. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 104)**

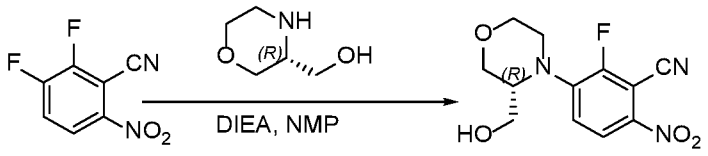


104

**[0744]** To a solution of 2-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (50.0 mg, 0.21 mmol) in HOAc (3.0 mL) was added (S,E)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (64.7 mg, 0.23 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with $H_2O/CH_3CN$ (1/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD $C_{18}$ Column, 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 104)** (3.9 mg, 3%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =487.1. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.23 (s, 1H), 8.98 (d, $J$ = 7.6 Hz, 1H), 8.44 (s, 1H), 8.35 (s, 1H), 8.12 - 8.08 (m, 1H), 7.39 - 7.36 (m, 1H), 7.27 (s, 1H), 7.19 - 7.16 (m, 2H), 7.08 - 7.06 (m, 1H), 4.75 - 4.72 (m, 1H), 4.46 - 4.43 (m, 1H), 4.09 - 3.96 (m, 3H), 3.79 - 3.52 (m, 2H), 3.27 - 3.21 (m, 1H), 3.07 - 3.01 (m, 1H).

***Example S105: Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 105)***

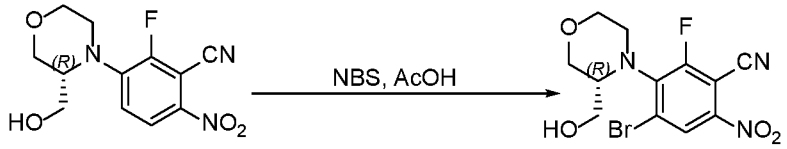
**[0745]** **Step 1. Synthesis of (R)-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile**




**[0746]** To a solution of 2,3-difluoro-6-nitrobenzonitrile (1.5 g, 8.14 mmol) in NMP (20.0 mL) was added (R)-morpholin-3-ylmethanol (2.1 g, 17.93 mmol) and DIEA (6.3 g, 48.88 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h under $N_2$.

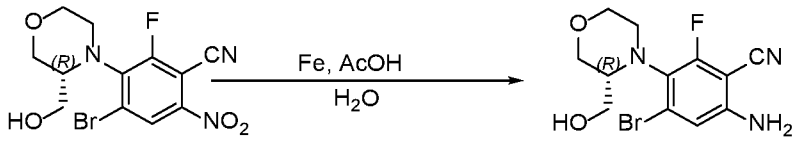
After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (37/63, v/v) to afford (R)-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (1.9 g, 84%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =282.1.

**[0747] Step 2. Synthesis of (R)-4-bromo-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile**



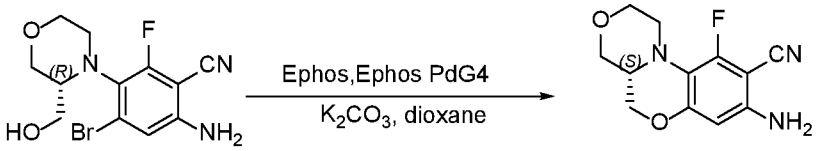

**[0748]** To a solution of (R)-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (500.0 mg, 1.78 mmol) in AcOH (15.0 mL) was added NBS (3.2 g, 17.78 mmol) at room temperature under $N_2$. The reaction mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was used in the next step directly without further purification. LCMS (ESI, m/z): $[M+H]^+$ =360.0.

**[0749] Step 3. Synthesis of (R)-6-amino-4-bromo-2-fluoro-3-(3-(hydroxymethyl)morpholino)benzonitrile**



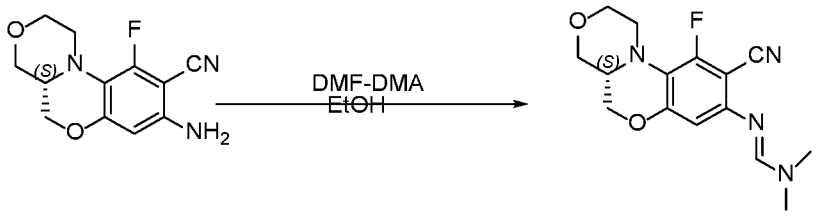

**[0750]** To a solution of (R)-4-bromo-2-fluoro-3-(3-(hydroxymethyl)morpholino)-6-nitrobenzonitrile (400.0 mg, crude) in AcOH/$H_2O$ (15.0 mL/1.0 mL) was added Fe (1.2 g, 22.22 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford (R)-6-amino-4-bromo-2-fluoro-3-(3-(hydroxymethyl)morpholino)benzonitrile ( 180.0 mg, 49%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =330.0.

**[0751] Step 4. Synthesis of (S)-8-amino-10-fluoro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-9-carbonitrile**



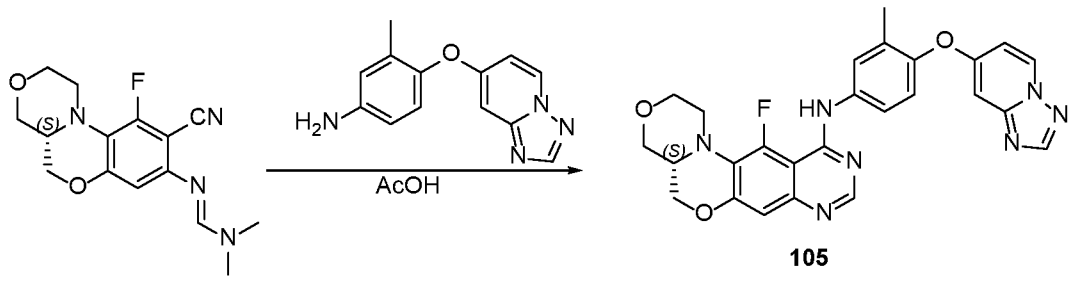

**[0752]** To a solution of (R)-6-amino-4-bromo-2-fluoro-3-(3-(hydroxymethyl)morpholino)benzonitrile (170.0 mg, 0.52 mmol) in 1,4-dioxane (5.0 mL) was added Ephos (55.1 mg, 0.10 mmol), $K_2CO_3$ (213.5 mg, 1.55 mmol) and Ephos Pd G4 (47.3 mg, 0.05 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C for 4 h under $N_2$. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (40/60, v/v) to afford (S)-8-amino-10-fluoro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-9-carbonitrile (80.0 mg, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =250.1.

**[0753] Step 5. Synthesis of (S,E)-N'-(9-cyano-10-fluoro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide**




**[0754]** To a solution of (S)-8-amino-10-fluoro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-9-carbonitrile (75.0 mg, 0.30 mmol) in EtOH (5.0 mL) was added DMF-DMA (179.3 mg, 1.51 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford (S,E)-N'-(9-cyano-10-fluoro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (70.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =305.1.

**[0755] Step 6. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 105)**

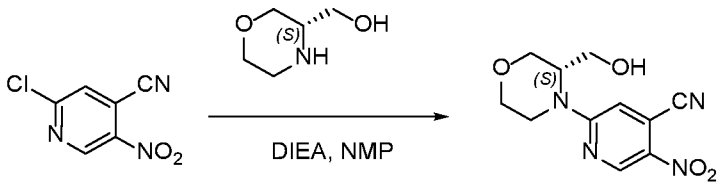



105

**[0756]** To a solution of (S,E)-N'-(9-cyano-10-fluoro-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (65.0 mg, crude) in HOAc (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (102.6 mg, 0.43 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (50/50, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 8 min; Wave Length: 254 nm) to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-12-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 105)** (12.3 mg, 11%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 8.99 - 8.93 (m, 2H), 8.47 - 8.39 (m, 2H), 7.78 (s, 2H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.02 - 6.96 (m, 2H), 6.80 (s, 1H), 4.38 - 4.20 (m, 2H), 3.93 - 3.60 (m, 6H), 3.32 - 3.25 (m, 1H), 2.19 (s, 3H).

***Example S106: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 106)***

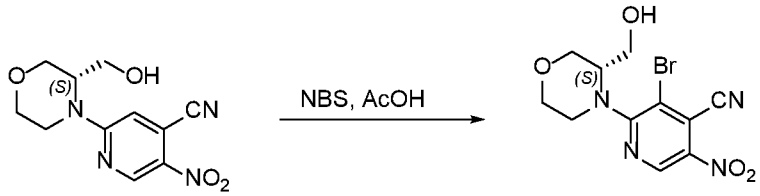
**[0757]** **Step 1. Synthesis of 2-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-5-nitropyridine-4-carbonitrile**




**[0758]** To a solution of 2-chloro-5-nitropyridine-4-carbonitrile (500.0 mg, 2.72 mmol) in NMP (5.0 mL) was added DIEA (1.1 g, 8.17 mmol) and (3S)-morpholin-3-ylmethanol hydrochloride (319.1 mg, 2.72 mmol) at room temperature. The resulting mixture was stirred at

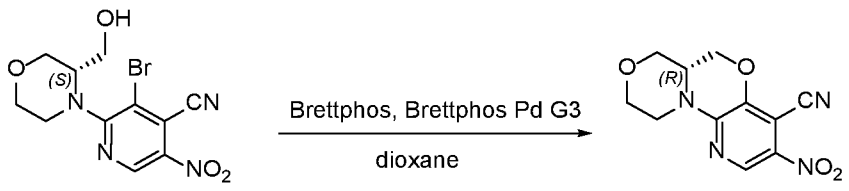
100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 2-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-5-nitropyridine-4-carbonitrile (600.0 mg, 75%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 265.1.

**[0759] Step 2. Synthesis of 3-bromo-2-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-5-nitropyridine-4-carbonitrile**




**[0760]** To a solution of 2-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-5-nitropyridine-4-carbonitrile (300.0 mg, 1.14 mmol) in acetic acid (3.0 mL) was added NBS (222.3 mg, 1.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ ethyl acetate (1/1, v/v) to afford 3-bromo-2-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-5-nitropyridine-4-carbonitrile (350.0 mg, 81%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 343.0.

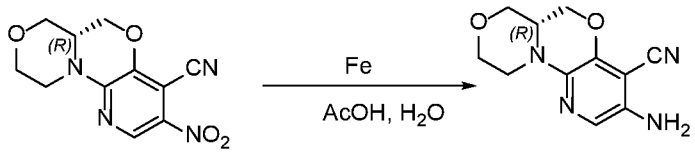
**[0761] Step 3. Synthesis of (R)-3-nitro-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-4-carbonitrile**




**[0762]** To a solution of 3-bromo-2-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-5-nitropyridine-4-carbonitrile (340.0 mg, 0.99 mmol) in dioxane (5.0 mL) were added $Cs_2CO_3$ (968.5 mg, 2.97 mmol), BrettPhos Pd G3 (179.6 mg, 0.20 mmol) and BrettPhos (212.8 mg, 0.40 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C for 16 h. After

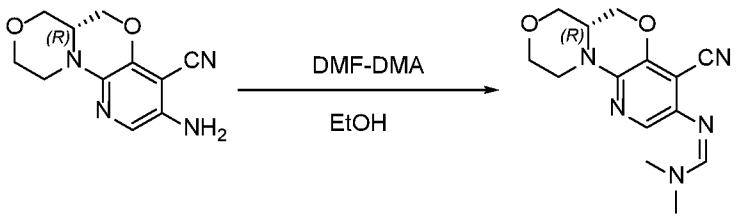
the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ ethyl acetate (3/1, v/v) to afford (R)-3-nitro-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-4-carbonitrile (180.0 mg, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 263.1.

**[0763] Step 4. Synthesis of (R)-3-amino-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-4-carbonitrile**




**[0764]** To a solution of (R)-3-nitro-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-4-carbonitrile (160.0 mg, 0.61 mmol) in AcOH/$H_2O$ (3.0 mL/0.3 mL) was added Fe (170.4 mg, 3.05 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (R)-3-amino-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-4-carbonitrile (80.0 mg, 50%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 233.2.

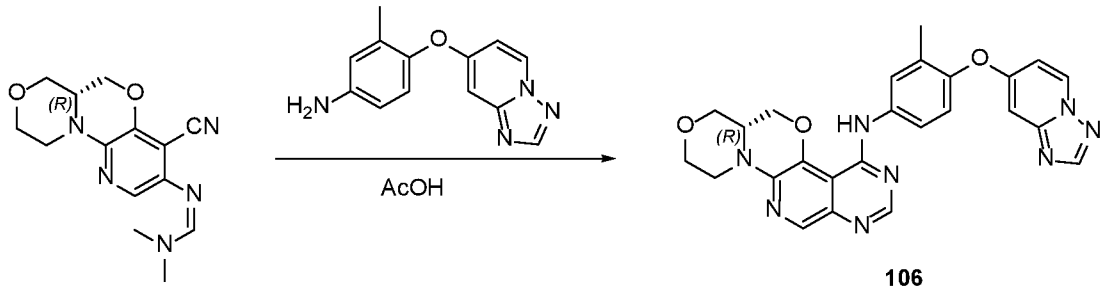
**[0765] Step 5. Synthesis of (R,Z)-N'-(4-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide**




**[0766]** To a solution of (R)-3-amino-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazine-4-carbonitrile (70.0 mg, 0.30 mmol) in EtOH (2.0 mL) was added DMF-DMA (71.8 mg, 0.60 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford (R,Z)-N'-(4-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-

b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (80.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 288.1.

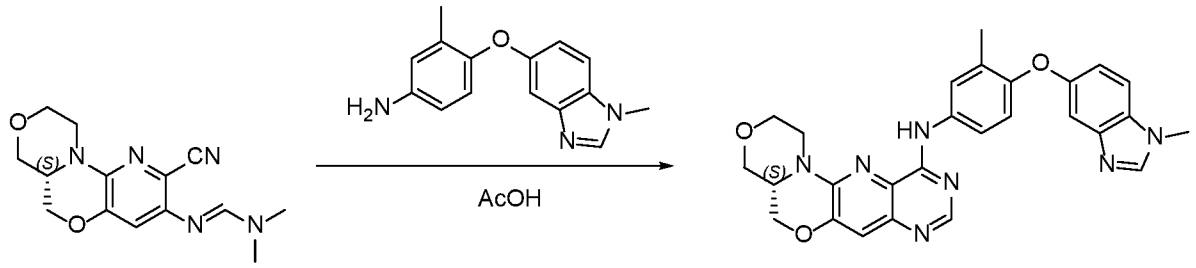
**[0767] Step 6. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 106)**




**[0768]** To a solution of (R,Z)-N'-(4-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (50.0 mg, 0.17 mmol) in acetic acid (2.0 mL) was added 3-methyl-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (41.8 mg, 0.17 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (5/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 10 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine **(Compound 106)** (7.2 mg, 8%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 483.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.84 (s, 1H), 8.96 - 8.94 (m, 1H), 8.48 (s, 1H), 8.40 - 8.38 (m, 2H), 7.89 - 7.83 (m, 2H), 7.23 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.71 - 4.67 (m, 1H), 4.33 - 4.30 (m, 1H), 4.23 - 4.18 (m, 1H), 4.03 - 3.97 (m, 2H), 3.60 - 3.56 (m, 2H), 3.30 - 3.26 (m, 1H), 2.92 - 2.88 (m, 1H), 2.20 (s, 3H).

***Example S107: Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 107)***

**[0769] Step 1. Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 107)**

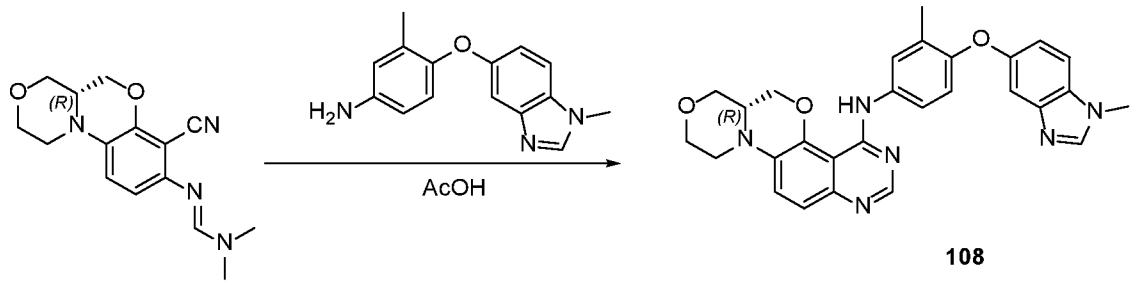



**107**

**[0770]** To a solution of (S,E)-N'-(2-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (150.0 mg, 0.53 mmol) in AcOH (4.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (158.7 mg, 0.63 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 50% B to 55% B in 8 min, Wave Length: 254 nm) to afford (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4,3-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 107)** (26.4 mg, 10%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 496.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.24 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 7.83 - 7.79 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.23 (s, 1H), 7.08 (d, $J$ = 1.6 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 4.95 - 4.92 (m, 1H), 4.45 - 4.41 (m, 1H), 4.09 - 3.95 (m, 3H), 3.84 (s, 3H), 3.72 - 3.59 (m, 2H), 3.26 - 3.21 (m, 1H), 3.03 - 2.92 (m, 1H), 2.24 (s, 3H).

***Example S108: Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 108)***

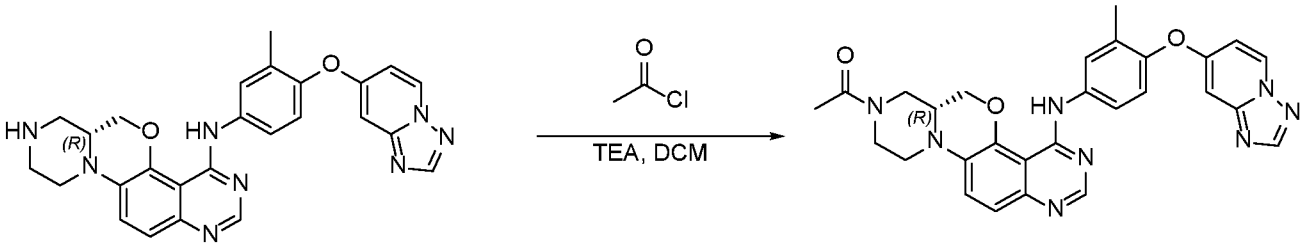
**[0771] Step 1. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 108)**




**[0772]** To a solution of (R,E)-N'-(7-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (200.0 mg, 0.70 mmol) in AcOH (4.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (176.9 mg, 0.70 mmol) at room temperature. The mixture was stirred at 85 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (93/7, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B in 8 min; Wave Length: 254 nm) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 108)** (132.5 mg, 38%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2.$^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.82 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.69 - 7.66 (m, 2H), 7.58 - 7.55 (m, 2H), 7.30 (d, $J$ = 8.8 Hz, 1H), 7.08 (s, 1H), 7.00 - 6.98 (m, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.69 - 4.66 (m, 1H), 4.24 - 4.14 (m, 1H), 4.01 - 3.91 (m, 2H), 3.84 - 3.73 (m, 4H), 3.68 - 3.62 (m, 1H), 3.28 - 3.26 (m, 2H), 2.86 - 2.81 (m, 1H), 2.24 (s, 3H).

***Example S109: Synthesis of (R)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)ethan-1-one (Compound 109)***

**[0773] Step 1. Synthesis of (R)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)ethan-1-one (Compound 109)**

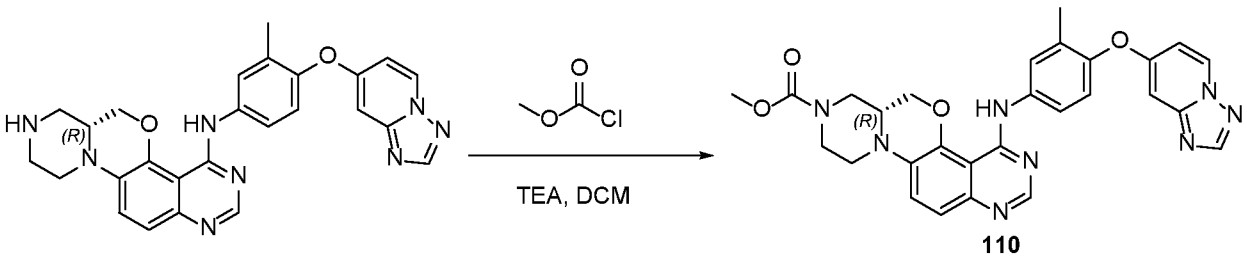



109

**[0774]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (150.0 mg, 0.31 mmol) in DCM (3.0 mL) was added TEA (94.8 mg, 0.94 mmol) and acetyl chloride (24.5 mg, 0.31 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/90, v/v) and then purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 34% B in 8 min; Wave Length: 254 nm) to afford (R)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)ethan-1-one **(Compound 109)** (41.1 mg, 25%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 523.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.93 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.38 (d, $J$ = 2.4 Hz, 2H), 7.89 - 7.82 (m, 2H), 7.68 -7.64 (m, 1H), 7.33 (d, $J$ = 8.8 Hz, 1H), 7.22 (d, $J$ = 8.8 Hz, 1H), 7.03 (d, $J$ = 6.4 Hz, 1H), 6.79 (d, $J$ = 2.8 Hz, 1H), 4.78 - 4.75 (m, 1H), 4.49 - 4.45 (m, 1H), 4.29 - 4.24 (m, 1H), 4.04 - 3.95 (m, 2H), 3.10 - 3.01 (m, 1H), 2.86 - 2.77 (m, 1H), 2.73 - 2.65 (m, 1H), 2.59 - 2.55 (m, 1H), 2.21 (s, 3H), 2.19 (s, 3H).

***Example S110: Synthesis of methyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (Compound 110)***

**[0775] Step 1. Synthesis of methyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (Compound 110)**

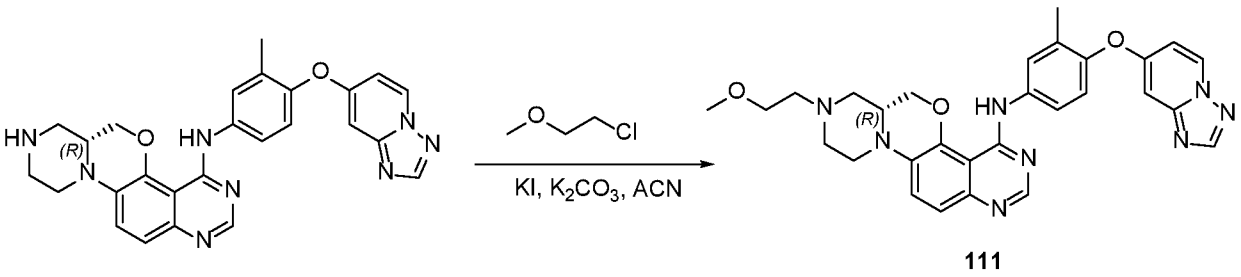



110

**[0776]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (150.0 mg, 0.31 mmol) in DCM (2.0 mL) was added methyl chloroformate (29.5 mg, 0.31 mmol) and TEA (94.7 mg, 0.94 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 40% B in 8 min; Wave Length: 254 nm) to afford methyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate **(Compound 110)** (22.3 mg, 13%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 539.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.93 (s, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.38 (d, $J$ = 2.0 Hz, 2H), 7.88 - 7.82 (m, 2H), 7.64 (d, $J$ = 9.2 Hz, 1H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.01 (m, 1H), 6.79 (d, $J$ = 2.8 Hz, 1H), 4.78 - 4.74 (m, 1H), 4.28 - 4.23 (m, 1H), 4.10 - 3.95 (m, 3H), 3.66 (s, 3H), 3.30 - 3.25 (m, 1H), 3.11 - 2.99 (m, 1H), 2.82 - 2.68 (s, 2H), 2.20 (s, 3H).

***Example S111: Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-(2-methoxyethyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 111)***

**[0777] Step 1. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-(2-methoxyethyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (Compound 111)**

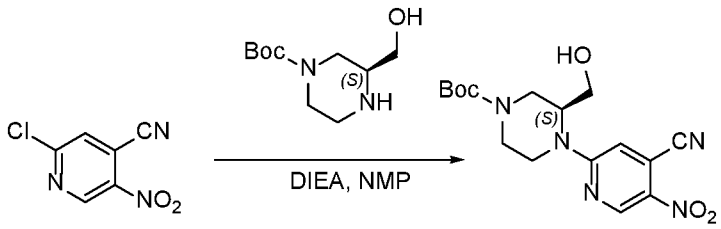



111

**[0778]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, 0.21 mmol) in ACN (2.0 mL) was added KI (31.1 mg, 0.19 mmol), 1-chloro-2-methoxyethane (59.0 mg, 0.62 mmol) and $K_2CO_3$ (25.9 mg, 0.19 mmol) at room temperature. The resulting mixture was stirred at 80°C for 24 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (45/55, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 45% B in 10 min; Wave Length: 254 nm) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-8-(2-methoxyethyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine **(Compound 111)** (13.8 mg, 12%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 539.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.93 (s, 1H), 8.94 (d, $J$ = 7.6 Hz, 1H), 8.38 - 8.37 (m, 2H), 7.90 - 7.87 (m, 1H), 7.83 (s, 1H), 7.60 (d, $J$ = 9.2 Hz, 1H), 7.31 (d, $J$ = 9.2 Hz, 1H), 7.21 (d, $J$ = 8.8 Hz, 1H), 7.04 - 7.02 (m, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 4.72 - 4.69 (m, 1H), 4.24 - 4.19 (m, 1H), 3.93 - 3.90 (m, 1H), 3.52 - 3.49 (m, 2H), 3.32 - 3.23 (m, 4H), 3.04 - 2.99 (m, 2H), 2.81 - 2.76 (m, 1H), 2.59 - 2.51 (m, 2H), 2.34 - 2.20 (m, 4H), 1.96 - 1.91 (m, 1H).

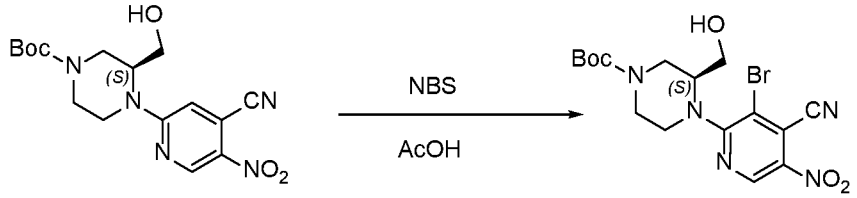
***Example S112: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 112)***

**[0779] Step 1. Synthesis of tert-butyl (S)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



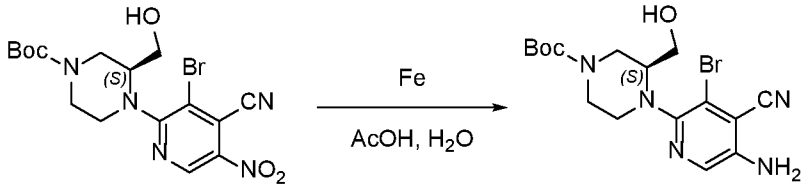

**[0780]** To a solution of 2-chloro-5-nitroisonicotinonitrile (1.0 g, 5.45 mmol) in NMP (12.0 mL) was added tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1.8 g, 8.17 mmol) and DIEA (2.1 g, 16.34 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (12/1, v/v) to afford tert-butyl (S)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.6 g, 80%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 364.2.

**[0781] Step 2. Synthesis of tert-butyl (S)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



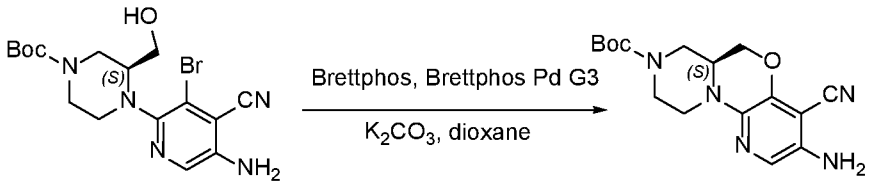

**[0782]** To a solution of tert-butyl (S)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.5 g, 2.06 mmol) in AcOH (15.0 mL) was added NBS (0.7 g, 4.13 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (S)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.8 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 442.1.

**[0783] Step 3. Synthesis of tert-butyl (S)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



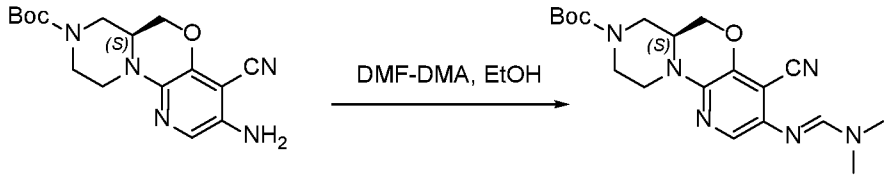

**[0784]** To a solution of tert-butyl (S)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.8 g, 4.07 mmol) in AcOH/$H_2O$ (15.0 mL/1.5 mL) was added Fe (2.3 g, 40.70 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ ethyl acetate (1/1, v/v) to afford tert-butyl (S)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (850.0 mg, 50%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 412.1.

**[0785] Step 4. Synthesis of tert-butyl (S)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



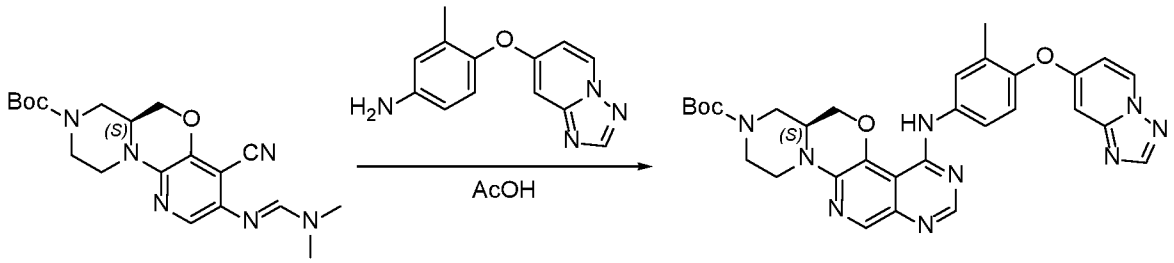

**[0786]** To a solution of tert-butyl (S)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (800.0 g, 1.94 mmol) in dioxane (10.0 mL) was added $K_2CO_3$ (804.5 mg, 5.82 mmol), Brettphos (208.3 mg, 0.39 mmol) and Brettphos Pd G3 (175.9 mg, 0.19 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl (S)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (280.0 mg, 30%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 332.2.

**[0787] Step 5. Synthesis of tert-butyl (S,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0788]** To a solution of tert-butyl (S)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (200.0 mg, 0.60 mmol) in EtOH (5.0 mL) was added DMF-DMA (214.5 mg, 1.80 mmol) room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford tert-butyl (S,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (190.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 387.2.

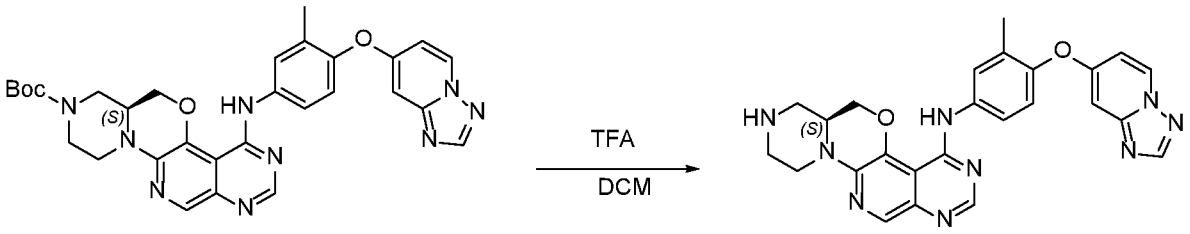
**[0789] Step 6. Synthesis of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0790]** To a solution of tert-butyl (S,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (190.0 mg, 0.49 mmol) in AcOH (4.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (130.0 mg, 0.54 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (10/1, v/v) to afford tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-

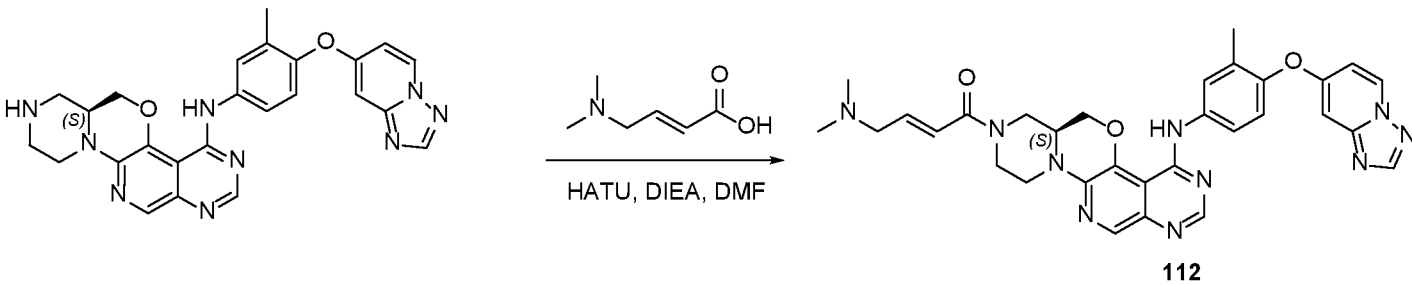
b][1,4]oxazine-8(6H)-carboxylate (160.0 mg, 33%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 582.2.

**[0791] Step 7. Synthesis of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine**




**[0792]** To a solution of tert-butyl (S)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (160.0 mg, 0.28 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 7 with aq.$NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (120.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.2.

**[0793] Step 8. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 112)**

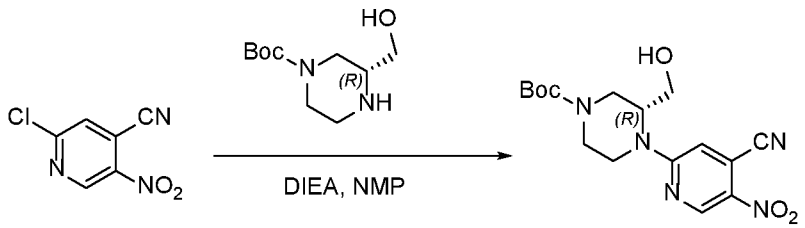



**112**

**[0794]** To a solution of (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (120.0 mg, crude) in DMF (5.0 mL) was added (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (64.4 mg, 0.50 mmol), DIEA (483.2 mg, 3.74 mmol) and HATU (236.9 mg, 0.62 mmol) at 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 38% B in 8 min, Wave Length: 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 112)** (40.3 mg, 26%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 593.4. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.77 - 9.74 (m, 1H), 8.94 (d, $J$ = 7.2 Hz, 1H), 8.49 - 8.47 (m, 1H), 8.41 - 8.39 (m, 2H), 7.87 - 7.84 (m, 2H), 7.25 - 7.23 (m, 1H), 7.04 - 7.02 (m, 1H), 6.80 (d, $J$ = 2.8 Hz, 1H), 6.74 - 6.65 (m, 2H), 4.79 - 4.77 (m, 1H), 4.64 - 4.53 (m, 2H), 4.33 - 4.23 (m, 2H), 3.52 - 3.48 (m, 1H), 3.32 - 3.21 (m, 1H), 3.06 (d, $J$ = 3.6 Hz, 2H), 2.81 - 2.67 (m, 2H), 2.21 - 2.17 (m, 9H).

***Example S113: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 113)***

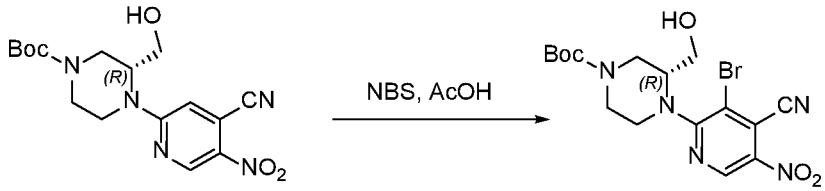
**[0795]** **Step 1. Synthesis of tert-butyl (R)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**




**[0796]** To a solution of 2-chloro-5-nitroisonicotinonitrile (2.4 g, 13.08 mmol) in NMP (30.0 mL) was added tert-butyl (R)-3-(hydroxymethyl)piperazine-1-carboxylate (4.2 g, 19.60 mmol) and DIEA (5.1 g, 39.23 mmol) at room temperature. The resulting mixture was stirred at 100 °C

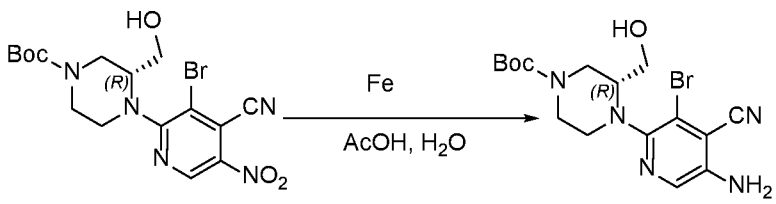
for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (51/49, v/v) to afford tert-butyl (R)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (3.7 g, 78%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 364.2.

**[0797] Step 2. Synthesis of tert-butyl (R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**




**[0798]** To a solution of tert-butyl (R)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.5 g, 2.06 mmol) in AcOH (15.0 mL) was added NBS (0.7 g, 4.13 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.7 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 442.1.

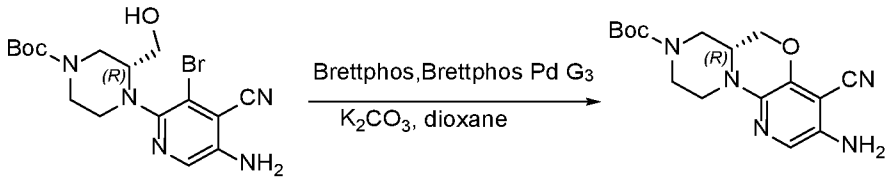
**[0799] Step 3. Synthesis of tert-butyl (R)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**




**[0800]** To a solution of tert-butyl (R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.7 g, 3.84 mmol) in AcOH/$H_2O$ (15.0 mL/3.0 mL) was added Fe (1.1 g, 19.22 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was filtered.

The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (29/71, v/v) to afford tert-butyl (R)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.2 g, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 412.1.

**[0801] Step 4. Synthesis of tert-butyl (R)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



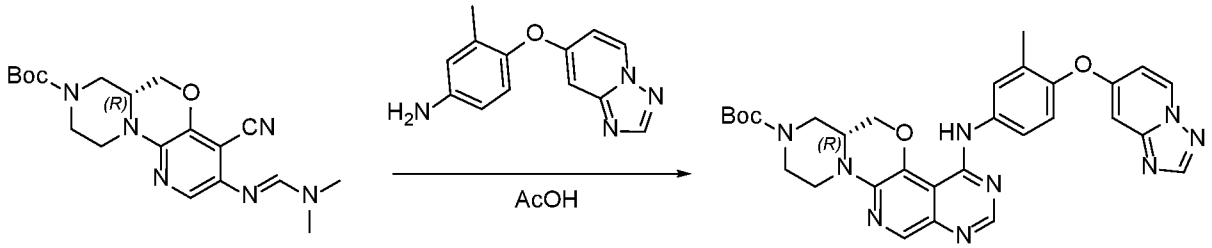

**[0802]** To a solution of tert-butyl (R)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (700.0 mg, 1.70 mmol) in dioxane (10.0 mL) was added $K_2CO_3$ (704.0 mg, 5.09 mmol), Brettphos (182.3 mg, 0.34 mmol) and Brettphos Pd G3 (153.9 mg, 0.17 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford tert-butyl (R)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (160.0 mg, 28%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 332.2.

**[0803] Step 5. Synthesis of tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**


**[0804]** To a solution of tert-butyl (R)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (160.0 mg, 0.48 mmol) in EtOH (6.0 mL) was added DMF-DMA (172.6 mg, 1.80 mmol) at room temperature. The resulting mixture was

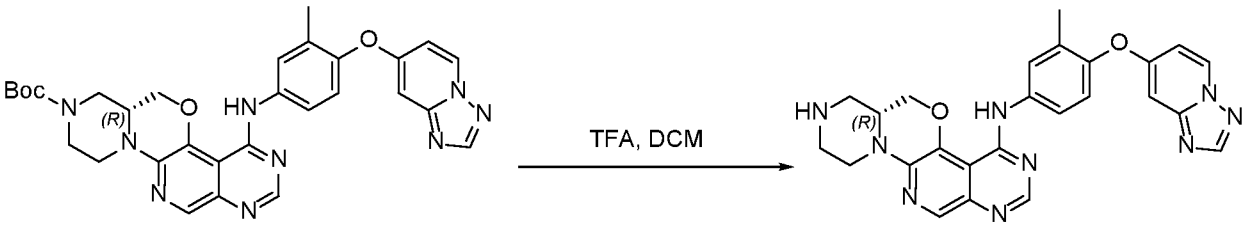
stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (190.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 387.2.

**[0805] Step 6. Synthesis of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



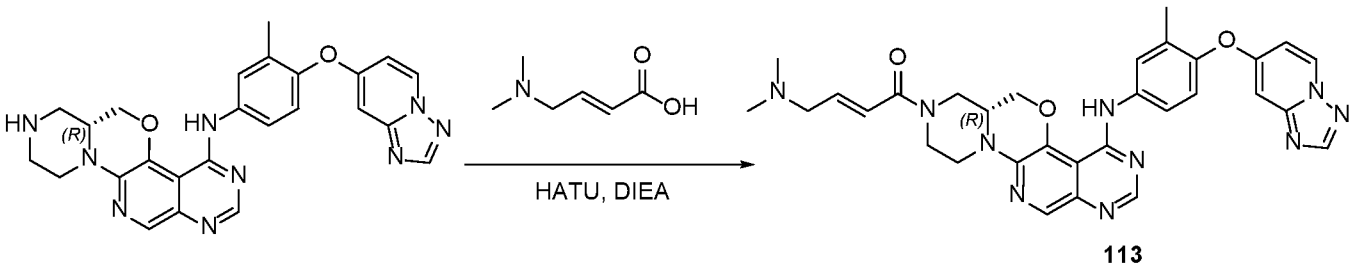

**[0806]** To a solution of tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (170.0 mg, crude) in AcOH (5.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylaniline (105.7 mg, 0.44 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/99, v/v) to afford tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (100.0 mg, 39%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 582.2.

**[0807] Step 7. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine**



**[0808]** To a solution of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (100.0 mg, 0.16 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 7 with aq.$NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (100.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 482.2.

**[0809] Step 8. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 113)**



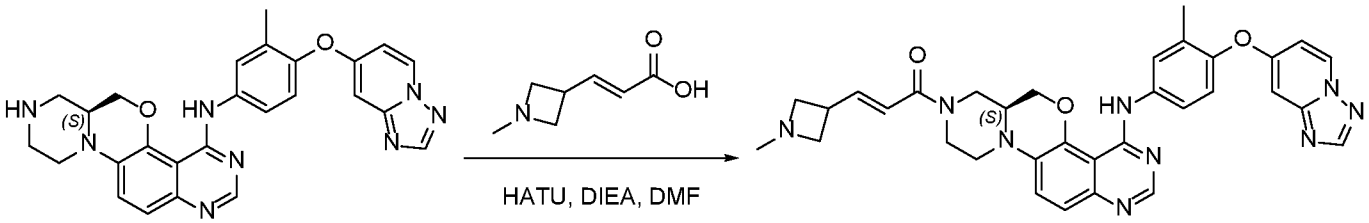

113

**[0810]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (100.0 mg, crude) in DMF (5.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid hydrochloride (68.8 mg, 0.42 mmol), DIEA (268.4 mg, 2.08 mmol) and HATU (173.7 mg, 0.46 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 39% B in 10 min; Wave Length: 254 nm) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-

(dimethylamino)but-2-en-1-one **(Compound 113)** (15.6 mg, 12%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 593.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.78 (s, 1H), 8.95 (d, $J$ = 7.6 Hz, 1H), 8.50 (s, 1H), 8.41 - 8.39 (m, 2H), 7.88 - 7.84 (m, 2H), 7.24 (d, $J$ = 8.4 Hz, 1H), 7.05 - 7.02 (m, 1H), 6.80 (d, $J$ = 2.0 Hz, 1H), 6.74 - 6.68 (m, 2H), 4.79 - 4.77 (m, 1H), 4.64 - 4.57 (m, 2H), 4.34 - 4.23 (m, 2H), 3.60 - 3.49 (m, 1H), 3.32 - 3.26 (m, 1H), 3.07 - 3.01 (m, 2H), 2.93 - 2.78 (m, 2H), 2.21 - 2.17 (m, 9H).

***Example S114: Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-3-(1-methylazetidin-3-yl)prop-2-en-1-one formic acid (Compound 114)***

**[0811] Step 1. Synthesis of (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-3-(1-methylazetidin-3-yl)prop-2-en-1-one formic acid (Compound 114)**



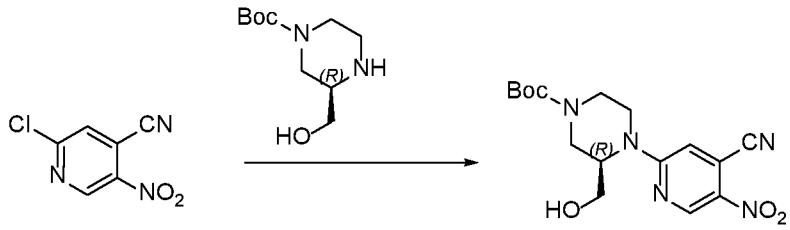

**114**

**[0812]** To a solution of (2E)-3-(1-methylazetidin-3-yl)prop-2-enoic acid (57.3 mg, 0.41 mmol) in DMF (3.0 mL) was added DIEA (87.4 mg, 0.68 mmol), (S)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (130.0 mg, 0.27 mmol) and HATU (102.9 mg, 0.27 mmol ) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH $C_{18}$ OBD Column 30×150 mm, 5 μm; Mobile Phase A: ACN, Mobile Phase B: Water (0.1% FA); Flow rate: 60 mL/min; Gradient: 3% B to 18% B in 10 min; Wave Length: 254 nm) to afford (S,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-3-(1-methylazetidin-3-yl)prop-2-en-1-one formic acid **(Compound 114)** (11.0 mg,

6%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =604.2. $^1H$ NMR (400 MHz, $CD_3OD$): δ 8.75 (d, $J$ = 7.6 Hz, 1H), 8.53 (s, 1H), 8.34 - 8.30 (m, 2H), 7.79 - 7.76 (m, 2H), 7.63 - 7.61 (m, 1H), 7.37 (d, $J$ = 9.2 Hz, 1H), 7.18 (d, $J$ = 8.4 Hz, 1H), 7.09 - 7.07 (m, 1H), 6.98 - 6.93 (m, 1H), 6.82 (d, $J$ = 2.0 Hz, 1H), 6.72 - 6.68 (m, 1H), 4.78 - 4.75 (m, 1H), 4.69 - 4.66 (m, 1H), 4.38 - 4.28 (m, 2H), 4.20 - 4.16 (m, 2H), 4.08 - 4.02 (m, 1H), 3.94 - 3.90 (m, 2H), 3.73 - 3.67 (m, 1H), 3.50 - 3.40 (m, 1H), 3.20 - 3.00 (m, 1H), 2.97 - 2.87 (m, 1H), 2.80 (s, 3H), 2.25 (s, 3H).

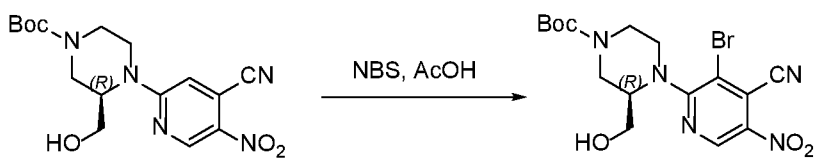
***Example S115: (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 115)***

**[0813] Step 1. Synthesis of tert-butyl (3R)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



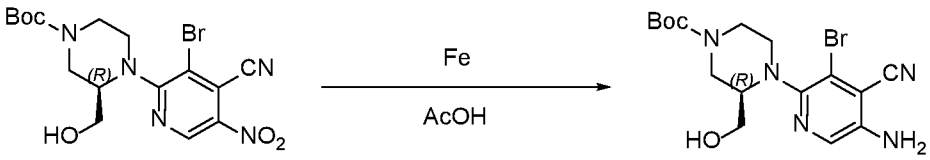

**[0814]** A mixture of 2-chloro-5-nitropyridine-4-carbonitrile (2.3 g, 12.53 mmol), tert-butyl (3R)-3-(hydroxymethyl)piperazine-1-carboxylate (13.5 g, 62.65 mmol) and DIEA (8.1 g, 62.65 mmol) in NMP (100.0 mL) was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) to afford tert-butyl (3R)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.1 g, 90%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 364.2.

**[0815] Step 2. Synthesis of tert-butyl (3R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**



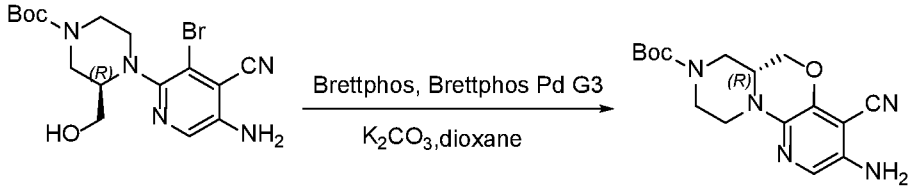
**[0816]** A mixture of tert-butyl (3R)-4-(4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (4.0 g, 11.00 mmol) and NBS (3.9 g, 22.01 mmol) in AcOH (80.0 mL) was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford tert-butyl (3R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.5 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 442.1.

**[0817]** **Step 3. Synthesis of tert-butyl (3R)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate**




**[0818]** A mixture of tert-butyl (3R)-4-(3-bromo-4-cyano-5-nitropyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.5 g, 3.39 mmol) and Fe (1.8 g, 33.92 mmol) in AcOH (30.0 mL) was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) to afford tert-butyl (3R)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.3 g, 92%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 412.1.

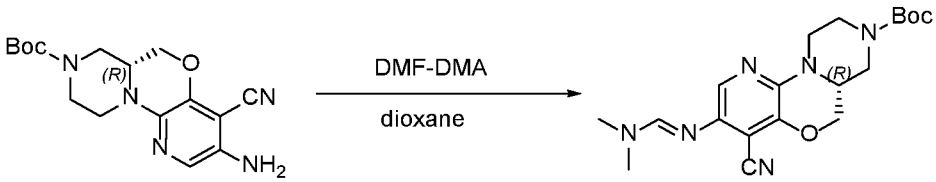
**[0819]** **Step 4. Synthesis of tert-butyl (R)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0820]** A solution of tert-butyl (3R)-4-(5-amino-3-bromo-4-cyanopyridin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.3 g, 3.15 mmol), $K_2CO_3$ (1.3 g, 9.45 mmol), BrettPhos (0.3 g, 0.63 mmol) and BrettPhos Pd G3 (0.2 g, 0.31 mmol) in dioxane (30.0 mL) was stirred at 100 °C for 2 h under $N_2$. After the reaction was completed, the resulting mixture was

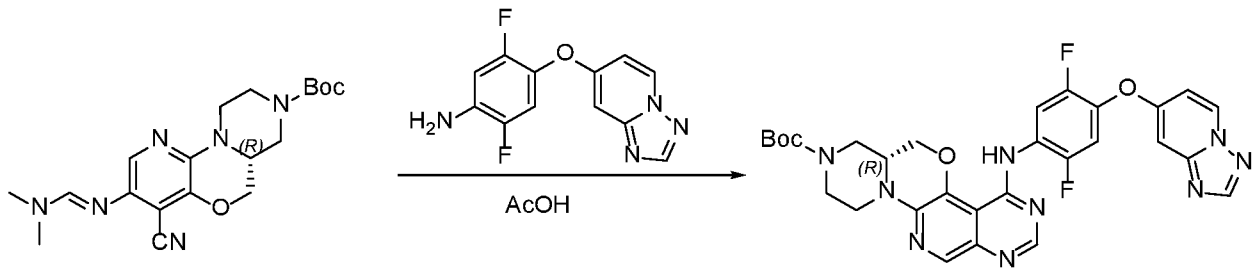
diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (84/16, v/v) to afford tert-butyl (R)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (1.0 g, 95%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 332.2.

**[0821] Step 5. Synthesis of tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0822]** A mixture of tert-butyl (R)-3-amino-4-cyano-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (1.0 g, 3.01 mmol) and DMF-DMA (0.7 g, 6.03 mmol) in dioxane (20.0 mL) was stirred at 90 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (90/10, v/v) to afford tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (950.0 mg, 81%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 387.2.

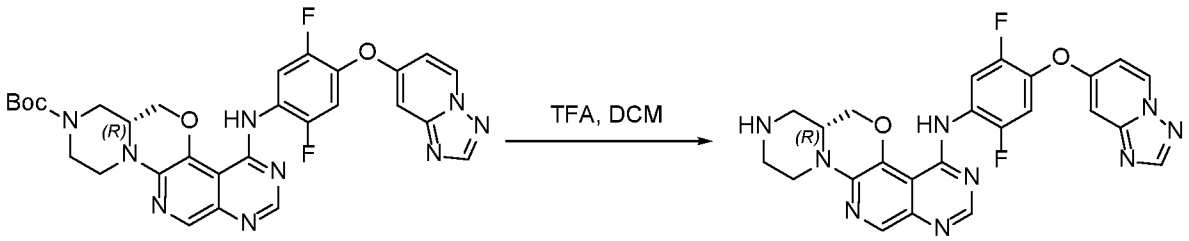
**[0823] Step 6. Synthesis of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**




**[0824]** A mixture of tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (900.0 mg,

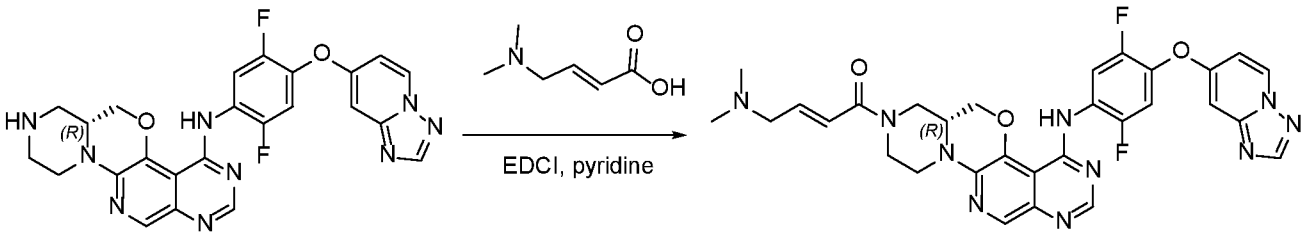
2.32 mmol) and 2,5-difluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (610.6 mg, 2.32 mmol) in AcOH (20.0 mL) was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) to afford tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (300.0 mg, 21%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 604.2.

**[0825] Step 7. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine**




**[0826]** A solution of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (300.0 mg, 0.49 mmol) and TFA (5.0 mL) in $CH_2Cl_2$ (5.0 mL) was stirred at room temperature for 1 h. After the reaction was completed, the pH value of the mixture was adjusted to 7 with saturated $Na_2CO_3$ (aq.). The resulting mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (84/16, v/v) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (200.0 mg, 79%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 504.2.

**[0827] Step 8. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 115)**

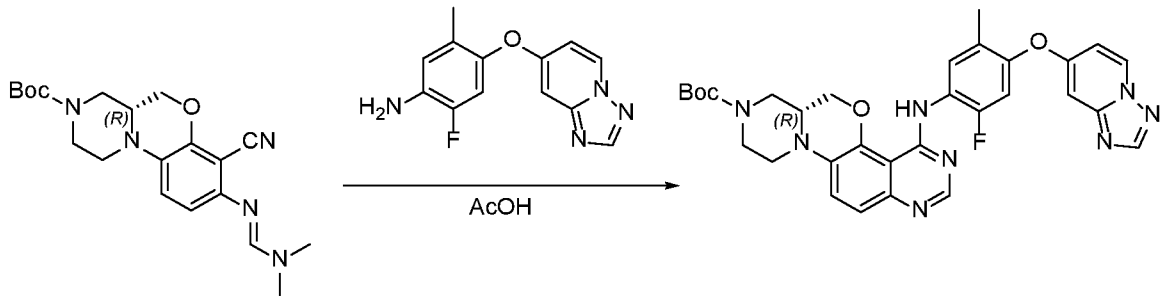



115

**[0828]** To a mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (100.0 mg, 0.20 mmol) and (2E)-4-(dimethylamino)but-2-enoic acid (102.6 mg, 0.80 mmol) in pyridine (5.0 mL) were added EDCI (76.2 mg, 0.40 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) and then purified by Prep-achiral-SFC with the following conditions: (Column: YMC-Actus Triart Diol-HILIC, 3x25 cm, 5 μm; Mobile Phase A: $CO_2$, Mobile Phase B: ACN: MeOH = 4: 1(0.1% 2M $NH_3$-MeOH); Flow rate: 75 mL/min; Gradient: isocratic 50% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 9.36 min) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2,5-difluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 115)** (5.5 mg, 4%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 615.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.37 (s, 1H), 9.00 (d, $J$ = 7.2 Hz, 1H), 8.74 - 8.67 (m, 1H), 8.55 - 8.43 (m, 3H), 7.72 - 7.68 (m, 1H), 7.19 - 7.12 (m, 2H), 6.73 - 6.65 (m, 2H), 4.78 - 4.75 (m, 1H), 4.60 - 4.56 (m, 2H), 4.34 - 4.24 (m, 2H), 3.58 - 3.43 (m, 1H), 3.08 - 2.75 (m, 4H), 2.68 - 2.57 (m, 1H), 2.17 (s, 6H).

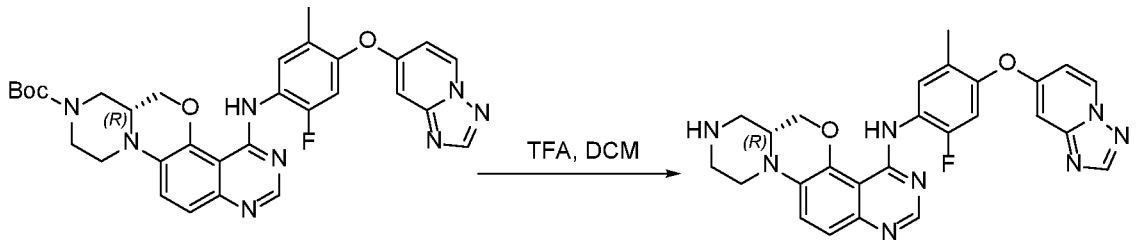
***Example S116: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 116)***

**[0829] Step 1. Synthesis of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**




**[0830]** To a solution of tert-butyl (R,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (463.0 mg, 1.20 mmol) in acetic acid (20.0 mL) was added 4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylaniline (310.2 mg, 1.20 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with acetonitrile/water (60/40, v/v) to afford tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (130.0 mg, 18%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =599.3.

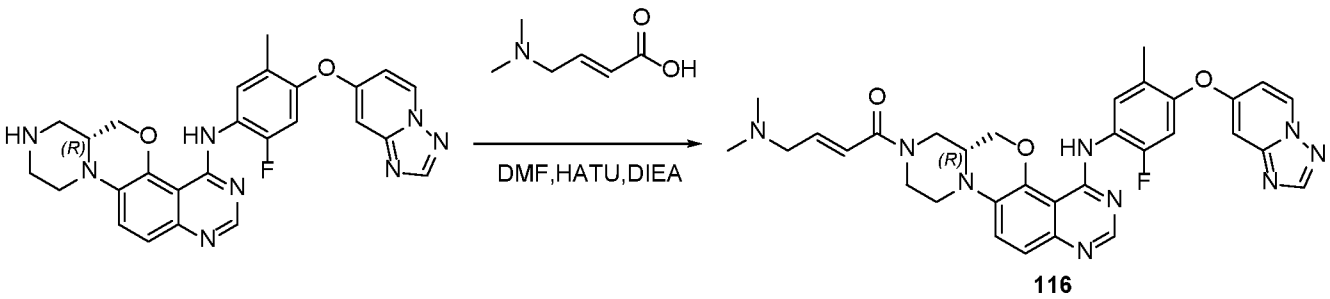
**[0831] Step 2. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0832]** To a solution of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (100.0 mg, 0.17 mmol) in dichloromethane (5.0 mL) was added TFA (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The pH value of the residue was adjusted to 8.0 with sat. $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-

hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (80.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 499.2.

**[0833] Step 3. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 116)**

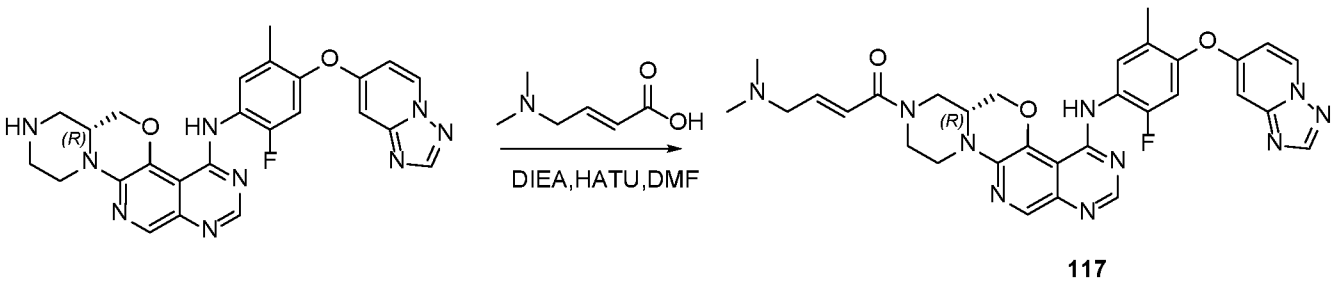



116

**[0834]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (80.0 mg, crude) in DMF (2.0 mL) was added (E)-4-(dimethylamino)but-2-enoic acid (22.8 mg, 0.18 mmol), HATU (73.2 mg, 0.19 mmol) and DIEA (207.4 mg, 1.60 mmol) at 0 °C under $N_2$. The reaction mixture was stirred at 0 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (92/8, v/v) and then purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: ACN, Mobile Phase B: Water (10 mmol/L $NH_4HCO_3$); Flow rate: 60 mL/min; Gradient: 29% B to 39% B in 10 min; Wave Length: 254 nm) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 116)** (20.7 mg, 21%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 610.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.97 (s, 1H), 8.97 (d, $J$ = 7.6 Hz, 1H), 8.41 - 8.35 (m, 3H), 7.68 (d, $J$ = 9.2 Hz, 1H), 7.37 - 7.32 (m, 2H), 7.07 - 7.05 (m, 1H), 6.92 (d, $J$ = 2.8 Hz, 1H), 6.74 - 6.65 (m, 2H), 4.75 - 4.71 (m, 1H), 4.55 - 4.49 (m, 1H), 4.29 - 4.21 (m, 2H), 4.08 - 4.03 (m, 1H), 3.29 - 3.20 (m, 1H), 3.06 (d, $J$ = 4.4 Hz, 2H), 2.92 - 2.82 (m, 1H), 2.78 - 2.72 (m, 1H), 2.67 - 2.62 (m, 1H), 2.20 - 2.17 (m, 9H).

***Example S117: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 117)***

**[0835] Step 1. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 117)**

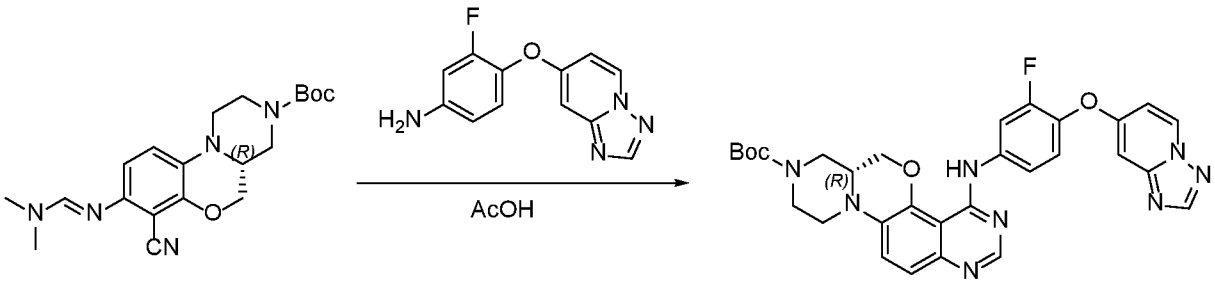



117

**[0836]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (70.0 mg, 0.14 mmol) in DMF (5.0 mL) was added (2E)-4-(dimethylamino)but-2-enoic acid (21.7 mg, 0.17 mmol), DIEA (181.1 mg, 1.40 mmol) and HATU (63.9 mg, 0.17 mmol) AT 0 °C under $N_2$. The resulting mixture was stirred at room temperature for 3 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 10 min; Wave Length: 254 nm) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluoro-5-methylphenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 117)** (30.7 mg, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 611.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 8.87 (d, $J$ = 7.2 Hz, 1H), 8.48 (s, 1H), 8.37 - 8.34 (m, 2H), 8.17 - 8.09 (m, 1H), 7.29 - 7.26 (m, 1H), 7.08 - 7.06 (m, 1H), 6.98 - 6.94 (s, 1H), 6.88 (s, 1H), 6.65 - 6.57 (m, 1H), 4.70 - 4.67 (m, 1H), 4.59 - 4.54 (m, 2H), 4.31 - 4.26 (m, 1H), 4.24 - 4.21 (m, 1H), 3.58 - 3.46 (m, 1H), 3.33 - 3.07 (m, 1H), 2.87 - 2.84 (m, 1H), 2.77 (s, 6H), 2.72 - 2.70 (m, 1H), 2.15 (s, 3H).

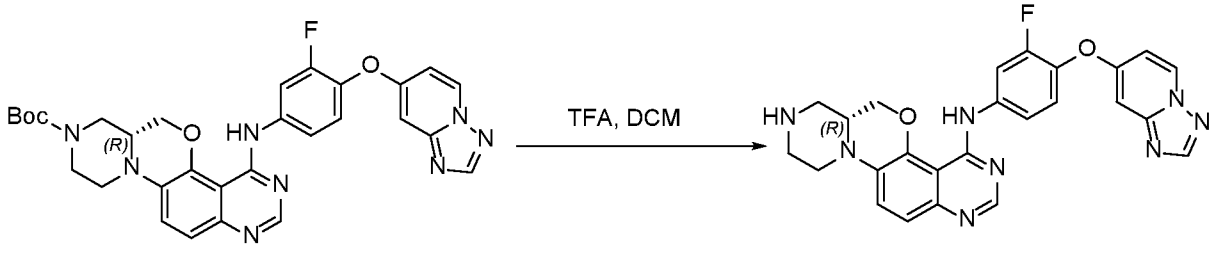
***Example S118: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 118)***

**[0837] Step 1. Synthesis of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**




**[0838]** A mixture of tert-butyl (R,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (1.0 g, 2.59 mmol) and 3-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (0.6 g, 2.59 mmol) in AcOH (20.0 mL) was stirred at 85 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) to afford tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (200.0 mg, 13%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 585.2.

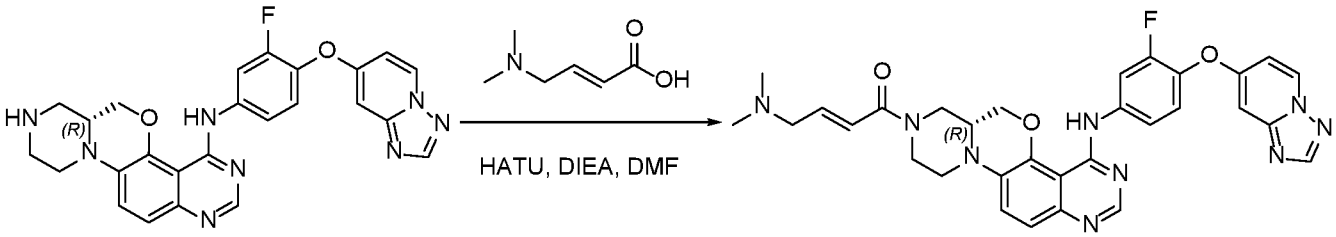
**[0839] Step 2. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**




**[0840]** A solution of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (200.0 mg, 0.34 mmol) and TFA (2.0 mL) in $CH_2Cl_2$ (2.0 mL) was stirred at room temperature for 1 h. After the reaction was completed, the pH value of the mixture was

adjusted to 7 with saturated $NaHCO_3$ (aq.). The mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (84/16, v/v) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (120.0 mg, 72%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 485.2.

**[0841] Step 3. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 118)**



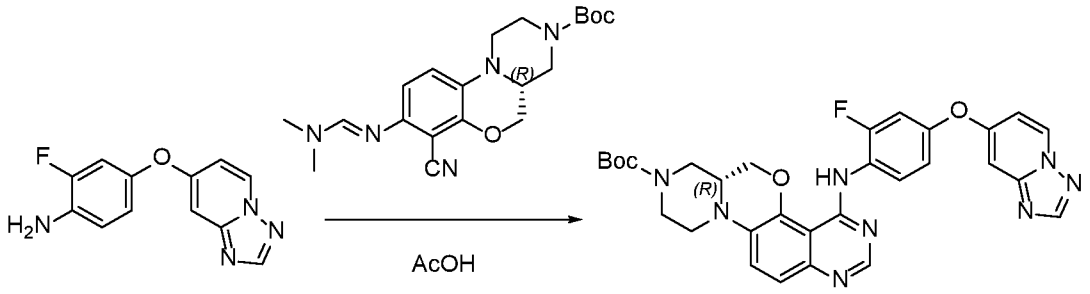

**118**

**[0842]** A mixture of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (100.0 mg, 0.20 mmol), (2E)-4-(dimethylamino)but-2-enoic acid (79.9 mg, 0.61 mmol), DIEA (133.3 mg, 1.03 mmol) and HATU (118.7 mg, 0.61 mmol) in DMF (5.0 mL) was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2/CH_3OH$ (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 8 min, Wave Length: 254 nm) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 118)** (3.5 mg, 2%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 596.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.05 (s, 1H), 8.96 (d, $J$ = 6.8 Hz, 1H), 8.44 - 8.42 (m, 2H), 8.29 - 8.26 (m, 1H), 7.74 - 7.66 (m, 2H), 7.50 - 7.35 (m, 2H), 7.16 - 7.02 (m, 2H), 6.75 - 6.62

(m, 2H), 4.80 - 4.78 (m, 1H), 4.62 - 4.50 (m, 1H), 4.33 - 4.17 (m, 2H), 4.11 - 4.03 (m, 1H), 3.11 - 3.06 (m, 3H), 2.90 - 2.66 (m, 3H), 2.17 (s, 6H).

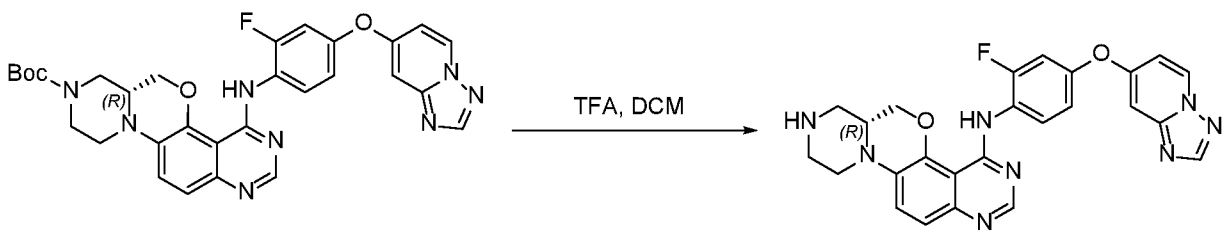
***Example S119: Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 119)***

**[0843] Step 1. Synthesis of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate**



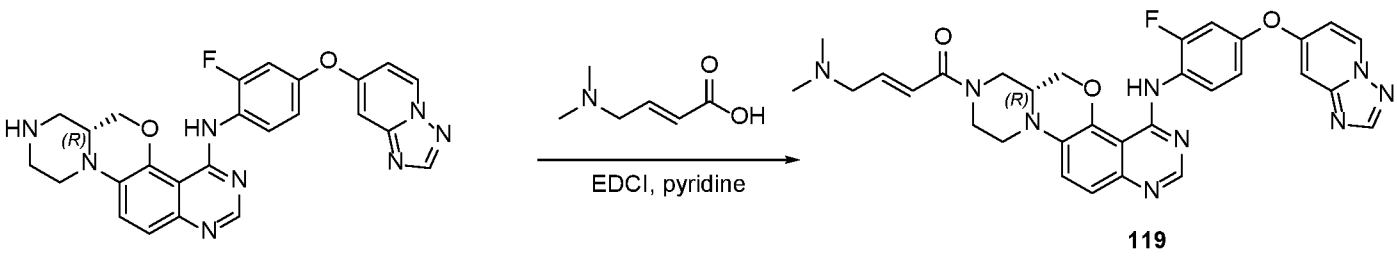

**[0844]** To a solution of 2-fluoro-4-{[1,2,4]triazolo[1,5-a]pyridin-7-yloxy}aniline (300.0 mg, 1.23 mmol) in acetic acid (10.0 mL) was added tert-butyl (R,E)-7-cyano-8-(((dimethylamino)methylene)amino)-1,2,4a,5-tetrahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (378.8 mg, 0.98 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the resulting mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (9/1, v/v) to afford tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (278.0 mg, 38%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 585.2.

**[0845] Step 2. Synthesis of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine**



**[0846]** To a solution of tert-butyl (R)-4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazoline-8(6H)-carboxylate (680.0 mg, 1.16 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was neutralized to pH=7 with saturated $NaHCO_3$ (aq). The mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (9/1, v/v) to afford (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (216.0 mg, 38%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 485.2.

**[0847] Step 3. Synthesis of (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one (Compound 119)**



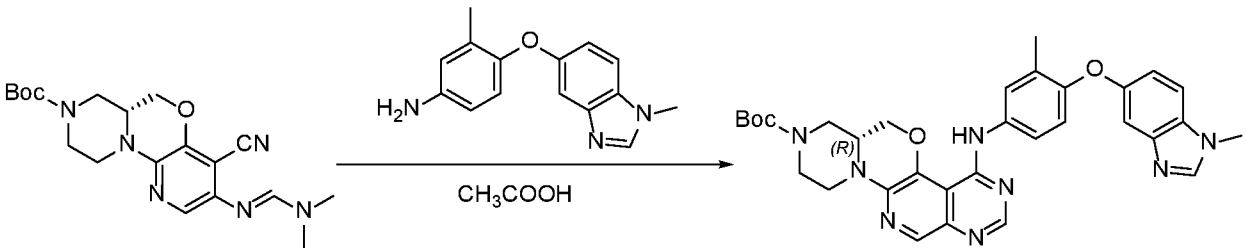

119

**[0848]** To a solution of (R)-N-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)-6,6a,7,8,9,10-hexahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-4-amine (166.0 mg, 0.34 mmol) in pyridine (8.0 mL) was added (2E)-4-(dimethylamino)but-2-enoic acid (132.8 mg, 1.03 mmol) and EDCI (197.0 mg, 1.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/MeOH (9/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19×250 mm, 5μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 35% B in 8 min; Wave Length: 254 nm) to afford (R,E)-1-(4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-2-fluorophenyl)amino)-6a,7,9,10-tetrahydropyrazino[1',2':4,5][1,4]oxazino[2,3-f]quinazolin-8(6H)-yl)-4-(dimethylamino)but-2-en-1-one **(Compound 119)** (34.8 mg, 16%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 596.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.00 (s,

1H), 8.97 (d, *J* = 7.6 Hz, 1H), 8.53 - 8.39 (m, 3H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.41 - 7.35 (m, 2H), 7.18 - 7.15 (m, 2H), 7.08 - 7.05 (m, 1H), 6.73 - 6.64 (m, 2H), 4.75 - 4.72 (m, 1H), 4.59 - 4.53 (m, 1H), 4.30 - 4.15 (m, 2H), 4.07 - 4.04 (m, 1H), 3.29 - 3.22 (m, 1H), 3.06 (d, *J* = 4.0 Hz, 2H), 2.90 - 2.63 (m, 3H), 2.17 (s, 6H).

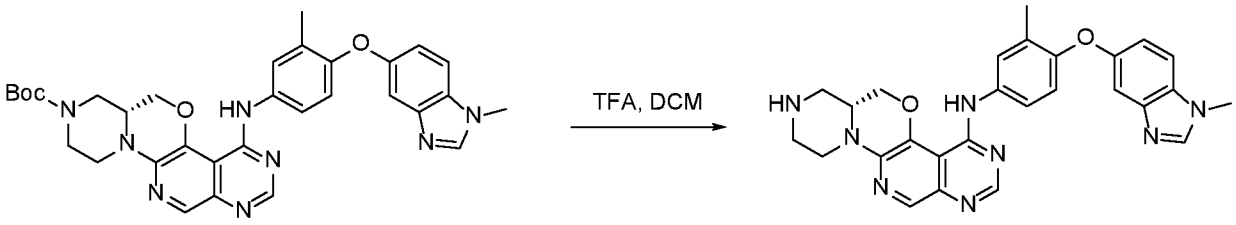
***Example S120: Synthesis of (R)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 120)***

**[0849] Step 1. Synthesis of tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



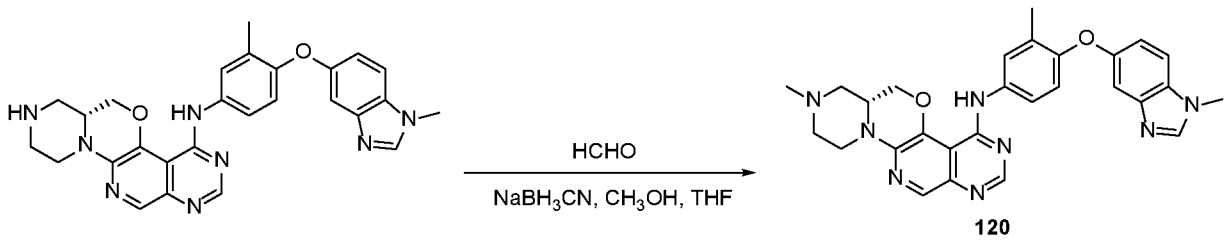

**[0850]** To a solution of tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (150.0 mg, 0.39 mmol) in $CH_3COOH$ (7.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (116.0 mg, 0.46 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (82/18, v/v) to afford tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (200.0 mg, 86%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 595.3.

**[0851] Step 2. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine**




**[0852]** To a solution of tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (180.0 mg, 0.30 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (120.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2.

**[0853] Step 3. Synthesis of (R)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 120)**

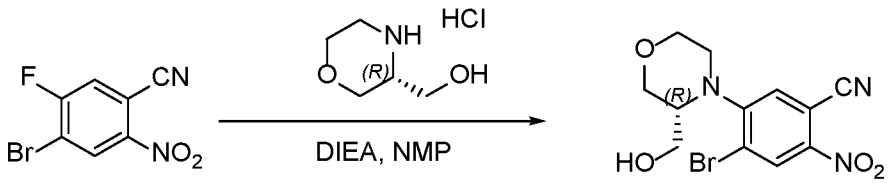



**[0854]** To a solution of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (100.0 mg, 0.20 mmol) in THF/MeOH (4.0 mL/1.0 mL) was added HCHO (45.5 mg, 30%) at room temperature. The resulting mixture was stirred at room temperature for 1.5 h. Then $NaBH_3CN$ (57.2 mg, 0.91 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the reaction mixture was quenched with water and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (91/9, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 4% B to 4% B in 2 min, 4% B to 13% B in 10 min; Wave Length: 254 nm/220 nm) to afford (R)-8-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine **(Compound 120)** (21.9 mg, 21%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 509.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.68 (s, 1H), 8.47 (s, 1H), 8.36 (s, 1H), 8.18 (s, 1H), 7.72 - 7.66 (m, 2H), 7.57 (d, $J$ = 8.4 Hz, 1H), 7.09 (d, $J$ = 2.4 Hz, 1H), 7.02 - 6.95 (m, 1H), 6.88 (d, $J$ = 8.8 Hz, 1H), 4.71 - 4.67 (m, 1H), 4.61 - 4.46 (m, 1H), 4.32 - 4.22 (m, 1H), 3.84 (s, 3H), 3.70 - 3.52 (m, 1H), 3.17 - 2.92 (m, 3H), 2.25 (s, 3H).

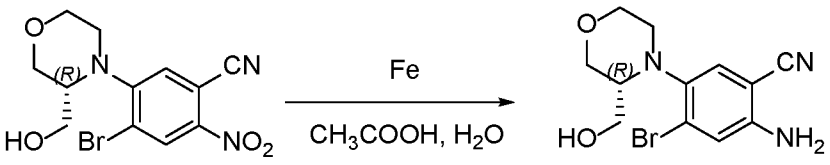
***Example S121: Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 121)***

**[0855] Step 1. Synthesis of (R)-4-bromo-5-(3-(hydroxymethyl)morpholino)-2-nitrobenzonitrile**



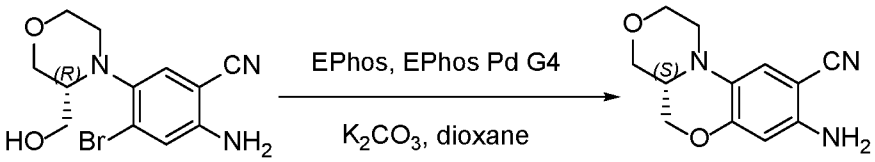

**[0856]** To a solution of 4-bromo-5-fluoro-2-nitrobenzonitrile (5.0 g, 20.41 mmol) in NMP (100.0 mL) was added (R)-morpholin-3-ylmethanol hydrochloride (4.7 g, 30.60 mmol) and DIEA (7.8 g, 60.35 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (93/7, v/v) to afford (R)-4-bromo-5-(3-(hydroxymethyl)morpholino)-2-nitrobenzonitrile (2.1 g, 30%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 342.0.

**[0857] Step 2. Synthesis of (R)-2-amino-4-bromo-5-(3-(hydroxymethyl)morpholino)benzonitrile**



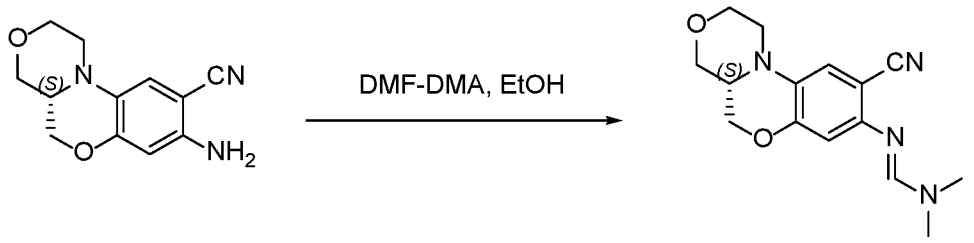

**[0858]** To a solution (R)-4-bromo-5-(3-(hydroxymethyl)morpholino)-2-nitrobenzonitrile (1.5 g, 4.38 mmol) in $CH_3COOH/H_2O$ (20.0 mL/2.0 mL) was added Fe (1.2 g, 21.49 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (9/1, v/v) to afford (R)-2-amino-4-bromo-5-(3-(hydroxymethyl)morpholino)benzonitrile (1.0 g, 73%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+ = 312.0$.

**[0859] Step 3. Synthesis of (S)-8-amino-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-9-carbonitrile**



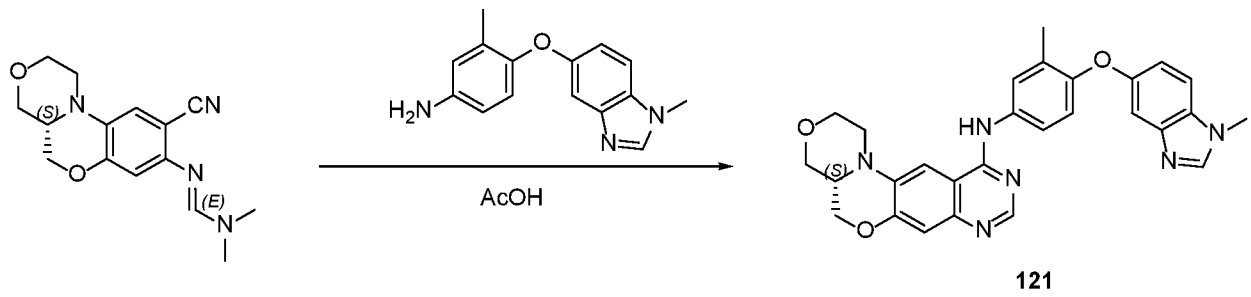

**[0860]** To a solution of (R)-2-amino-4-bromo-5-(3-(hydroxymethyl)morpholino)benzonitrile (1.0 g, 3.20 mmol) in dioxane (10.0 mL) was added $K_2CO_3$ (1.3 g, 9.64 mmol), EPhos (0.3 g, 0.64 mmol) and EPhos Pd G4 (0.3 g, 0.10 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 2 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (40/60, v/v) to afford (S)-8-amino-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-9-carbonitrile (0.4 g, 54%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 232.1$.

**[0861] Step 4. Synthesis of (S,E)-N'-(9-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide**




**[0862]** To a solution of (S)-8-amino-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazine-9-carbonitrile (400.0 mg, 1.73 mmol) in EtOH (8.0 mL) was added DMF-DMA (624.5 mg, 5.24 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford (S,E)-N'-(9-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (450.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 287.1.

**[0863] Step 5. Synthesis of (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine (Compound 121)**



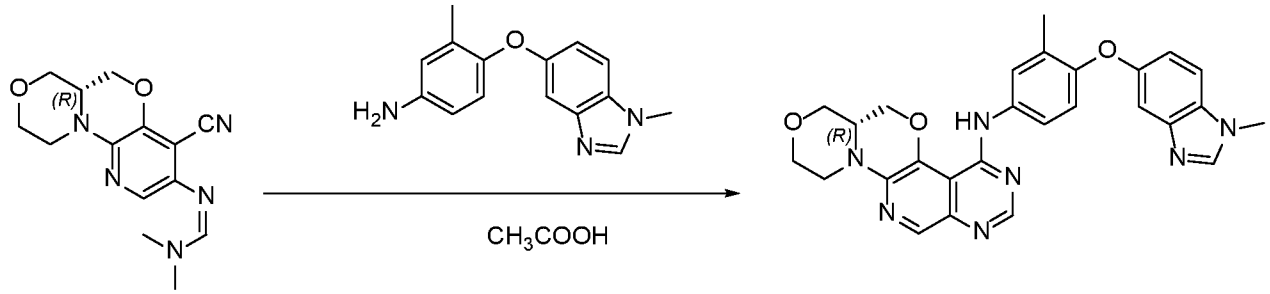

121

**[0864]** To a solution of (S,E)-N'-(9-cyano-1,2,4a,5-tetrahydro-4H-benzo[b][1,4]oxazino[4,3-d][1,4]oxazin-8-yl)-N,N-dimethylformimidamide (150.0 mg, crude) in AcOH (3.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (132.0 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 5% B in 2 min, 6% B to 16% B in 10 min; Wave Length: 254 nm/220 nm) to afford (S)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-g]quinazolin-11-amine **(Compound 121)** (10.5 mg, 3%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.35 (s, 1H), 8.34 (s, 1H), 8.26 (s, 1H), 8.17 (s, 1H), 7.69 (s, 2H), 7.63 - 7.51 (m, 2H), 7.10 (s, 1H), 7.01 - 6.99 (m, 2H), 6.89 - 6.86 (m, 1H), 4.39 - 4.36 (m, 1H), 4.13 - 4.05 (m, 1H), 4.03 - 3.93 (m, 1H), 3.84 (s, 3H), 3.74 - 3.69 (m, 1H), 3.44 - 3.15 (m, 4H), 2.92 - 2.82 (m, 1H), 2.25 (s, 3H).

***Example S122: Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 122)***

**[0865] Step 1. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 122)**



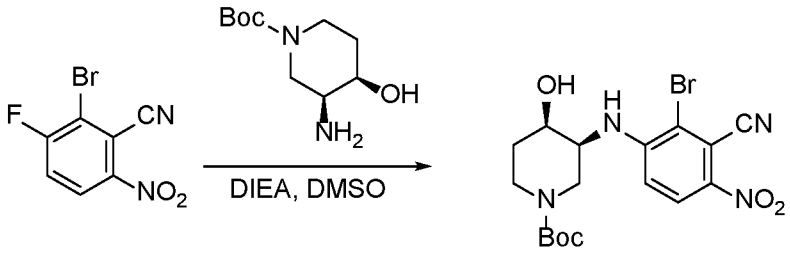

**122**

**[0866]** To a solution of (R,Z)-N'-(4-cyano-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrido[3,2-b][1,4]oxazin-3-yl)-N,N-dimethylformimidamide (80.0 mg, 0.28 mmol) in acetic acid (2.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (98.7 mg, 0.39 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with $CH_2Cl_2$/$CH_3OH$ (9/1, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xcelect CSH F-pheny OBD Column 19x250 mm, 5 nm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 12% B to 20% B in 10 min; Wave Length: 254 nm/220 nm) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6a,7,9,10-tetrahydro-6H-[1,4]oxazino[4,3-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine **(Compound 122)** (13.3 mg, 9%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 496.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.65 (s, 1H), 8.43 (s, 1H), 8.34 (s, 1H), 8.17 (s, 1H), 7.69 - 7.65 (m, 2H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.10 (s, 1H), 6.99 (d, $J$ = 8.4 Hz, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.67 - 4.64 (m, 1H), 4.30 - 4.27 (m,

1H), 4.19 - 4.14 (m, 1H), 4.02 - 3.95 (m, 2H), 3.84 (s, 3H), 3.66 - 3.52 (m, 2H), 3.29 - 3.15 (m, 1H), 2.92 - 2.86 (m, 1H), 2.24 (s, 3H).

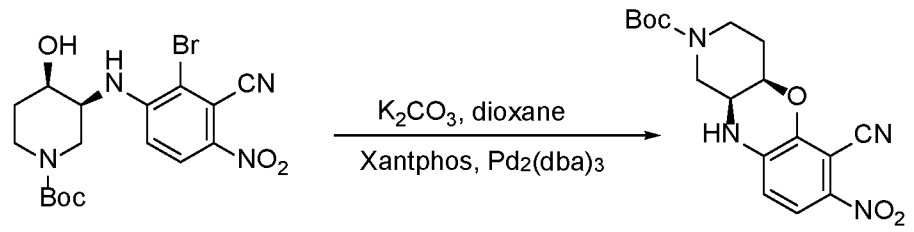
***Example S123: Synthesis of (7aS,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 123)***

**[0867] Step 1. Synthesis of tert-butyl (3S,4R)-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate**




**[0868]** To a solution of 2-bromo-3-fluoro-6-nitrobenzonitrile (4.7 g, 19.18 mmol) in DMSO (40.0 mL) was added tert-butyl (3S,4R)-3-amino-4-hydroxypiperidine-1-carboxylate (6.2 g, 28.77 mmol) and DIEA (7.4 g, 57.55 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3S,4R)-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate (5.6 g, 66%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.1.

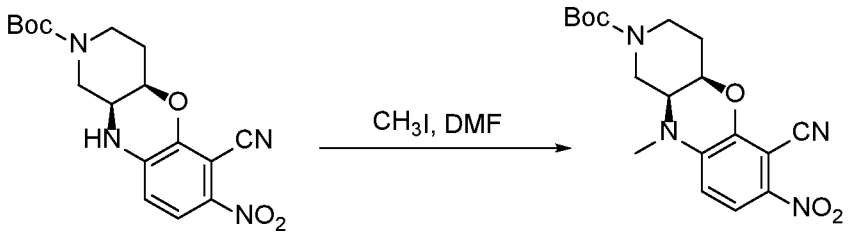
**[0869] Step 2. Synthesis of tert-butyl (4aR,10aS)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0870]** To a solution of tert-butyl (3S,4R)-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate (2.7 g, 6.12 mmol) in dioxane (25.0 mL) was added $K_2CO_3$

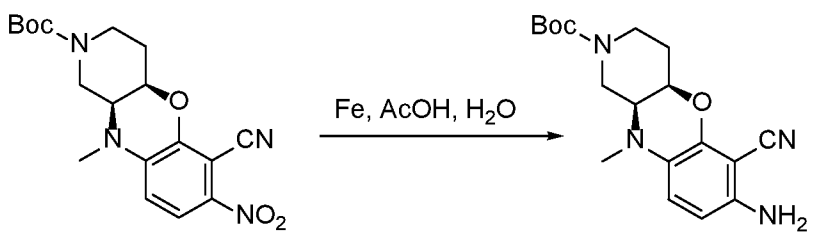
(2.5 g, 18.36 mmol), $Pd_2(dba)_3$ (1.2 g, 1.29 mmol) and Xantphos (1.5 g, 2.58 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C for 16 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (4aR,10aS)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (2.0 g, 90%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.1.

**[0871] Step 3. Synthesis of tert-butyl (4aR,10aS)-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**



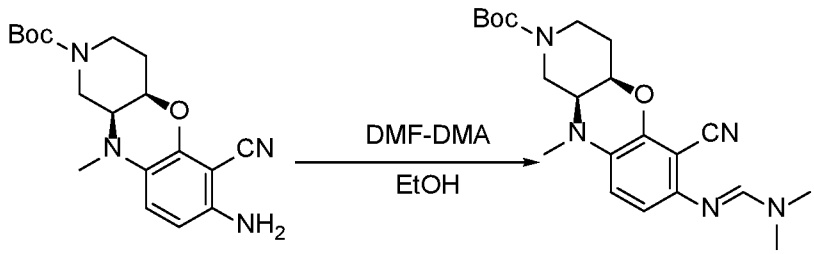

**[0872]** To a solution of tert-butyl (4aR,10aS)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (800.0 mg, 2.22 mmol) in DMF (10.0 mL) was added $Cs_2CO_3$ (3.6 g, 11.05 mmol) and $CH_3I$ (1.6 g, 11.27 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (4aR,10aS)-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (780.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =375.2.

**[0873] Step 4. Synthesis of tert-butyl (4aR,10aS)-7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**



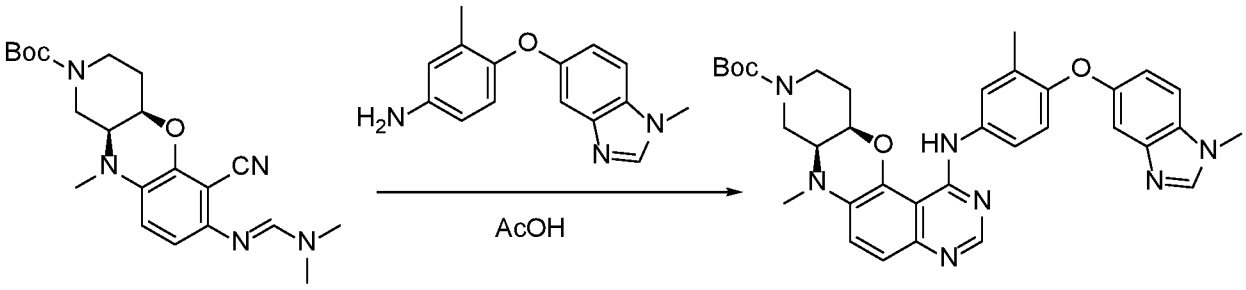
**[0874]** To a solution of tert-butyl (4aR,10aS)-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (700.0 mg, crude) in AcOH (15.0 mL) was added Fe (523.0 mg, 9.34 mmol) and $H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford tert-butyl (4aR,10aS)-7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (550.0 mg, 85%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =345.2.

**[0875] Step 5. Synthesis of tert-butyl (4aR,10aS)-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**



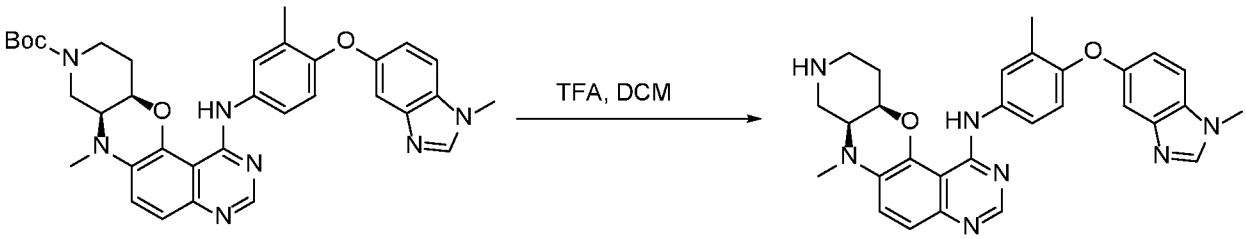

**[0876]** To a solution of tert-butyl (4aR,10aS)-7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (500.0 mg, 1.45 mmol) in EtOH (6.0 mL) was added DMF-DMA (467.1 mg, 3.92 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (4aR,10aS)-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (500.0 mg, 86%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =400.2.

**[0877] Step 6. Synthesis of tert-butyl (7aS,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate**




**[0878]** To a solution of tert-butyl (4aR,10aS)-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (200.0 mg, 0.50 mmol) in acetic acid (10.0 mL) were added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (254.0 mg, 1.00 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/ACN (10/90, v/v) to afford tert-butyl (7aS,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate (150.0 mg, 49%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =608.3.

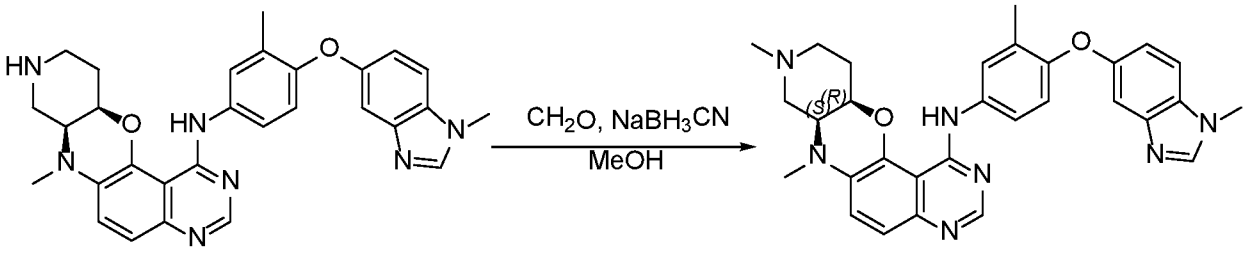
**[0879] Step 7. Synthesis of (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine**




**[0880]** To a solution of tert-butyl (7aS,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate (200.0 mg, 0.33 mmol) in DCM (9.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

filtered. The filtrate was concentrated under reduced pressure to afford (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (160.0 mg, crude) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =508.2.

**[0881] Step 8. Synthesis of (7aS,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 123)**



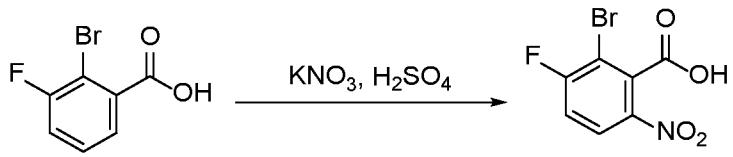

**123**

**[0882]** To a solution of (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (200.0 mg, crude) in methanol (10.0 mL) were added HCHO (200.0 mg, 40% in water) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (125.0 mg, 1.99 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm; Mobile Phase A: Water (0.05% $NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 20mL/min; Gradient: 41% B to 51% B in 10 min; Wave Length: 254 nm) to afford (7aS,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine **(Compound 123)** (8.1 mg, 3%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =522.2. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.12 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.81 (d, $J$ = 2.4 Hz, 1H), 7.66 - 7.52 (m, 2H), 7.41 - 7.27 (m, 2H), 7.08 (d, $J$ = 2.1 Hz, 1H), 7.02 - 6.95 (m, 1H), 6.90 (d, $J$ = 9.0 Hz, 1H), 4.53 - 4.49 (m, 1H), 3.84 (s, 3H), 3.66 - 3.51 (m, 1H), 3.04 (s, 3H), 2.92 -

2.81 (m, 1H), 2.74 - 2.63 (m, 1H), 2.38 - 2.31 (m, 4H), 2.25 - 2.21 (m, 4H), 2.12 - 2.02 (m, 1H), 1.91 - 1.82 (m, 1H).

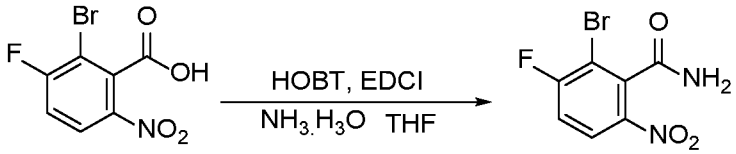
***Example S124: Synthesis of trans-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 124)***

**[0883] Step 1. Synthesis of 2-bromo-3-fluoro-6-nitrobenzoic acid**



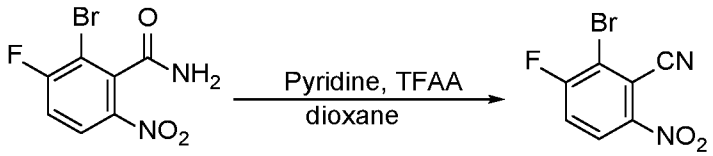

**[0884]** To a solution of 2-bromo-3-fluorobenzoic acid (10.0 g, 45.66 mmol) in $H_2SO_4$ (50.0 mL) was added $KNO_3$ (10.0 g, 98.91 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/ACN (70/30, v/v) to afford 2-bromo-3-fluoro-6-nitrobenzoic acid (4.0 g, 33%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =263.9.

**[0885] Step 2. Synthesis of 2-bromo-3-fluoro-6-nitrobenzamide**



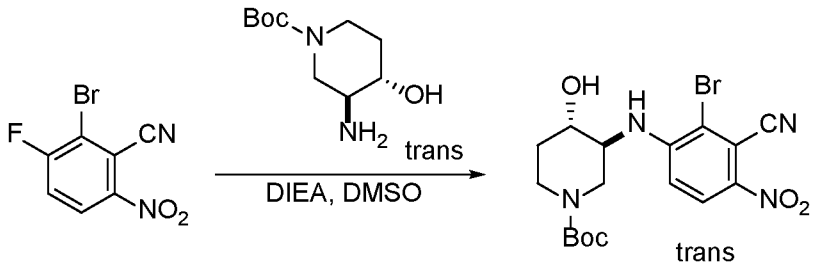

**[0886]** To a solution of 2-bromo-3-fluoro-6-nitrobenzoic acid (17.0 g, 64.39 mmol) in tetrahydrofuran (600.0 mL) was added HOBT (10.4 g, 77.27 mmol), EDCI (14.8 g, 77.27 mmol) and $NH_3.H_2O$ (22.5 g, 25% ~ 28%) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-bromo-3-fluoro-6-nitrobenzamide (13.3 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =262.9.

**[0887] Step 3. Synthesis of 2-bromo-3-fluoro-6-nitrobenzonitrile**



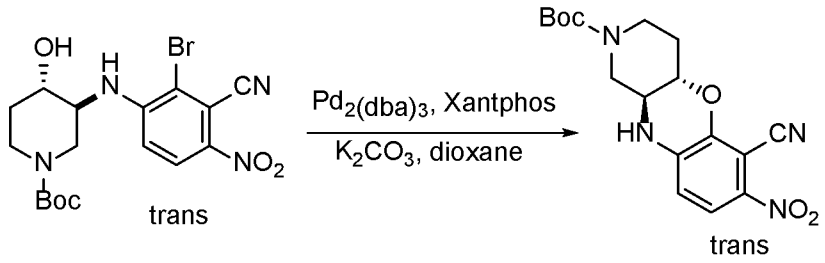

**[0888]** To a solution of 2-bromo-3-fluoro-6-nitrobenzamide (13.3 g, crude) in dioxane (650.0 mL) was added pyridine (65.0 mL) and TFAA (45.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-bromo-3-fluoro-6-nitrobenzonitrile (12.0 g, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =244.9.

**[0889] Step 4. Synthesis of trans-tert-butyl -3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate**



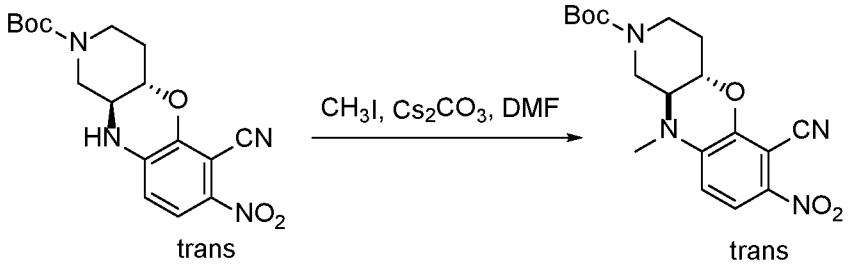

**[0890]** To a solution of 2-bromo-3-fluoro-6-nitrobenzonitrile (4.0 g, crude) in DMSO (30.0 mL) was added trans-tert-butyl -3-amino-4-hydroxypiperidine-1-carboxylate (4.2 g, 19.59 mmol) and DIEA (6.3 g, 48.97 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford trans-tert-butyl-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate (4.9 g, 68%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.1.

**[0891] Step 5. Synthesis of trans-tert-butyl-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0892]** To a solution of trans-tert-butyl-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate (5.7 g, 12.91 mmol) in dioxane (100.0 mL) was added $K_2CO_3$ (5.4 g, 38.75 mmol), $Pd_2(dba)_3$ (1.2 g, 1.29 mmol) and Xantphos (1.5 g, 2.58 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C for 16 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford trans-tert-butyl-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (4.5 g, 96%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.1.

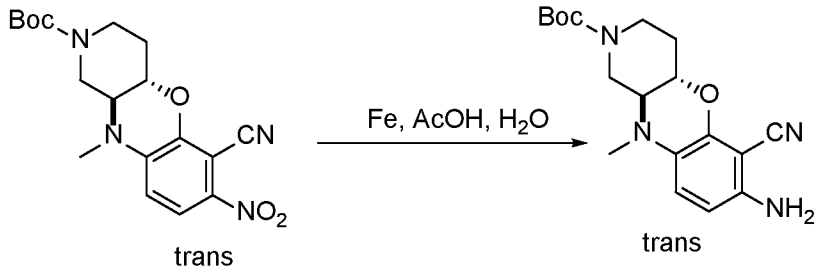
**[0893] Step 6. Synthesis of trans-tert-butyl-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0894]** To a solution of trans-tert-butyl-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (800.0 mg, 2.22 mmol) in DMF (10.0 mL) was added $Cs_2CO_3$ (2.2 g, 6.66 mmol) and $CH_3I$ (630.2 mg, 4.44 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans- tert-butyl -6-

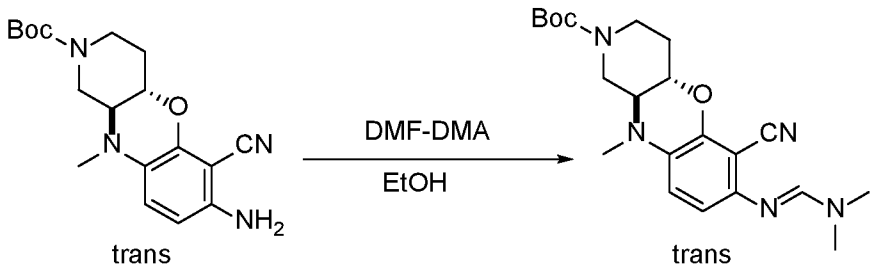
cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (850.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =375.2.

**[0895] Step 7. Synthesis of trans-tert-butyl -7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0896]** To a solution of trans-tert-butyl -6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (750.0 mg, crude) in AcOH (15.0 mL) was added Fe (558.5 mg, 10.0 mmol) and $H_2O$ (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford trans-tert-butyl -7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (450.0 mg, 65%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =345.2.

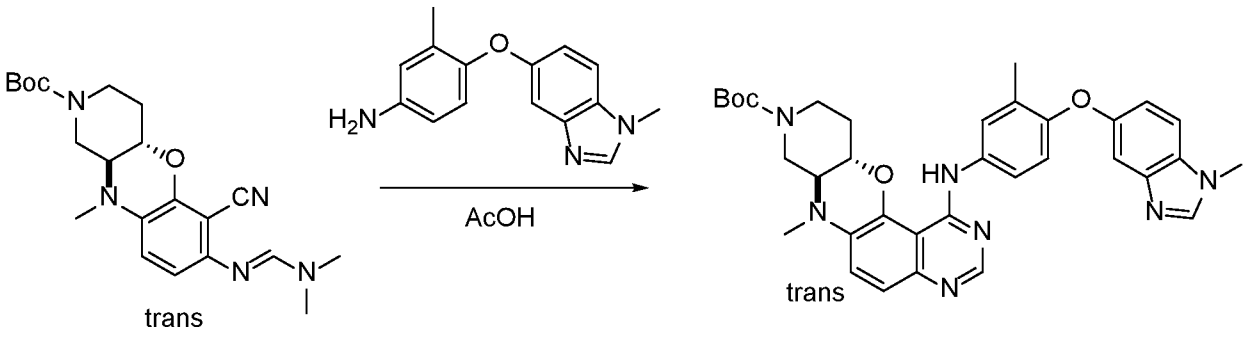
**[0897] Step 8. Synthesis of trans-tert-butyl -6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0898]** To a solution of trans-tert-butyl -7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (450.0 mg, 1.30 mmol) in EtOH (6.0 mL) was added DMF-DMA (467.1 mg, 3.92 mmol) at room temperature. The resulting mixture

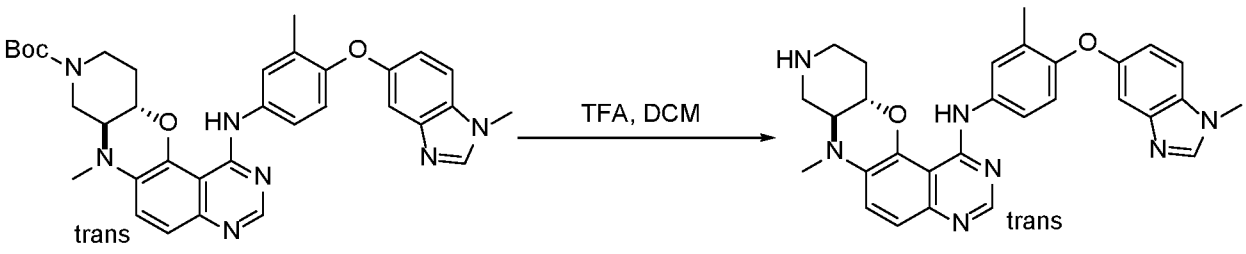
was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford trans-tert-butyl -6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (450.0 mg, 86%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =400.2.

**[0899] Step 9. Synthesis of trans-tert-butyl -7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate**



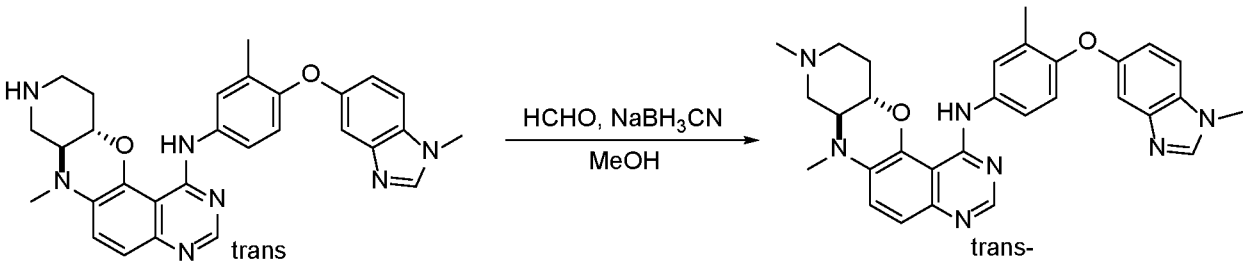

**[0900]** To a solution of trans-tert-butyl-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (150.0 mg, 0.37 mmol) in acetic acid (10.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (190.2 mg, 0.75 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/ACN (10/90, v/v) to afford trans-tert-butyl-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate (150.0 mg, 65%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =608.3.

**[0901] Step 10. Synthesis of trans- 7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine**




**[0902]** To a solution of trans-tert-butyl-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate (250.0 mg, 0.41 mmol) in DCM (9.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH value of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans- 7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (125.0 mg, crude) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =508.2.

**[0903] Step 11. Synthesis of trans-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 124)**



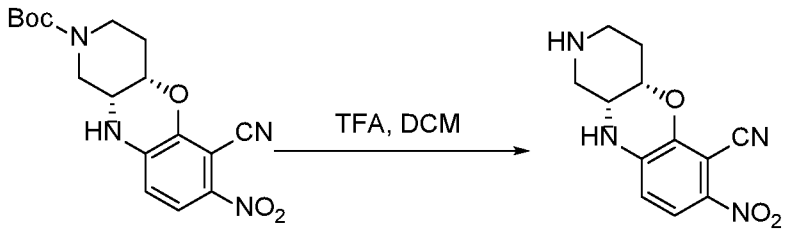

**124**

**[0904]** To a solution of trans-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (280.0 mg, crude) in methanol (15.0 mL, 0.62 mmol) was added HCHO (200.0 mg, 40% in water) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (173.3 mg, 2.76 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was

completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 3% B in 2 min, 3% B to 8% B in 10 min; Wave Length: 254 nm) to afford trans-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine **(Compound 124)** (7.2 mg, 2%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =522.2. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.94 (s, 1H), 8.36 (s, 1H), 8.17 - 8.14 (m, 2H), 7.76 (d, $J$ = 2.0 Hz, 1H), 7.65 - 7.62 (m, 1H), 7.57 - 7.53 (m, 2H), 7.33 (d, $J$ = 9.2 Hz, 1H), 7.07 (s, 1H), 7.00 - 6.97 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 4.13 - 4.06 (m, 1H), 3.83 (s, 3H), 3.61 - 3.58 (m, 1H), 3.15 - 3.09 (m, 2H), 2.90 (s, 3H), 2.49 - 2.39 (m, 5H), 2.32 (s, 3H), 2.20 - 2.10 (m, 1H), 2.00 - 1.92 (m, 1H).

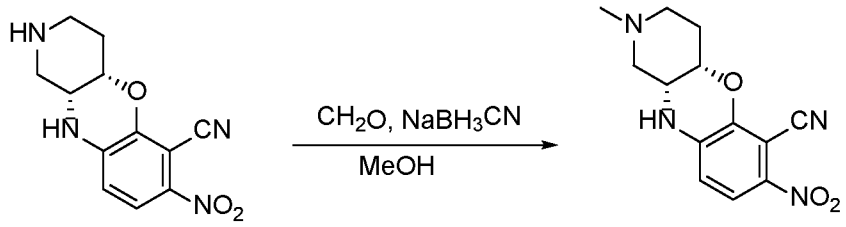
***Example S125: Synthesis of (7aR,11aS)-9-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 125)***

**[0905] Step 1. Synthesis of (4aS,10aR)-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile**



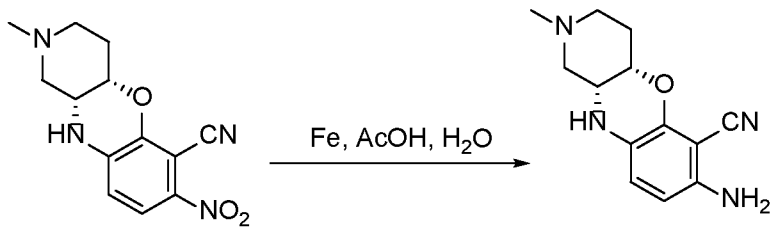

**[0906]** To a solution of tert-butyl (4aS,10aR)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (500.0 mg, 1.39 mmol) in DCM (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH of the mixture was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (4aS,10aR)-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (350.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =261.1

**[0907] Step 2. Synthesis of (4aS,10aR)-2-methyl-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile**




**[0908]** To a solution of (4aS,10aR)-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (300.0 mg, crude) in MeOH (10.0 mL) was added formaldehyde (460.5 mg, 40% in water) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (579.5 mg, 9.22 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/$H_2O$ (52/48, v/v) to afford (4aS,10aR)-2-methyl-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (150.0 mg, 47%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =275.1.

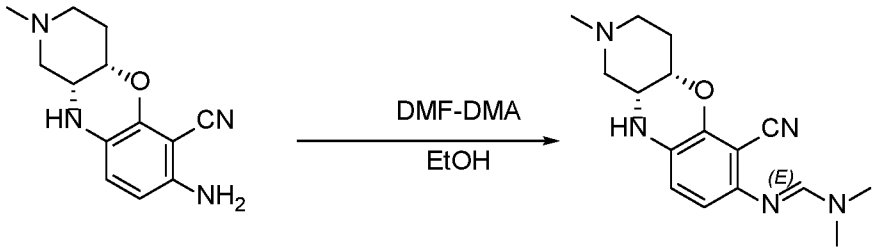
**[0909] Step 3. Synthesis of (4aS,10aR)-7-amino-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile**




**[0910]** To a solution of (4aS,10aR)-2-methyl-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (280.0 mg, 1.02 mmol) in HOAc (10.0 mL) was added Fe (285.1 mg, 5.11 mmol) and $H_2O$ (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was diluted with $H_2O$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

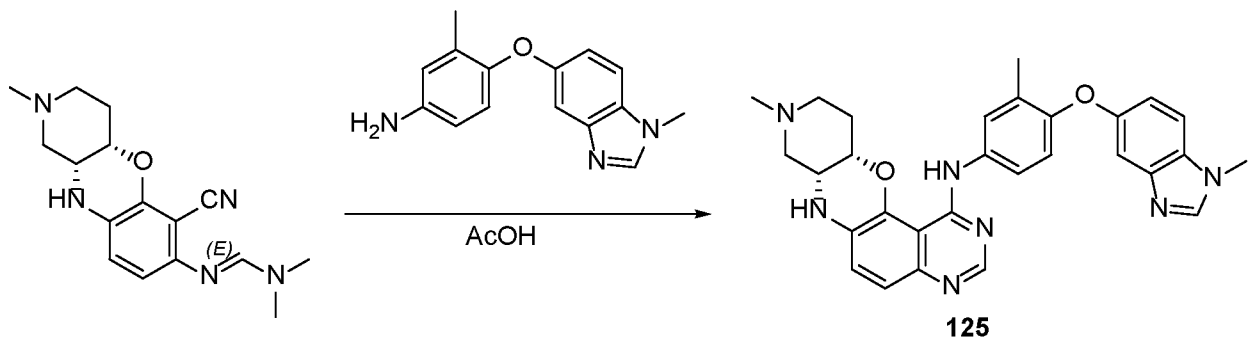
filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (90/10, v/v) to afford (4aS,10aR)-7-amino-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (200.0 mg, 80%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =245.1

**[0911] Step 4. Synthesis of (E)-N'-((4aS,10aR)-6-cyano-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazin-7-yl)-N,N-dimethylformimidamide**




**[0912]** To a solution of (4aS,10aR)-7-amino-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (150.0 mg, 0.61 mmol) in EtOH (20.0 mL) was added DMF-DMA (109.7 mg, 0.92 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford (E)-N'-((4aS,10aR)-6-cyano-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazin-7-yl)-N,N-dimethylformimidamide (150.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =300.2.

**[0913] Step 5. Synthesis of (7aR,11aS)-9-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 125)**



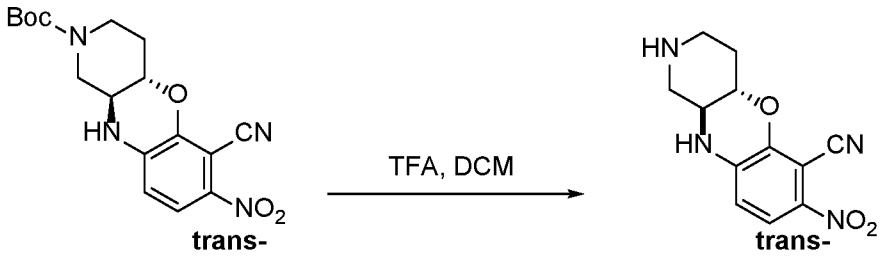

125

**[0914]** To a solution of (E)-N'-((4aS,10aR)-6-cyano-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazin-7-yl)-N,N-dimethylformimidamide (100.0 mg, crude) in acetic acid (20.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline

(169.2 mg, 0.67 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was diluted with $H_2O$. The pH value of the mixture was adjusted to 7 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 10 min; 254 nm) to afford (7aR,11aS)-9-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine **(Compound 125)** (19.9 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =508.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.05 (s, 1H), 8.30 (s, 1H), 8.16 (s, 1H), 7.79 (s, 1H), 7.64 - 7.54 (m, 2H), 7.27 - 7.18 (m, 2H), 7.07 (s, 1H), 6.99 (d, $J$ = 8.8 Hz, 1H), 6.90 (d, $J$ = 8.8 Hz, 1H), 6.53 - 6.45 (m, 1H), 4.41 (s, 1H), 3.83 (s, 3H), 3.66 - 3.61 (m, 1H), 2.88 - 2.78 (m, 2H), 2.30 - 2.16 (m, 9H), 2.09 - 1.91 (m, 1H).

***Example S126: Synthesis of trans-9-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 126)***

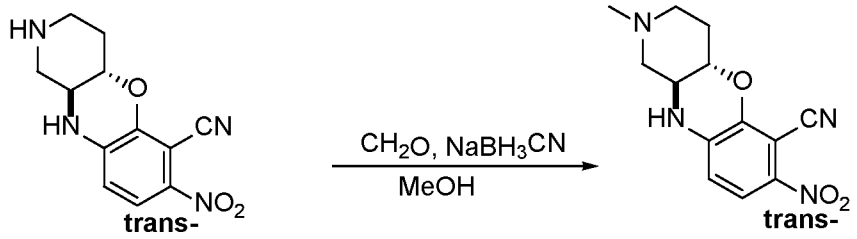
**[0915] Step 1. Synthesis of trans-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile**




**[0916]** To a solution of trans-tert-butyl -6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (1.0 g, 2.77 mmol) in DCM (30.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH value of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The

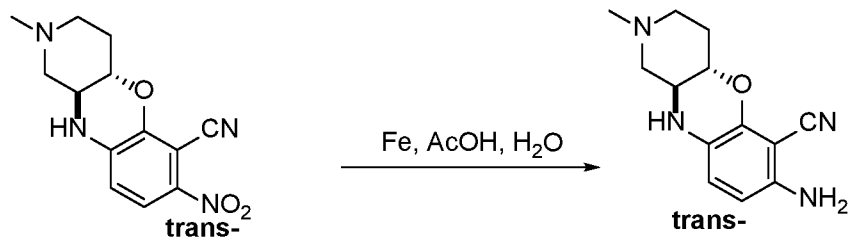
filtrate was concentrated under reduced pressure to afford trans -7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (700.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =261.1

**[0917] Step 2. Synthesis of trans-2-methyl-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile**




**[0918]** To a solution of trans-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (800.0 mg, crude) in MeOH (15.0 mL) was added formaldehyde (460.5 mg, 6.14 mmol, 40% in water) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (579.5 mg, 9.22 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/$H_2O$ (50/50, v/v) to afford trans-2-methyl-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (380.0 mg, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =275.1

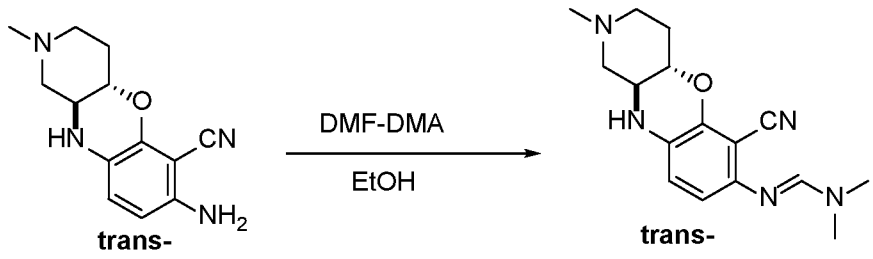
**[0919] Step 3. Synthesis of trans-7-amino-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile**




**[0920]** To a solution of trans-2-methyl-7-nitro-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (380.0 mg, 1.38 mmol) in AcOH (30.0 mL) and $H_2O$ (3.0 mL) was added Fe (386.8 mg, 6.95 mmol) at room temperature. The resulting

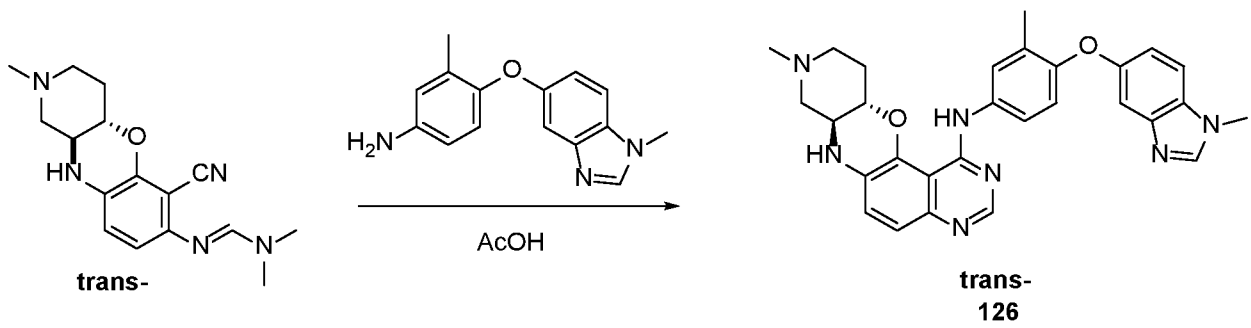
mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (90/10, v/v) to afford trans-7-amino-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (330.0 mg, 97%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =245.1

**[0921] Step 4. Synthesis of (E)-N'-(trans-6-cyano-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazin-7-yl)-N,N-dimethylformimidamide**




**[0922]** To a solution of trans-7-amino-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-6-carbonitrile (330.0 mg, 1.35 mmol) in EtOH (20.0 mL) was added DMF-DMA (93.3 mg, 4.05 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford (E)-N'-(trans-6-cyano-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazin-7-yl)-N,N-dimethylformimidamide (250.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =300.2

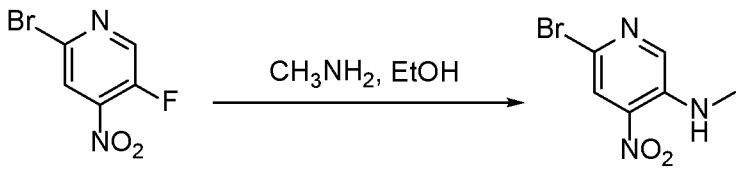
**[0923] Step 5. Synthesis of trans-9-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 126)**



**[0924]** To a solution of (E)-N'-(trans-6-cyano-2-methyl-2,3,4,4a,10,10a-hexahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazin-7-yl)-N,N-dimethylformimidamide (250.0 mg, crude) in acetic acid (20.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (317.2 mg, 1.25 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The pH value of the residue was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_4HCO_3$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 10 min; Wave Length: 254 nm) to afford trans-9-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine **(Compound 126)** (12.7 mg, 3%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =508.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.01 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 7.77 (s, 1H), 7.66 - 7.63 (m, 1H), 7.55 (d, $J$ = 8.4 Hz, 1H), 7.26 - 7.20 (m, 2H), 7.07 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.89 (d, $J$ = 8.8 Hz, 1H), 6.28 (s, 1H), 3.89 - 3.79 (m, 4H), 3.26 - 3.20 (m, 1H), 3.08 - 3.06 (m, 1H), 3.01 - 2.92 (m, 1H), 2.45 - 2.28 (m, 4H), 2.24 (s, 3H), 2.19 - 2.08 (m, 1H), 1.93 - 1.83 (m, 2H).

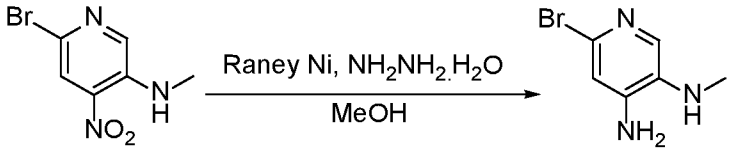
***Example S127: Synthesis of (S)-3-methyl-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 127)***

**[0925]** **Step 1. Synthesis of 6-bromo-N-methyl-4-nitropyridin-3-amine**



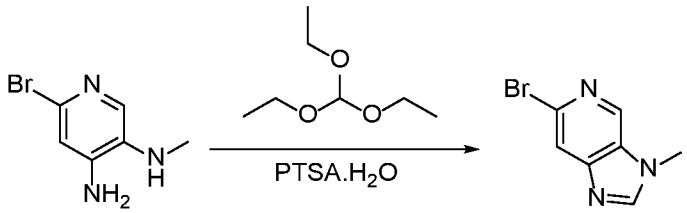

**[0926]** To a solution of 2-bromo-5-fluoro-4-nitropyridine (4.0 g, 18.10 mmol) in EtOH (96.0 mL) was added a solution of methylamine in EtOH (16.0 mL, 30%) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford 6-bromo-N-methyl-4-nitropyridin-3-amine (5.0 g, crude) as a red solid. LCMS (ESI, m/z): $[M+H]^+$ = 232.0.

**[0927] Step 2. Synthesis of 6-bromo-N3-methylpyridine-3,4-diamine**



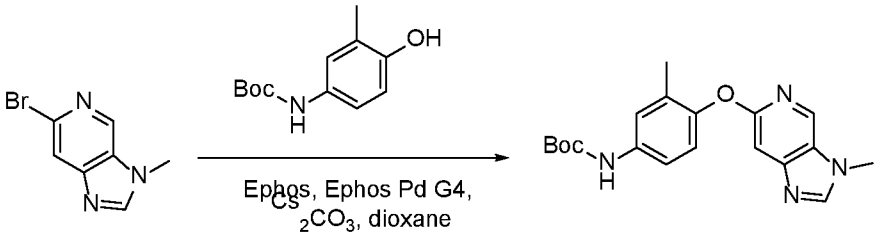

**[0928]** To a solution of 6-bromo-N-methyl-4-nitropyridin-3-amine (4.5 g, crude) in MeOH (40.0 mL) was added Raney Ni (1.9 g, 21.94 mmol) and $NH_2NH_2.H_2O$ (3.8 mL, 80%) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 6-bromo-N3-methylpyridine-3,4-diamine (1.2 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 202.0$.

**[0929] Step 3. Synthesis of 6-bromo-3-methyl-3H-imidazo[4,5-c]pyridine**




**[0930]** To a solution of 6-bromo-$N^3$-methylpyridine-3,4-diamine (1.0 g, crude) in triethoxymethane (40.0 mL) was added PTSA.$H_2O$ (85.3 mg, 0.50 mmol) at room temperature. The resulting mixture was stirred at 90 °C for 16 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 6-bromo-3-methyl-3H-imidazo[4,5-c]pyridine (800.0 mg, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 212.0$.

**[0931] Step 4. Synthesis of tert-butyl (3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)carbamate**

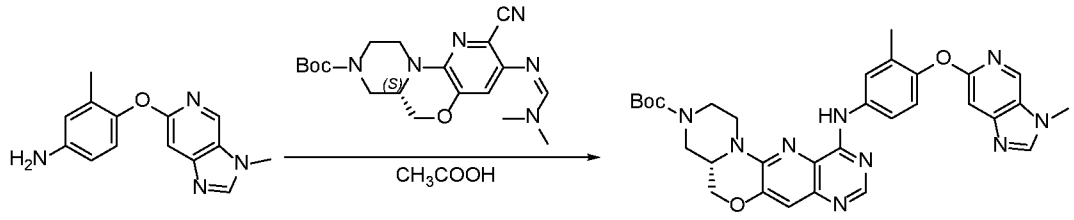



**[0932]** To a solution of 6-bromo-3-methyl-3H-imidazo[4,5-c]pyridine (700.0 mg, 3.30 mmol) in dioxane (10.0 mL) was added tert-butyl (4-hydroxy-3-methylphenyl)carbamate (828.9 mg, 3.96 mmol), $Cs_2CO_3$ (3.2 g, 9.91 mmol), Ephos (353.1 mg, 0.66 mmol) and Ephos Pd G4 (303.2 mg, 0.33 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 100 °C for 16 h under $N_2$. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) to afford tert-butyl (3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)carbamate (350.0 mg, 29%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 355.2.

**[0933] Step 5. Synthesis of 3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)aniline**

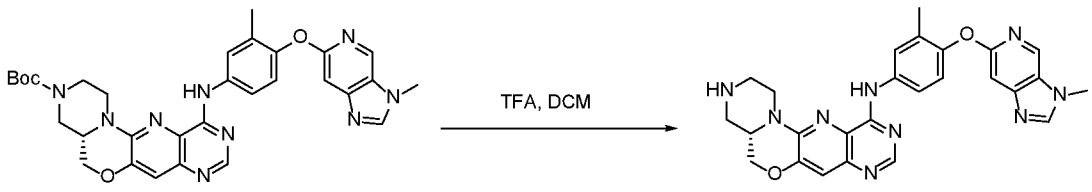

**[0934]** To a solution of tert-butyl (3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)carbamate (335.0 mg, 0.95 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)aniline (200.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 255.1.

**[0935] Step 6. Synthesis of tert-butyl (S)-11-((3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate**




**[0936]** To a solution of 3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)aniline (186.0 mg, crude) in AcOH (5.0 mL) was added tert-butyl (S,Z)-2-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (280.0 mg, 0.73 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) to afford tert-butyl (S)-11-((3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (110.0 mg, 25%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 596.3.

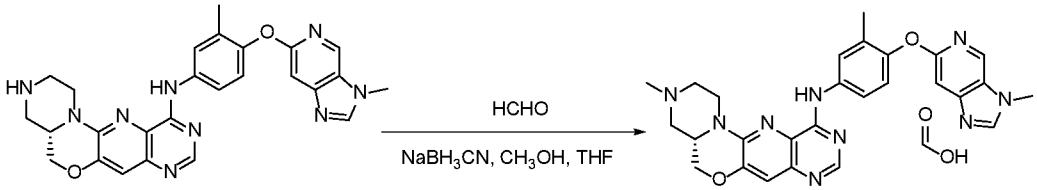
**[0937] Step 7. Synthesis of (S)-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine**




**[0938]** To a solution of tert-butyl (S)-11-((3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)amino)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazine-3(4H)-carboxylate (110.0 mg, 0.19 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.).

The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (S)-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (70.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 496.2.

**[0939] Step 8. Synthesis of (S)-3-methyl-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (Compound 127)**



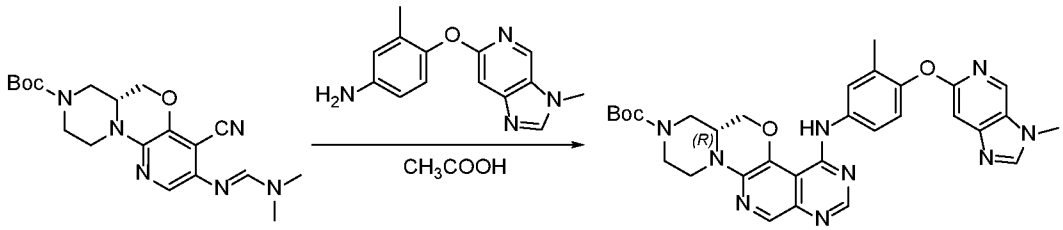

127

**[0940]** To a solution of (S)-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine (70.0 mg, crude) in THF (5.0 mL)/MeOH (1.0 mL) was added HCHO (97.6 mg, 30% in $H_2O$) at room temperature. The resulting mixture was stirred at room temperature for 30 min. Then $NaBH_3CN$ (17.8 mg, 0.28 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for additional 1 h. After the reaction was completed, the reaction mixture was quenched with water at 0 °C. The resulting mixture was diluted with $H_2O$ and extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (2/3, v/v) and then purified by Prep-HPLC with the following conditions: (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 5% B in 2 min, 3% B to 8% B in 10 min; Wave Length: 254/220 nm) to afford (S)-3-methyl-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrimido[4',5':5,6]pyrido[3,2-b][1,4]oxazin-11-amine **(Compound 127)** (7.5 mg, 9%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 510.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 8.60 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 8.01 (s, 1H), 7.50 (d, $J$ = 2.0 Hz, 1H), 7.38 - 7.35 (m, 1H), 7.25 (s, 1H), 7.18 (s, 1H), 7.07 (d, $J$ = 8.4 Hz, 1H), 4.70 - 4.67 (m, 1H), 4.46 - 4.42 (m, 1H), 4.07 -

4.02 (m, 1H), 3.91 (s, 3H), 3.59 - 3.54 (m, 1H), 2.98 - 2.89 (m, 3H), 2.26 (s, 3H), 2.23 (s, 3H), 2.07 - 2.01 (m, 1H), 1.81 -1.73 (m, 1H).

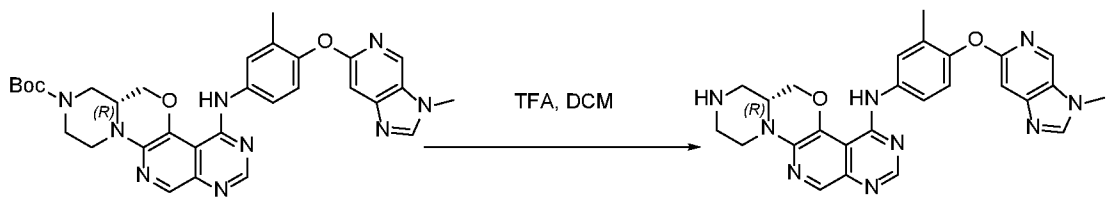
***Example S128: Synthesis of (R)-8-methyl-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 128)***

**[0941] Step 1. Synthesis of tert-butyl (R)-4-((3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate**



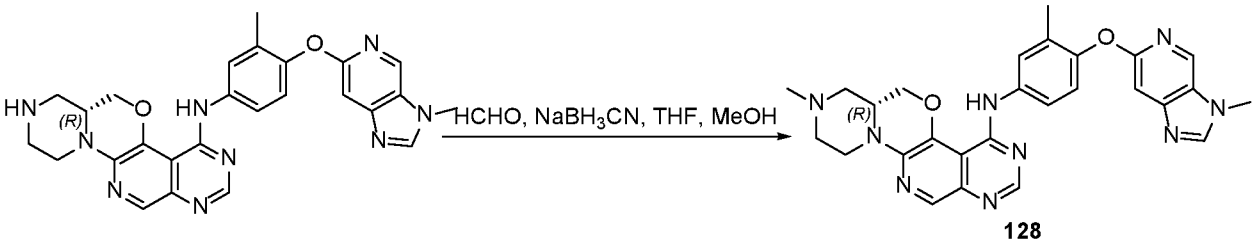

**[0942]** To a solution of tert-butyl (R,E)-4-cyano-3-(((dimethylamino)methylene)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (130.0 mg, 0.34 mmol) in HOAc (5.0 mL) was added 3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)aniline (139.4 mg, 0.55 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol (10/1, v/v) to afford tert-butyl (R)-4-((3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (110.0 mg, 54%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 596.3.

**[0943] Step 2. Synthesis of (R)-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine**



**[0944]** To a solution of tert-butyl (R)-4-((3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (100.0 mg, 0.17 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (R)-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (110.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 496.2.

**[0945] Step 3. Synthesis of (R)-8-methyl-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 128)**

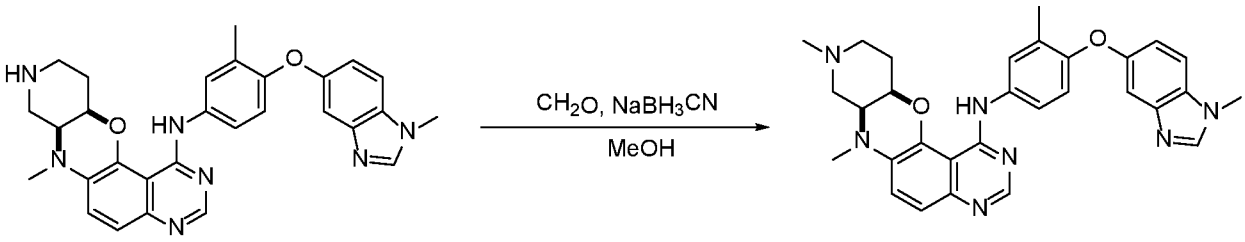



**[0946]** To a solution of (R)-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (100.0 mg, crude) in THF/MeOH (5.0 mL/1.0 mL) was added HCHO (139.4 mg, 30%) and $NaBH_3CN$ (25.4 mg, 0.40 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. After the reaction was completed, the reaction mixture was quenched with water at 0 °C. The resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with ACN/$H_2O$ (2/3, v/v) and then purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 34% B in 10 min; Wave Length: 254/220 nm) to afford (R)-8-methyl-N-(3-methyl-4-((3-methyl-3H-imidazo[4,5-c]pyridin-6-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine **(Compound 128)** (10.7 mg, 10%) as a

yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 510.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.69 (s, 1H), 8.53 (s, 1H), 8.43 (s, 1H), 8.37 - 8.34 (m, 2H), 7.71 - 7.68 (m, 2H), 7.12 (s, 1H), 6.99 (d, $J$ = 8.4 Hz, 1H), 4.69 - 4.67 (m, 1H), 4.44 - 4.41 (m, 1H), 4.24 - 4.19 (m, 1H), 3.89 (s, 3H), 3.51 - 3.46 (m, 1H), 2.92 - 2.81 (m, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 2.08 - 2.01 (m, 1H), 1.82 - 1.77 (m, 1H).

***Example S129: Synthesis of (7aS,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 129)***

**[0947] Step 1. Synthesis of (7aS,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 129)**



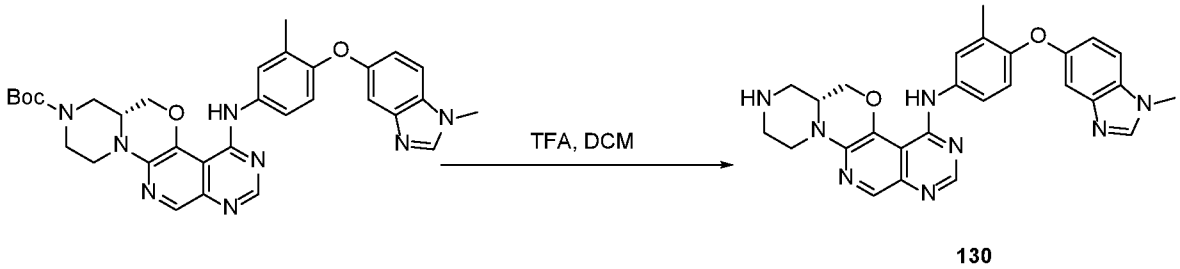

129

**[0948]** To a solution of (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (100.0 mg, 0.19 mmol) in methanol (10.0 mL) was added $CH_2O$ (100.0 mg, 40% in water) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (62.0 mg, 0.98 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm; Mobile Phase A: Water (0.05% $NH_3H_2O$), Mobile Phase B: MEOH; Flow rate: 20 mL/min; Gradient: 75% B to 80% B in 10 min; Wave Length: 254 nm) to afford (7aS,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine **(Compound 129)** (3.8 mg, 3%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =522.3. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.12 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.80 (d, $J$ = 1.6 Hz,

1H), 7.63 - 7.55 (m, 2H), 7.37 - 7.30 (m, 2H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.51 (s, 1H), 3.84 (s, 3H), 3.66 - 3.51 (m, 1H), 3.04 (s, 3H), 2.88 - 2.84 (m, 1H), 2.70 - 2.67 (m, 1H), 2.40 - 2.21 (m, 8H), 2.11 - 2.03 (m, 1H), 1.99 - 1.81 (m, 1H).

***Example S130: Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 130)***

**[0949] Step 1. Synthesis of (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine (Compound 130)**

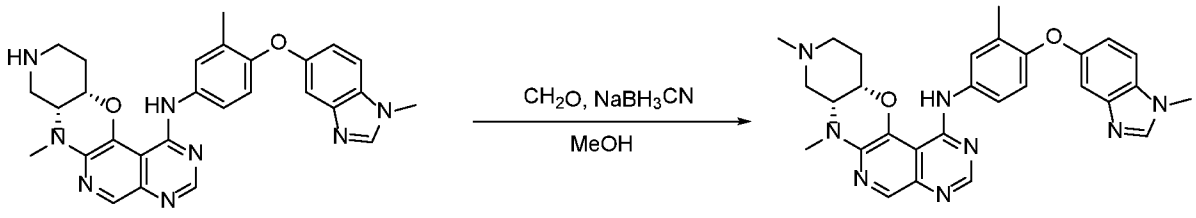



130

**[0950]** To a solution of tert-butyl (R)-4-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-6a,7,9,10-tetrahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazine-8(6H)-carboxylate (100.0 mg, 0.17 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl Column, 19x250 mm, 5 μm; Mobile Phase A: Water, Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 45% B in 9.5 min; Wave Length: 254/220 nm) to afford (R)-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-6,6a,7,8,9,10-hexahydropyrazino[1,2-d]pyrimido[5',4':4,5]pyrido[3,2-b][1,4]oxazin-4-amine **(Compound 130)** (26.2 mg, 29%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 495.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.68 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.71 - 7.67 (m, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.66 - 4.63 (m, 1H), 4.38 - 4.33 (m, 1H), 4.22 - 4.15 (m, 1H), 3.84 (s, 3H), 3.04 - 2.96 (m, 2H), 2.76 - 2.62 (m, 3H), 2.43 - 2.37 (m, 1H), 2.25 (s, 3H).

***Example S131: Synthesis of (7aR,11aS)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 131)***

**[0951] Step 1. Synthesis of (7aR,11aS)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 131)**

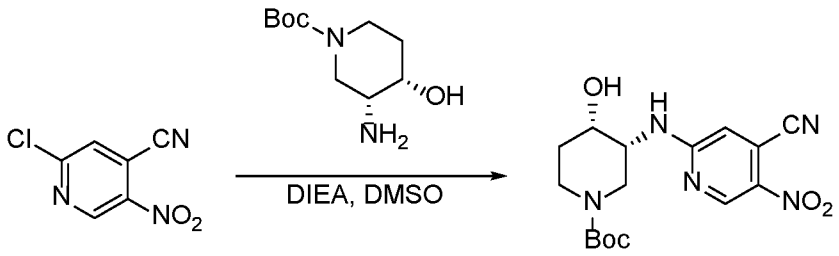



131

**[0952]** To a solution of (7aR,11aS)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (120.0 mg, 0.23 mmol) in methanol (8.0 mL) was added $CH_2O$ (36.0 mg, 40% in water) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (75.0 mg, 1.19 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 20% B to 25% B in 10 min; Wave Length: 254 nm) to afford (7aR,11aS)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine **(Compound 131)** (56.0 mg, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =523.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.83 (s, 1H), 8.43 (s, 1H), 8.32 (s, 1H), 8.17 - 8.16 (m, 3H), 7.80 (d, $J$ = 2.4 Hz, 1H), 7.64 - 7.55 (m, 2H), 7.09 (d, $J$ = 2.4 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 4.55 (s, 1H), 3.84 (s, 3H), 3.78 - 3.75 (m, 1H), 3.17 (s, 3H), 3.02 - 2.97 (m, 1H), 2.73 - 2.69 (m, 1H), 2.34 - 2.24 (m, 8H), 2.12 - 2.06 (m, 1H), 1.99 - 1.94 (m, 1H).

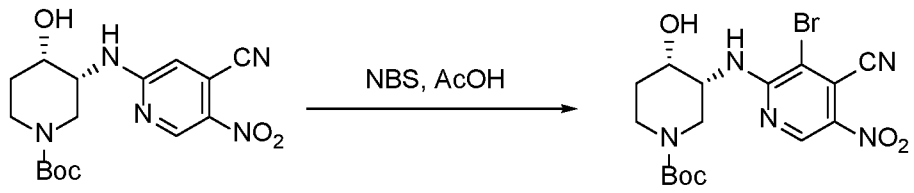
***Example S132: Synthesis of (7aR,11aS)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 132)***

**[0953] Step 1. Synthesis of tert-butyl (3R,4S)-3-((4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate**




**[0954]** To a solution of 2-chloro-5-nitroisonicotinonitrile (1.4 g, 7.63 mmol) in DMSO (20.0 mL) was added DIEA (3.0 g, 23.19 mmol) and tert-butyl (3R,4S)-3-amino-4-hydroxypiperidine-1-carboxylate (1.3 g, 6.0 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/90, v/v) to afford tert-butyl (3R,4S)-3-((4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.8 g, 64%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =364.2.

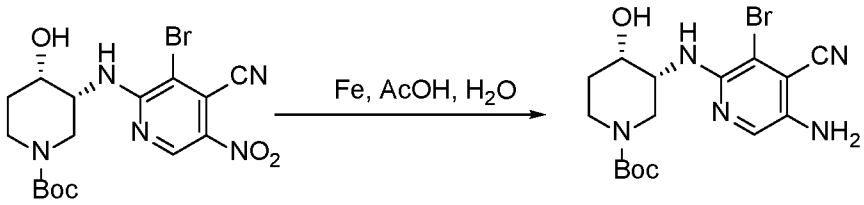
**[0955] Step 2. Synthesis of tert-butyl (3R,4S)-3-((3-bromo-4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate**




**[0956]** To a solution of tert-butyl (3R,4S)-3-((4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.2 g, 3.30 mmol) in HOAc (25.0 mL) was added NBS (870.0 mg, 4.88 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium

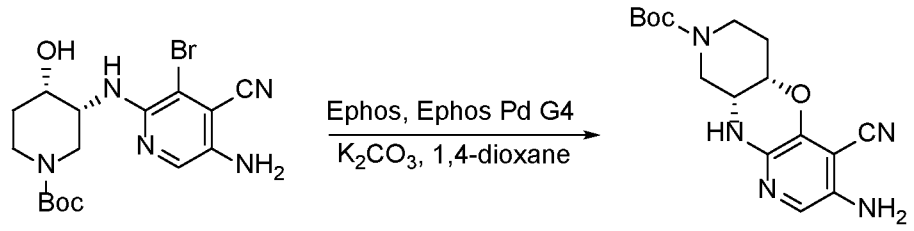
sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3R,4S)-3-((3-bromo-4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.0 g, 68%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =442.1.

**[0957] Step 3. Synthesis of tert-butyl (3R,4S)-3-((5-amino-3-bromo-4-cyanopyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate**




**[0958]** To a solution of tert-butyl (3R,4S)-3-((3-bromo-4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (800.0 mg, 1.80 mmol) in HOAc (10.0 mL) and $H_2O$ (2.0 mL) was added Fe (500.0 mg, 8.95 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3R,4S)-3-((5-amino-3-bromo-4-cyanopyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (480.0 mg, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =412.1

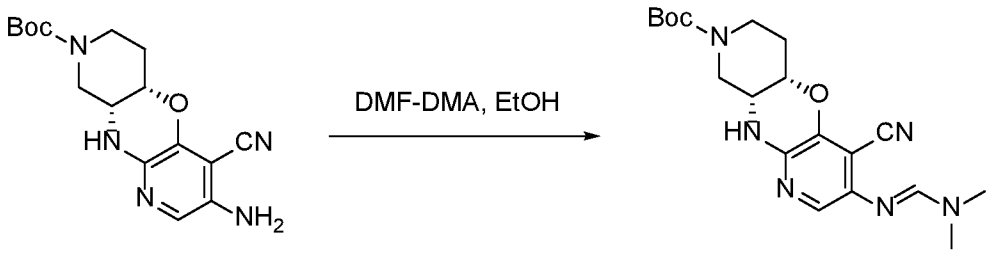
**[0959] Step 4. Synthesis of tert-butyl (5aS,9aR)-3-amino-4-cyano-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate**




**[0960]** To a solution of tert-butyl (3R,4S)-3-((5-amino-3-bromo-4-cyanopyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (400.0 mg, 0.97 mmol) in 1,4-dioxane (20.0 mL) were added Ephos (120.0 mg, 0.22 mmol), EPhos Pd G4 (100.0 mg, 0.11 mmol) and $K_2CO_3$ (430.0 mg, 3.11 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C

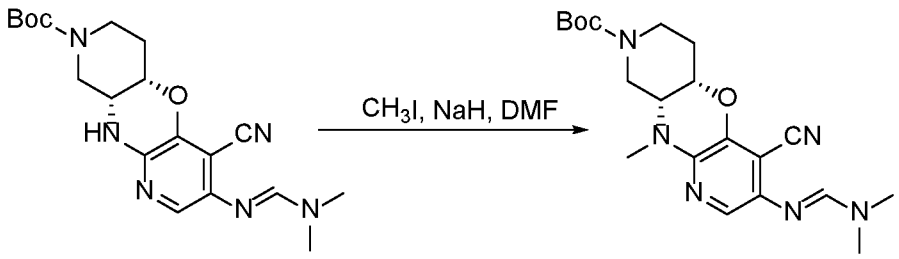
for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30/70, v/v) to afford tert-butyl (5aS,9aR)-3-amino-4-cyano-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (200.0 mg, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$=332.2.

**[0961] Step 5. Synthesis of tert-butyl (5aS,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate**



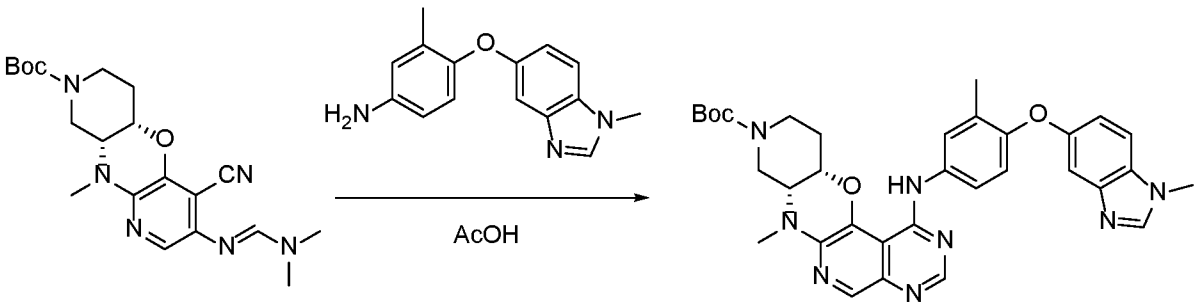

**[0962]** To a solution of tert-butyl (5aS,9aR)-3-amino-4-cyano-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (200.0 mg, 0.60 mmol) in ethyl alcohol (15.0 mL) was added DMF-DMA (220.0 mg, 1.84 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (5aS,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (230.0 mg, 98%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$=387.2.

**[0963] Step 6. Synthesis of tert-butyl (5aS,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-10-methyl-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate**




**[0964]** To a solution of tert-butyl (5aS,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (230.0 mg, 0.59 mmol) in DMF (15.0 mL) was added NaH (74.8 mg, 60% in oil) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Then $CH_3I$ (130.0 mg, 0.91 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (5aS,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-10-methyl-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (200.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$=401.2.

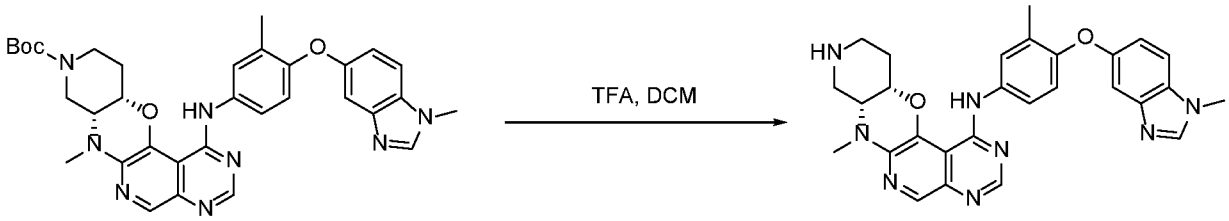
**[0965] Step 7. Synthesis of tert-butyl (7aR,11aS)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazine-9(8H)-carboxylate**




**[0966]** To a solution of tert-butyl (5aS,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-10-methyl-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (200.0 mg, crude) in acetic acid (20.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (250.0 mg, 0.98 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was

purified by reverse phase flash column chromatography with $H_2O$/ACN (10/90, v/v) to afford tert-butyl (7aR,11aS)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazine-9(8H)-carboxylate (110.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =609.3.

**[0967] Step 8. Synthesis of (7aR,11aS)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 132)**

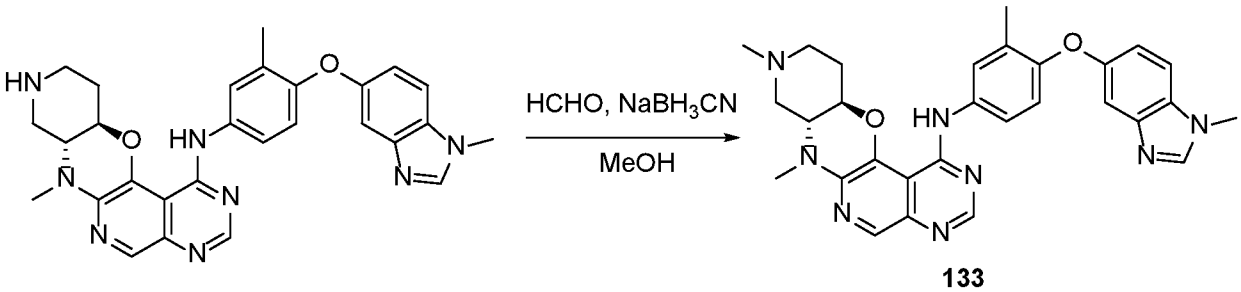



132

**[0968]** To a solution of tert-butyl (7aR,11aS)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazine-9(8H)-carboxylate (110.0 mg, 0.18 mmol) in DCM (6.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 μm; Mobile Phase A: Water (0.05% $NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 37% B in 10 min; Wave Length: 254 nm) to afford (7aR,11aS)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine **(Compound 132)** (10.8 mg, 11%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =509.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.86 (s, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 7.79 (d, $J$ = 2.0 Hz, 1H), 7.63 - 7.55 (m, 2H), 7.09 (d, $J$ = 2.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 4.64 (s, 1H), 3.84 (s, 3H), 3.66 - 3.59 (m, 1H), 3.16 (s, 3H), 3.11 - 3.07 (m, 1H), 2.81 - 2.75 (m, 2H), 2.56 - 2.51 (m, 1H), 2.26 - 2.22 (m, 5H), 2.01 - 1.91 (m, 1H).

***Example S133: Synthesis of (7aR,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 133)***

**[0969] Step 1. Synthesis of (7aR,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 133)**

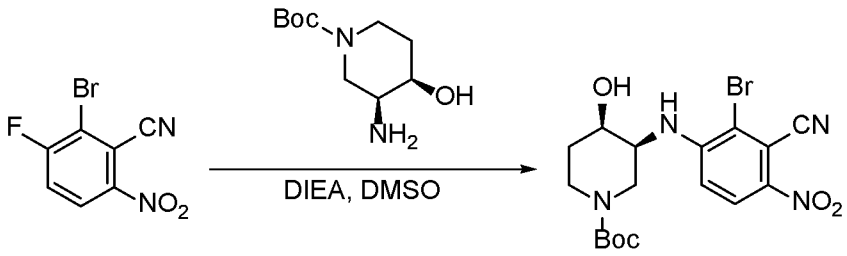



**133**

**[0970]** To a solution of (7aR,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (100.0 mg, 0.20 mmol) in MeOH (5.0 mL) was added HCHO (110.7 mg, 40% in water) at room temperature.The resulting mixture was stirred at room temperature for 0.5 h. Then $NaBH_3CN$ (55.6 mg, 0.89 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19 x 250 mm, 5 μm; Mobile Phase A: Water (0.05% $NH_3H_2O$), Mobile Phase B: ACN -----Preparative; Flow rate: 25 mL/min; Gradient: 35% B to 45% B in 10 min; Wave Length: 254 nm) to afford (7aR,11aR)-7,9-dimethyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine **(Compound 133)** (28.2 mg, 27%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =523.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.65 - 9.62 (m, 1H), 8.49 - 8.44 (m, 1H), 8.39 - 8.36 (m, 1H), 8.19 (s, 1H), 7.74 - 7.63 (m, 2H), 7.58 - 7.55 (m, 1H), 7.09 (s, 1H), 6.99 (d, $J$ = 8.8 Hz, 1H), 6.90 - 6.87 (m, 1H), 4.25 - 4.11 (m, 1H), 3.89 - 3.81 (m, 4H), 3.08 - 3.06 (m, 3H), 2.81 - 2.66 (m, 4H), 2.59 - 2.50 (m, 4H), 2.23 (s, 3H), 2.03 - 1.98 (m, 1H).

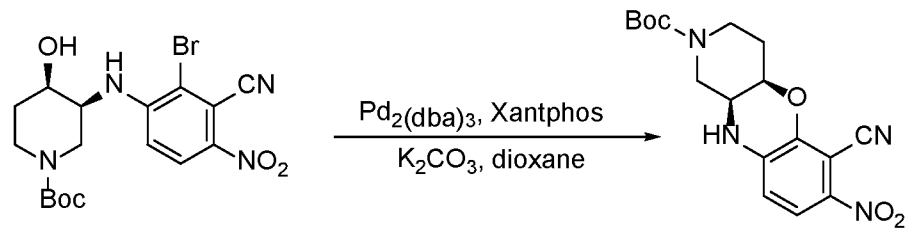
***Example S134: Synthesis of (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 134)***

**[0971] Step 1. Synthesis of tert-butyl (3S,4R)-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate**




**[0972]** To a solution of 2-bromo-3-fluoro-6-nitrobenzonitrile (500.0 mg, 2.04 mmol) in DMSO (18.0 mL) was added tert-butyl (3S,4R)-3-amino-4-hydroxypiperidine-1-carboxylate (529.6 mg, 2.45 mmol) and DIEA (791.3 mg, 6.12 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 18 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3S,4R)-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate (600.0 mg, 66%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.1.

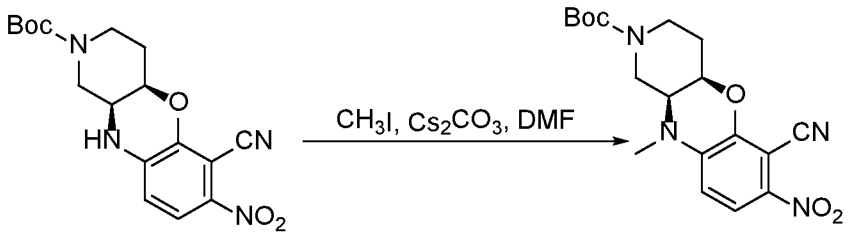
**[0973] Step 2. Synthesis of tert-butyl (4aR,10aS)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0974]** To a solution of tert-butyl (3S,4R)-3-((2-bromo-3-cyano-4-nitrophenyl)amino)-4-hydroxypiperidine-1-carboxylate (550.0 mg, 1.25 mmol) in dioxane (14.0 mL) was added $Pd_2(dba)_3$ (114.1 mg, 0.12 mmol), XantPhos (144.2 mg, 0.24 mmol) and $K_2CO_3$ (516.7 mg, 3.73 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C for 2 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted

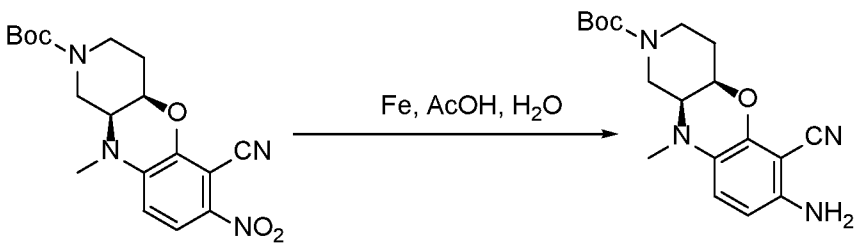
with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (4aR,10aS)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (370.0 mg, 82%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =361.0.

**[0975] Step 3. Synthesis of tert-butyl (4aR,10aS)-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0976]** To a solution of tert-butyl (4aR,10aS)-6-cyano-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (370.0 mg, 1.03 mmol) in DMF (12.0 mL) was added $CH_3I$ (291.4 mg, 2.05 mmol) and $Cs_2CO_3$ (1.0 g, 3.08 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl (4aR,10aS)-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (450.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =375.2.

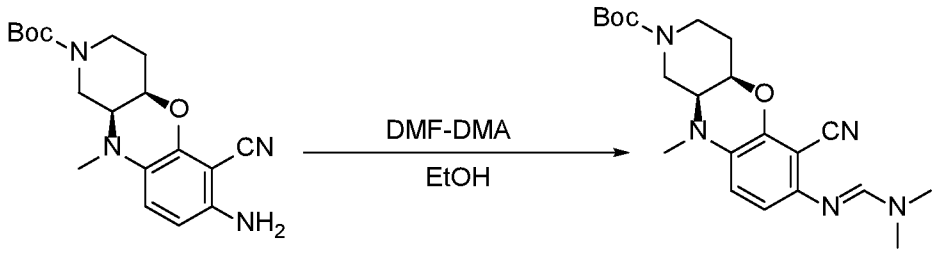
**[0977] Step 4. Synthesis of tert-butyl (4aR,10aS)-7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**




**[0978]** To a solution of tert-butyl (4aR,10aS)-6-cyano-10-methyl-7-nitro-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (450.0 mg, crude) in

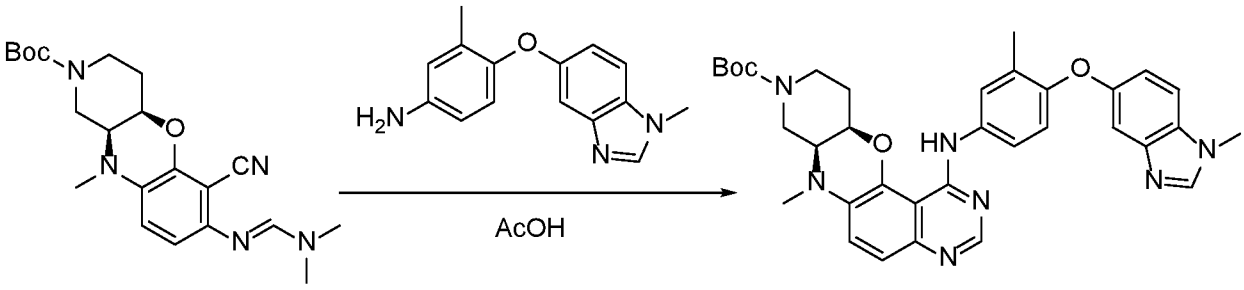
HOAc (15.0 mL) and $H_2O$ (2.0 mL) was added Fe (335.6 mg, 6.00 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford tert-butyl (4aR,10aS)-7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (270.0 mg, 65%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =345.2.

**[0979] Step 5. Synthesis of tert-butyl (4aR,10aS)-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate**



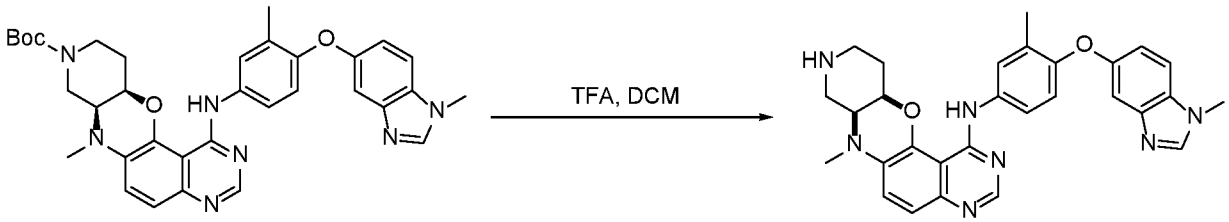

**[0980]** To a solution of tert-butyl (4aR,10aS)-7-amino-6-cyano-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (270.0 mg, 0.78 mmol) in ethyl alcohol (15.0 mL) were added DMF-DMA (280.2 mg, 2.35 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (4aR,10aS)-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (270.0 mg, 86%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =400.2.

**[0981] Step 6. Synthesis of tert-butyl (7aS,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate**




**[0982]** To a solution of tert-butyl (4aR,10aS)-6-cyano-7-(((E)-(dimethylamino)methylene)amino)-10-methyl-4,4a,10,10a-tetrahydro-1H-benzo[b]pyrido[3,4-e][1,4]oxazine-2(3H)-carboxylate (220.0 mg, 0.55 mmol) in acetic acid (15.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (279.0 mg, 1.10 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/ACN (10/90, v/v) to afford tert-butyl (7aS,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate (170.0 mg, 50%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =608.3.

**[0983] Step 7. Synthesis of (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine (Compound 134)**



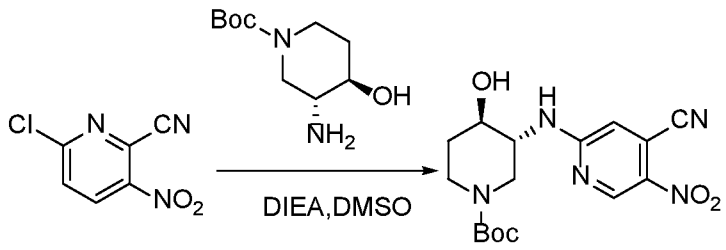

**134**

**[0984]** To a solution of tert-butyl (7aS,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazoline-9(8H)-carboxylate (170.0 mg, 0.28 mmol) in DCM (9.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH of the mixture was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane. The

combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19x250 mm, 5μm; Mobile Phase A: Water (0.05% $NH_3·H_2O$), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 31% B to 42% B in 10 min; Wave Length: 254 nm) to afford (7aS,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[3',4':5,6][1,4]oxazino[2,3-f]quinazolin-1-amine **(Compound 134)** (14.5 mg, 17%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =508.3. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.16 (s, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 7.80 (d, $J$ = 2.4 Hz, 1H), 7.62 - 7.55 (m, 2H), 7.37 - 7.29 (m, 2H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.90 (d, $J$ = 8.8 Hz, 1H), 4.58 (s, 1H), 3.84 (s, 3H), 3.52 - 3.42 (m, 2H), 3.02 - 2.97 (m, 4H), 2.80 - 2.68 (m, 2H), 2.50 - 2.47 (m, 1H), 2.25 - 2.21 (m, 4H), 2.01 - 1.95 (m, 1H).

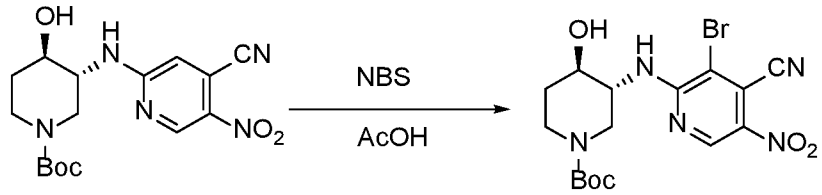
***Example S135: Synthesis of (7aR,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 135)***

**[0985] Step 1. Synthesis of tert-butyl (3R,4R)-3-((4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate**



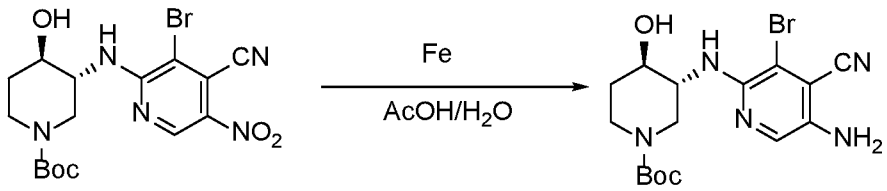

**[0986]** To a solution of 6-chloro-3-nitropicolinonitrile (2.5 g, 13.62 mmol) in DMSO (25.0 mL) was added tert-butyl (3R,4R)-3-amino-4-hydroxypiperidine-1-carboxylate (2.3 g, 10.89 mmol) and DIEA (5.3 g, 40.86 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/90, v/v) to afford tert-butyl (3R,4R)-3-((4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (3.5 g, 70%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =364.2.

**[0987] Step 2. Synthesis of tert-butyl (3R,4R)-3-((3-bromo-4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate**



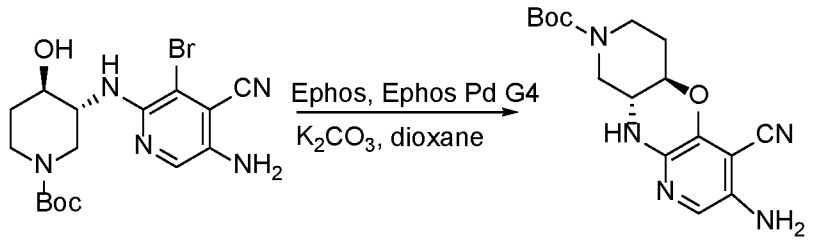

**[0988]** To a solution of tert-butyl (3R,4R)-3-((4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.5 g, 4.13 mmol) in HOAc (20.0 mL) was added NBS (2.9 g, 16.51 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3R,4R)-3-((3-bromo-4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.5 g, 82%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =442.1.

**[0989] Step 3. Synthesis of tert-butyl (3R,4R)-3-((5-amino-3-bromo-4-cyanopyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate**



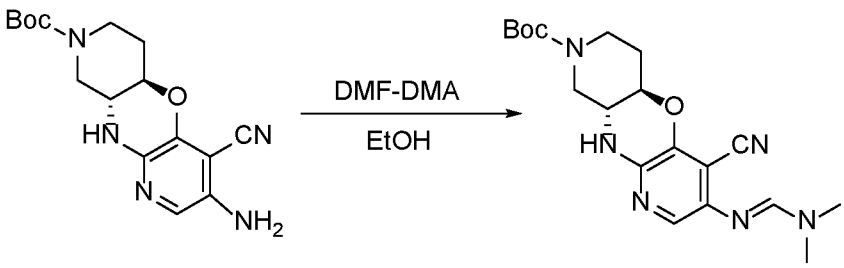

**[0990]** To a solution of tert-butyl (3R,4R)-3-((3-bromo-4-cyano-5-nitropyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.4 g, 3.17 mmol) in AcOH (20.0 mL) was added Fe (885.0 mg, 15.83 mmol) and $H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (40/60, v/v) to afford tert-butyl (3R,4R)-3-((5-amino-3-bromo-4-cyanopyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (1.0 g, 76%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =412.2.

**[0991] Step 4. Synthesis of tert-butyl (5aR,9aR)-3-amino-4-cyano-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate**




**[0992]** To a solution of tert-butyl (3R,4R)-3-((5-amino-3-bromo-4-cyanopyridin-2-yl)amino)-4-hydroxypiperidine-1-carboxylate (800.0 mg, 1.94 mmol) in dioxane (20.0 mL) was added EPhos (415.0 mg, 0.78 mmol), $K_2CO_3$ (799.0 mg, 5.78 mmol) and EPhos Pd G4 (356.0 mg, 0.39 mmol) at room temperature under $N_2$. The resulting mixture was stirred at 80 °C for 16 h under $N_2$. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford tert-butyl (5aR,9aR)-3-amino-4-cyano-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (560.0 mg, 87%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =332.2.

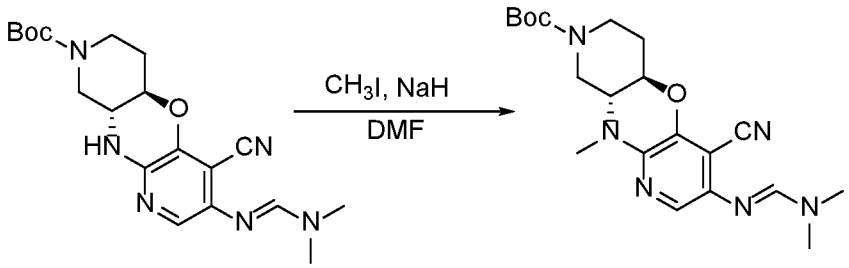
**[0993] Step 5. Synthesis of tert-butyl (5aR,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate**




**[0994]** To a solution of tert-butyl (5aR,9aR)-3-amino-4-cyano-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (560.0 mg, 1.69 mmol) in EtOH (5.0 mL) was added DMF-DMA (1.0 g, 8.45 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum to afford tert-butyl (5aR,9aR)-4-cyano-3-(((E)-

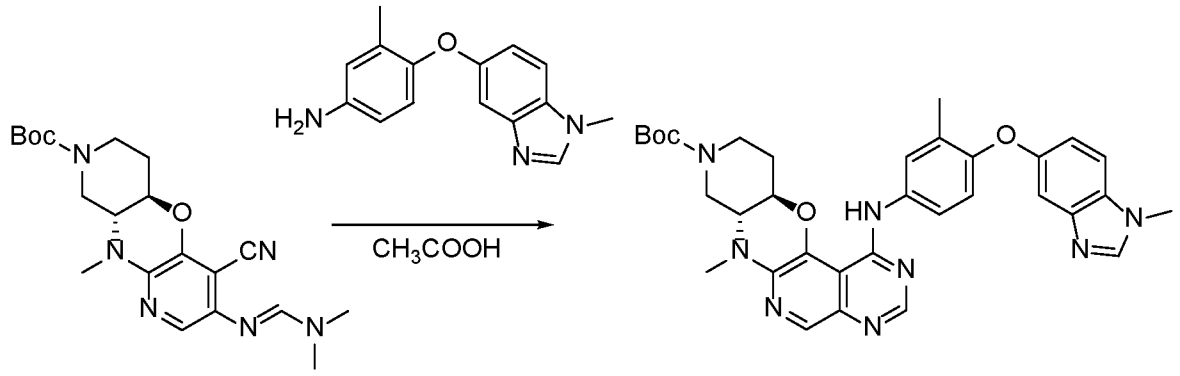
(dimethylamino)methylene)amino)-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (550.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =387.2.

**[0995] Step 6. Synthesis of tert-butyl (5aR,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-10-methyl-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate**



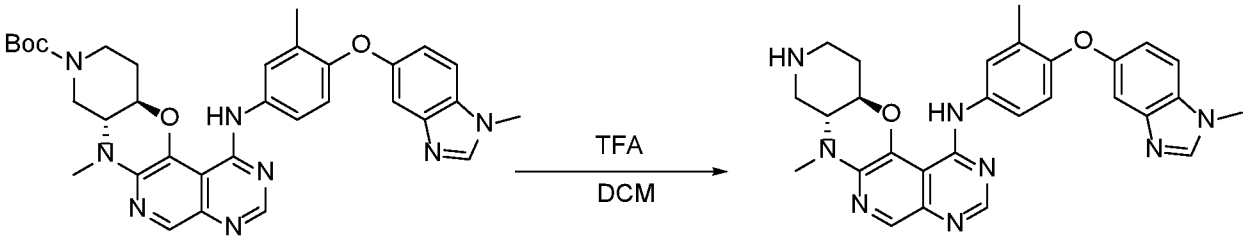

**[0996]** To a solution of tert-butyl (5aR,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (500.0 mg, 1.29 mmol) in DMF (10.0 mL) was added NaH (104.0 mg, 60%) at room temperature under $N_2$. The resulting mixture was stirred at room temperature for 1 h. Then $CH_3I$ (630.2 mg, 4.44 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with $H_2O$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (5aR,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-10-methyl-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (400.0 mg, 77%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =401.2.

**[0997] Step 7. Synthesis of tert-butyl (7aR,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazine-9(8H)-carboxylate**



**[0998]** To a solution of tert-butyl (5aR,9aR)-4-cyano-3-(((E)-(dimethylamino)methylene)amino)-10-methyl-5a,6,9a,10-tetrahydro-7H-dipyrido[3,2-b:3',4'-e][1,4]oxazine-8(9H)-carboxylate (400.0 mg, 1.00 mmol) in acetic acid (10.0 mL) was added 3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)aniline (505.0 mg, 1.99 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with $H_2O$/ACN (10/90, v/v) to afford tert-butyl (7aR,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazine-9(8H)-carboxylate (370.0 mg, 60%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =609.3.

**[0999] Step 8. Synthesis of (7aR,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine (Compound 135)**



135

**[1000]** To a solution of tert-butyl (7aR,11aR)-7-methyl-1-((3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)amino)-7a,10,11,11a-tetrahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazine-9(8H)-carboxylate (100.0 mg, 0.16 mmol) in DCM (4.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the pH value of the mixture was adjusted to 8.0 with saturated $NaHCO_3$ (aq.). The mixture was extracted with dichloromethane.

The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L $NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 10 min; Wave Length: 254 nm) to afford (7aR,11aR)-7-methyl-N-(3-methyl-4-((1-methyl-1H-benzo[d]imidazol-5-yl)oxy)phenyl)-7a,8,9,10,11,11a-hexahydro-7H-pyrido[4,3-b]pyrimido[5',4':4,5]pyrido[2,3-e][1,4]oxazin-1-amine **(Compound 135)** (17.4 mg, 31%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 509.2. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.72 (s, 1H), 8.46 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 7.74 (s, 1H), 7.67 - 7.64 (m, 1H), 7.56 (d, $J$ = 8.8 Hz, 1H), 7.08 (d, $J$ = 2.0 Hz, 1H), 7.00 - 6.97 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 4.85 - 4.50 (m, 1H), 4.22 - 4.16 (m, 1H), 3.84 (s, 3H), 3.71 - 3.68 (m, 1H), 3.24 - 3.12 (m, 2H), 3.07 (s, 3H), 2.76 - 2.70 (m, 1H), 2.55 - 2.50 (m, 1H), 2.39 - 2.34 (m, 1H), 2.25 (s, 3H), 1.81 - 1.73 (m, 1H).

## BIOLOGICAL EXAMPLES

### *Example B1: Cell Viability Assays*

**[1001]** Cells were treated with compounds, and cell viability was measured as a metric of kinase inhibition.

**[1002]** BT-474, A431, MDA-MB-175VII, NCI-H1781, MCF7, and Ba/F3 cell lines were tested. The Ba/F3 cell line is IL-3-dependent mouse cell line derived from the C3H mouse strain. Ba/F3 cell lines were engineered to express human ERBB2 or EGFR kinases, rendering the cells IL-3 independent. The lines were generated via retroviral transduction utilizing a Moloney murine leukemia virus (MMLV) promoter, and constructs are stably integrated into the cell genome. The sequences of the ERBB2 and EGFR genes used were NCBI Reference Sequences NM_004448.3 and NM_005228.3, respectively.

**[1003]** BT-474, A431, MDA-MB-175VII, NCI-H1781 and MCF7 cells were grown in the appropriate growth medium as described in Table B2 below, and harvested at 50-80% confluence. BT-474, A431, MDA-MB-175VII, NCI-H1781 and MCF7 cells were counted and seeded at 2,000 or 1,500 cells per well in 384-well tissue culture plates (see Table B2). Similarly, Ba/F3 cell lines engineered to express EGFR, ERBB2, or ERBB2 mutants were grown, harvested, counted and seeded at 3000 cells per well in 96-well plates. A subset of wells contained media only (low control, “LC”).

**[1004]** Table B1 provides the growth media and number of cells seeded per well for the each cell line.

**Table B1**

| Cell Line | Growth Medium | Number of cells seeded per well |
|---|---|---|
| BT-474 | Dulbecco's Modified Eagle Medium (DMEM) + 10% fetal bovine serum (FBS) | 2000 |
| A431 | DMEM + 10% FBS | 1500 |
| MDA-MB-175VII | RPMI + 10% FBS | 2000 |
| NCI-H1781 | RPMI + 10% FBS | 1500 |
| MCF7 | EMEM + 10% FBS + 100ng/ml human insulin | 2000 |
| Ba/F3 | RPMI+ 10% FBS | 3000 |

**[1005]** Compounds were dissolved in DMSO and serially diluted. Serially-diluted compound or a DMSO only control (high control, "HC") was added to the plated cells in each well. Compounds were tested at concentrations of about 10 μM to 0.51 nM, using three-fold dilutions. The final proportion of DMSO never exceeded 0.1%.

**[1006]** Plates were placed in a 37°C, 5% $CO_2$ incubator for 72 hours. Plates were then removed from the incubator and equilibrated for 15 minutes at room temperature. 40 μl of CellTiter Glo reagent (Promega) was added to measure the relative level of metabolically active cells by quantifying intracellular ATP concentrations. Plates were incubated for 30 minutes at room temperature, and luminescence was measured. Percent viability was normalized to a vehicle control only using the following formula: % viability = 100 x ($Lum_{Sample}$ – $Lum_{LC}$) / ($Lum_{HC}$ – $Lum_{LC}$). $IC_{50}$ values were calculated using XLFit software or Prism (GraphPad Software), as shown in Table B2, below. Graphical curves were fitted using a nonlinear regression model with a sigmoidal dose response.

**Table B2**

| Compound | Ba/F3 ERBB2 YVMA, $IC_{50}$, nM |
|---|---|
| 1 | 1.6 |
| 2 | 4.54 |
| 3 | 10.4 |
| 4 | 62.4 |
| 5 | 4.62 |
| 6 | 6.23 |
| 7 | 112 |
| 8 | 13.3 |

| | |
|---|---|
| 9 | 41.2 |
| 10 | 84.9 |
| 11 | 65.3 |
| 12 | 206 |
| 13 | 6.24 |
| 14 | 14.4 |
| 15 | 4.89 |
| 16 | 1.47 |
| 17 | 5.11 |
| 18 | 223 |
| 19 | 5 |
| 20 | 19.7 |
| 21 | 16.2 |
| 22 | 2.12 |
| 23 | 13.8 |
| 24 | > 500 |
| 25 | 15.5 |
| 26 | > 500 |
| 27 | 7.69 |
| 28 | > 500 |
| 29 | 23.9 |
| 30 | > 500 |
| 31 | 12.6 |
| 32 | 18.3 |
| 33 | 271 |
| 34 | 474 |
| 35 | > 500 |
| 49 | > 500 |
| 50 | > 500 |
| 51 | > 500 |
| 52 | > 500 |
| 76 | 5.86 |
| 77 | 14.4 |
| 78 | 10.9 |
| 79 | 6.04 |
| 80 | 77.2 |
| 81 | 8.51 |
| 82 | 6.9 |
| 83 | 14 |
| 84 | 2.95 |
| 85 | 181 |
| 88 | 60.3 |
| 89 | 264 |
| 90 | 28.7 |
| 91 | 164 |
| 92 | 18 |

| | |
|---|---|
| 93 | 7.75 |
| 94 | 19.9 |
| 95 | 19.6 |
| 96 | 9.12 |
| 97 | 3.6 |
| 98 | 16.6 |
| 112 | 13.3 |
| 113 | 3.57 |
| 114 | 172 |
| 115 | 7.22 |
| 116 | 14 |
| 117 | 6.57 |
| 118 | 35.7 |
| 119 | 11.7 |
| 120 | 44.3 |
| 121 | 71 |
| 122 | 30.9 |
| 123 | 46.4 |
| 124 | 93.7 |
| 125 | 164 |
| 126 | 140 |
| 127 | > 500 |
| 128 | 211 |
| 129 | 111 |
| 130 | 170 |
| 131 | 87.1 |
| 132 | > 500 |
| 133 | 60.1 |
| 134 | > 500 |
| 135 | 88.9 |

***Example B2: Detection of phosphorylated ERBB2 (pERBB2) and phosphorylated EGFR (pEGFR)***

**[1007]** BT-474 cells were seeded into a 96-well at $2.0*10^4$cells/100µl/well.

**[1008]** Compounds were dissolved and serially diluted in DMSO. The compounds were then were added, mixed, and incubated for four hours at 37°C, 5% $CO_2$. Compounds were added using four-fold dilutions at final concentrations ranging from 10 µM to 0.01 nM.

**[1009]** Following the four hour incubation with compounds, cell lysates were prepared. Plates were centrifuged for 5 min at 3000 RPM, and supernatant was removed from each well.

Cells were washed 3 times by resuspension in 150µl PBS, followed by centrifugation and removal of the supernatant, as above. 100µl of cell lysis buffer (Boston BioProducts, cat # BP-115D) supplied with 1x complete ULTRA cocktail inhibitor (Thermo Scientific™, cat #78443) was then added to the washed cells. Cells were incubated with lysis buffer for 1 hour at 4°C, and then stored at -80°C.

**[1010]** Enzyme-linked immunosorbent assays (ELISA) were performed to measure phosphorylated ERBB2 levels. A capture antibody able to detect phosphorylated and non-phosphorylated ERBB2 (R&D Systems, cat # 841425) was added to ELISA plates and incubated at 4°C overnight. The next day, plates were washed with PBS + 0.05% Tween20 (PBST). 150µl of 5% BSA blocking solution was added for 1 hour at room temperature, with shaking. Plates were washed with PBST. Cell lysates were thawed and 100µl of lysate was added to the ELISA plate. The plates were incubated for 2 hours at room temperature, with shaking. ELISA plates were then washed with PBST and 100µl of an HRP-labeled detection antibody that binds phosphorylated tyrosine (R&D Systems, cat # 841913) was added to each well. Plates were incubated for 1 hour at room temperature, with shaking. Plates were then washed with PBST, and 100µl TMB substrate solution (R&D Systems, cat #DY999) was added. Plate were incubated in the dark for 20 minutes at room temperature. 50µl of Stop solution (R&D Systems, cat #DY994) (50µl) was added to each well and mixed.

**[1011]** Optical density at 450nm was read on an EnSpire plate reader (Perkin Elmer). The remaining kinase activity by calculated using the following formula: % Relative activity = 100 x ($A450_{sample}$- $A450_{LC}$) / ($A450_{HC}$ -$A450_{LC}$). The low and high control values ("LC" and "HC") were generated from lysate from wells without cells or with cells treated with 0.1% DMSO, respectively. $IC_{50}$ values were calculated using XLFit software using a nonlinear regression model with a sigmoidal dose response, as shown in Table B3 below.

**Table B3**

| Compound | pERBB2 $IC_{50}$ (nM) |
|---|---|
| 1 | 5.77 |
| 2 | 8.97 |
| 3 | 12.8 |
| 4 | 14.1 |
| 5 | 7.89 |
| 6 | 7.19 |
| 7 | 30.7 |
| 8 | 18.1 |

| | |
|---|---|
| 9 | 36.1 |
| 10 | 32.7 |
| 11 | 73.3 |
| 12 | 83.7 |
| 13 | 13 |
| 14 | 82.8 |
| 15 | 6.93 |
| 16 | 5.8 |
| 17 | 34.3 |
| 18 | 240 |
| 19 | 11.1 |
| 20 | 27.5 |
| 21 | 22.7 |
| 22 | 22.8 |
| 23 | 27.4 |
| 24 | 430 |
| 25 | 11.5 |
| 26 | 434 |
| 27 | 8.75 |
| 28 | 417 |
| 29 | 30.7 |
| 30 | 304 |
| 31 | 19.9 |
| 32 | 51.4 |
| 33 | 52.4 |
| 34 | 53.6 |
| 35 | 127 |
| 36 | 234 |
| 37 | 77.6 |
| 38 | 60.6 |
| 39 | 279 |
| 40 | 153 |
| 41 | 57.7 |
| 42 | 31.5 |
| 43 | 76.5 |
| 44 | 218 |
| 45 | 54 |
| 46 | 22.3 |
| 47 | 91.2 |
| 48 | 146 |
| 49 | 466 |
| 50 | 195 |
| 51 | 128 |
| 52 | 219 |
| 53 | 541 |
| 54 | 82.1 |

| | |
|---|---|
| 55 | 108 |
| 56 | 127 |
| 57 | 26.7 |
| 58 | 21.9 |
| 59 | 91.7 |
| 60 | 97.2 |
| 61 | 118 |
| 62 | 38.5 |
| 63 | 153 |
| 64 | 223 |
| 65 | 94.9 |
| 66 | 119 |
| 67 | 46.4 |
| 68 | 55.5 |
| 69 | 99.8 |
| 70 | 185 |
| 71 | 227 |
| 72 | 417 |
| 73 | 198 |
| 74 | 98.1 |
| 75 | 73.9 |
| 76 | 5.66 |
| 77 | 6.51 |
| 78 | 8.87 |
| 79 | 14.2 |
| 80 | 22.8 |
| 81 | 17.2 |
| 82 | 7.9 |
| 83 | 17.3 |
| 84 | 14.6 |
| 85 | 17.2 |
| 86 | 40.7 |
| 87 | 75.5 |
| 88 | 44.3 |
| 89 | 172 |
| 90 | 50.4 |
| 91 | 147 |
| 92 | 20.8 |
| 93 | 18.1 |
| 94 | 19.6 |
| 95 | 32.3 |
| 96 | 19.1 |
| 97 | 15.2 |
| 98 | 60 |
| 99 | 211 |
| 100 | 82.2 |

| | |
|---|---|
| 101 | 503 |
| 102 | 257 |
| 103 | 154 |
| 104 | 495 |
| 105 | 225 |
| 106 | 37.1 |
| 107 | 78.2 |
| 108 | 57.2 |
| 109 | 85 |
| 110 | 74.7 |
| 111 | 45.7 |
| 112 | 21.8 |
| 113 | 11.3 |
| 114 | 43.1 |
| 115 | 30.2 |
| 116 | 10.9 |
| 117 | 13.1 |
| 118 | 25 |
| 119 | 29 |
| 120 | 26.4 |
| 121 | 27.2 |
| 122 | 26.4 |
| 123 | 13.9 |
| 124 | 63 |
| 125 | 58 |
| 126 | 62.1 |
| 127 | 828 |
| 128 | 35.3 |
| 129 | 45.6 |
| 130 | 65 |
| 131 | 32.7 |
| 132 | 307 |
| 133 | 41.9 |
| 134 | 113 |
| 135 | 56.1 |

**[1012]** Enzyme-linked immunosorbent assays (ELISA) were performed to measure phosphorylated EGFR levels using A431 cells (10% FBS). A431 ($1.0*10^4$cells/40µl/well) cells were seeded in 384 well. Compounds were dissolved in DMSO, serially diluted in DMSO and then were added, mixed, and incubated for 4 hours at 37°C, 5% $CO_2$. Following the 4-hours incubation, cells were stimulated for 10 minutes with EGF (Invitrogen, cat #PHG0311) at a final concentration of 30 ng/mL in the incubator. The media was aspirated and cells were lysed in 10 µL lysis buffer with protease and phosphatase inhibitors (PerkinElmer, cat # ALSU-PEGFR-

A50K). The plates were placed on a shaker for 5 minutes and then incubated for 30 min at 4°C for complete lysis. The lysate was transferred to an Optiplate (Perkin Elmer, cat #6007290).

**[1013]** Acceptor mix (PerkinElmer, cat # ALSU-PEGFR-A50K) was prepared just before use and 5 µL was dispensed to all the wells, followed by a 1.5-2h incubation at room temperature in dark. The donor mix (PerkinElmer, cat # ALSU-PEGFR-A50K) was prepared under low light conditions prior to use and 5µl of donor mix was added to all the wells under subdued lighting or green filters. The plates were placed on a shaker for 5 min, sealed, and incubated overnight at room temperature in dark. Plates were read on the Envision (PerkinElmer) using standard AlphaLISA settings.

**[1014]** The percentage of inhibition on EGFR phosphorylation was calculated following equation: %Inhibition = 100 x (LumHC – LumSample) / (LumHC –LumLC). The low and high controls (LC/HC) are generated from lysate from wells with cells treated with DMSO or 10 mM Staurosporine (BioAustralis, cat # BIA-S1086), respectively. IC50 values were calculated by fitting the Curve using XLfit (v5.3.1.3), equation 201: Y = Bottom + (Top - Bottom)/(1 + 10^((LogIC50 - X)*HillSlope)). The $IC_{50}$ values are shown in Table B4 below.

**Table B4**

| Compound | pEGFR $IC_{50}$ (nM) |
|---|---|
| 1 | 84.7 |
| 2 | 421 |
| 3 | 212 |
| 4 | 1330 |
| 5 | 517 |
| 6 | 540 |
| 7 | 1780 |
| 8 | 643 |
| 9 | 1680 |
| 10 | 3280 |
| 11 | 1180 |
| 12 | 2840 |
| 13 | 254 |
| 14 | 545 |
| 15 | 284 |
| 16 | 130 |
| 17 | 307 |
| 18 | > 10.0E+03 |
| 19 | 679 |
| 20 | 150 |

| | |
|---|---|
| 21 | 575 |
| 22 | 544 |
| 23 | 817 |
| 24 | > 10.0E+03 |
| 25 | 1580 |
| 26 | > 10.0E+03 |
| 27 | 189 |
| 28 | > 10.0E+03 |
| 29 | 2930 |
| 30 | > 10.0E+03 |
| 31 | 246 |
| 32 | 4770 |
| 33 | > 10.0E+03 |
| 34 | > 10.0E+03 |
| 35 | > 10.0E+03 |
| 36 | > 10.0E+03 |
| 37 | > 10.0E+03 |
| 38 | > 10.0E+03 |
| 39 | > 10.0E+03 |
| 40 | > 10.0E+03 |
| 41 | > 10.0E+03 |
| 42 | > 10.0E+03 |
| 43 | > 10.0E+03 |
| 44 | > 10.0E+03 |
| 45 | > 10.0E+03 |
| 46 | > 10.0E+03 |
| 47 | > 10.0E+03 |
| 48 | > 10.0E+03 |
| 49 | > 10.0E+03 |
| 50 | > 10.0E+03 |
| 51 | > 10.0E+03 |
| 52 | > 10.0E+03 |
| 53 | > 10.0E+03 |
| 54 | > 10.0E+03 |
| 55 | > 10.0E+03 |
| 56 | > 10.0E+03 |
| 57 | > 10.0E+03 |
| 58 | > 10.0E+03 |
| 59 | > 10.0E+03 |
| 60 | > 10.0E+03 |
| 61 | > 10.0E+03 |
| 62 | > 10.0E+03 |
| 63 | > 10.0E+03 |
| 64 | > 10.0E+03 |
| 65 | > 10.0E+03 |
| 66 | > 10.0E+03 |

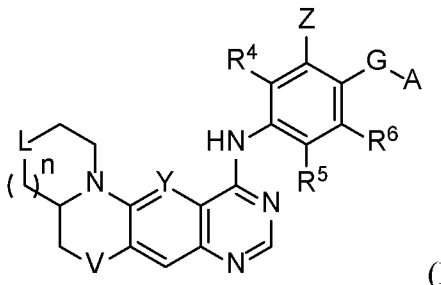
| | |
|---|---|
| 67 | > 10.0E+03 |
| 68 | > 10.0E+03 |
| 69 | > 10.0E+03 |
| 70 | > 10.0E+03 |
| 71 | > 10.0E+03 |
| 72 | > 10.0E+03 |
| 73 | > 10.0E+03 |
| 74 | > 10.0E+03 |
| 75 | > 10.0E+03 |
| 76 | 381 |
| 77 | 460 |
| 78 | 341 |
| 79 | 84.4 |
| 80 | 701 |
| 81 | 785 |
| 82 | 199 |
| 83 | 344 |
| 84 | 60.1 |
| 85 | > 10.0E+03 |
| 86 | > 10.0E+03 |
| 87 | > 10.0E+03 |
| 88 | 2820 |
| 89 | > 10.0E+03 |
| 90 | > 10.0E+03 |
| 91 | > 10.0E+03 |
| 92 | 2160 |
| 93 | 308 |
| 94 | 2160 |
| 95 | 2780 |
| 96 | 221 |
| 97 | 8060 |
| 98 | > 10.0E+03 |
| 99 | > 10.0E+03 |
| 100 | > 10.0E+03 |
| 101 | > 10.0E+03 |
| 102 | > 10.0E+03 |
| 103 | > 10.0E+03 |
| 104 | > 10.0E+03 |
| 105 | > 10.0E+03 |
| 106 | > 10.0E+03 |
| 107 | > 10.0E+03 |
| 108 | 9520 |
| 109 | > 10.0E+03 |
| 110 | > 10.0E+03 |
| 111 | > 10.0E+03 |
| 112 | 1170 |

| | |
|---|---|
| 113 | 593 |
| 114 | > 10.0E+03 |
| 115 | 4770 |
| 116 | 572 |
| 117 | 1510 |
| 118 | 3120 |
| 119 | 1950 |
| 120 | > 10.0E+03 |
| 121 | > 10.0E+03 |
| 122 | > 10.0E+03 |
| 123 | > 10.0E+03 |
| 124 | > 10.0E+03 |
| 125 | > 10.0E+03 |
| 126 | > 10.0E+03 |
| 127 | > 10.0E+03 |
| 128 | > 10.0E+03 |
| 129 | > 10.0E+03 |
| 130 | > 10.0E+03 |
| 131 | > 10.0E+03 |
| 132 | > 10.0E+03 |
| 133 | > 10.0E+03 |
| 134 | 727 |
| 135 | > 10.0E+03 |

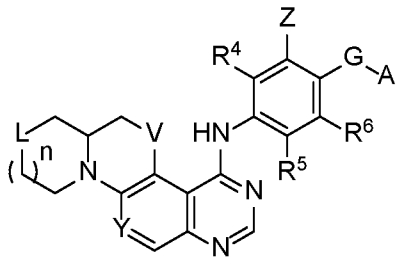
CLAIMS

What is claimed is:

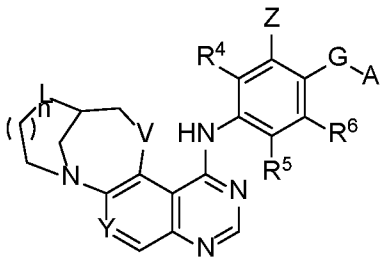
Claim 1. A compound of formula (I-A), (I-B'), (I-C'), or (I-D):



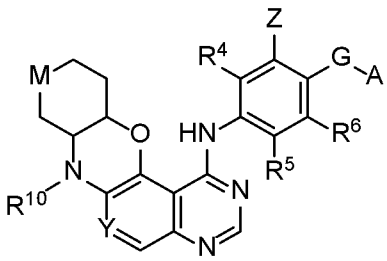
(I-A),



(I-B'),

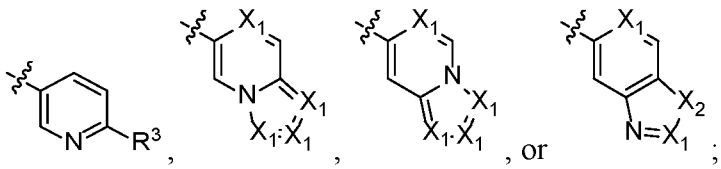


(I-C'), or



(I-D),

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

M is NH or N($C_1$-$C_6$ alkyl);

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -S(O)$_2$-, or $CH_2$;

V is O, S, or $NR^2$;

each $X_1$ is independently N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, -$OCH_3$, or $C_1$-$C_2$ alkyl;

$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

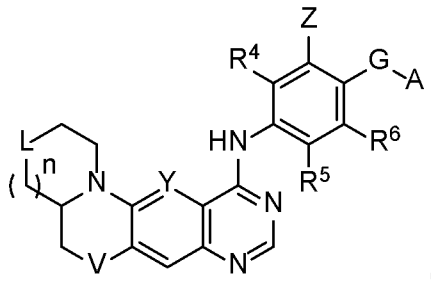
$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, -$CD_3$, or $C_3$-$C_6$ cycloalkyl;

$R^4$, $R^5$, and $R^6$ are each independently -H or halogen; and

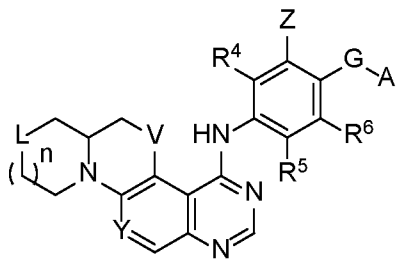
$R^{10}$ is -H or $C_1$-$C_6$ alkyl.

Claim 2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-A)



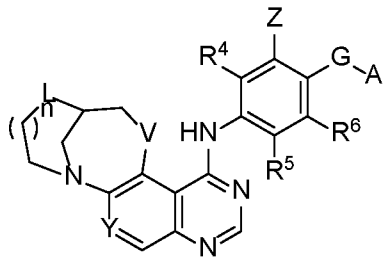

(I-A).

Claim 3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-B')



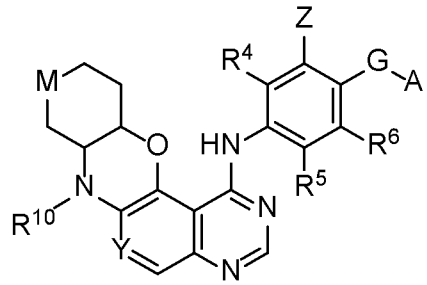

(I-B').

Claim 4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-C')

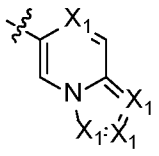
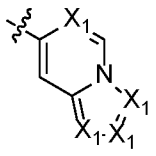
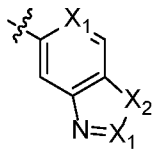


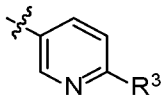
(I-C').

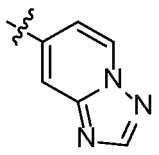
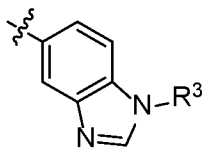
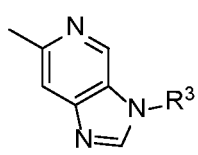
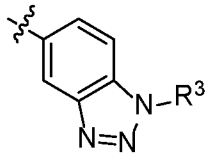
Claim 5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-D)



(I-D).

Claim 6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein A is  ,  , or  .

Claim 7. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein A is  .

Claim 8. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein A is  ,  ,  , or  .

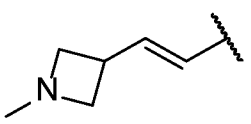
Claim 9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein $R^3$ is -H or -$CH_3$.

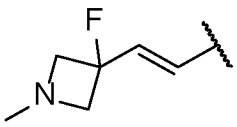
Claim 10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein L is N-E.

Claim 11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein E is -C(O)-$R^1$.

Claim 12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 4 membered heterocycle or -$N(CH_3)_2$, wherein the 4 membered heterocycle is optionally substituted by -F or -$CH_3$.

Claim 13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein $R^1$
is -$CH_3$, -CH=$CH_2$, -CH=CH-$CH_2$-$N(CH_3)_2$, -C≡C-$CH_3$, -CH=CH-$CH(CH_3)$-$N(CH_3)_2$,



, or


.

Claim 14. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein E is -H, -C(O)O-($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro.

Claim 15. The compound of any one of claims 1 to 10 and 14, or a pharmaceutically acceptable salt thereof, wherein E is -H, -$CH_3$, -$CH_2CH_3$, -$CH_2CH_3OCH_3$, or -C(O)O-$CH_3$.

Claim 16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein G is -O-.

Claim 17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein G is -C(=O)-.

Claim 18. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein G is -S-, -S(O)-, or -$S(O)_2$-.

Claim 19. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein G is -$CH_2$-.

Claim 20. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein V is O.

Claim 21. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein V is S.

Claim 22. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein V is $NR^2$

Claim 23. The compound of any one of claims 1 to 22, wherein Y is N.

Claim 24. The compound of any one of claims 1 to 22, wherein Y is C-$R^y$.

Claim 25. The compound of any one of claims 1 to 22 and 24, or a pharmaceutically acceptable salt thereof, wherein Y is C-$R^y$, and $R^y$ is -H.

Claim 26. The compound of any one of claims 1 to 22 and 24, or a pharmaceutically acceptable salt thereof, wherein Y is C-$R^y$, and $R^y$ is -F.

Claim 27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Z is -H, halogen, -C≡CH, $-OCH_3$, or $-CH_3$.

Claim 28. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein Z is -H, -F, or $-CH_3$.

Claim 29. The compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is -H.

Claim 30. The compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is -F.

Claim 31. The compound of any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein $R^5$ is -H.

Claim 32. The compound of any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein $R^5$ is -F.

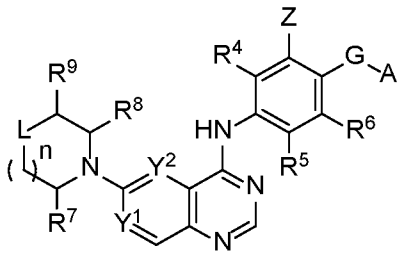
Claim 33. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is -H.

Claim 34. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is -F.

Claim 35. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^{10}$ is -H.

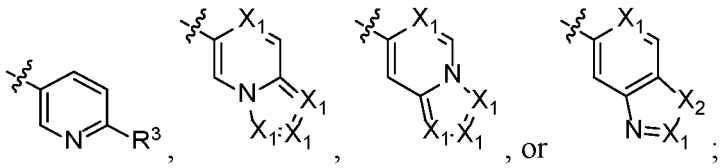
Claim 36. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^{10}$ is $-CH_3$.

Claim 37. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is  ;

L is N-E, $CH_2$, O, or a bond;

either $Y^1$ is C-$R^{Y1}$, $Y^2$ is Y, $R^8$ is -H, $R^9$ is -H, and $R^{Y1}$ is taken together with $R^7$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^1$,

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^9$ is -H, and $R^{Y2}$ is taken together with $R^8$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$, or

$Y^2$ is C-$R^{Y2}$, $Y^1$ is Y, $R^7$ is -H, $R^8$ is -H, and $R^{Y2}$ is taken together with $R^9$ to form -V-$CH_2$-, wherein V attaches to the carbon of $Y^2$;

n is 0 or 1;

E is -H, -C(O)O-($C_1$-$C_6$ alkyl), -C(O)-$R^1$, or $C_1$-$C_6$ alkyl, wherein the $C_1$-$C_6$ alkyl is optionally substituted by $C_1$-$C_6$ alkoxy or 1 to 4 fluoro;

G is -O-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, or $CH_2$;

V is O, S, or $NR^2$;

$X_1$ is N or CH;

$X_2$ is O, S, or N-$R^3$;

Y is independently N or C-$R^y$, wherein $R^y$ is -H or -F;

Z is -H, halogen, -C≡CH, $-OCH_3$, or $C_1$-$C_2$ alkyl;

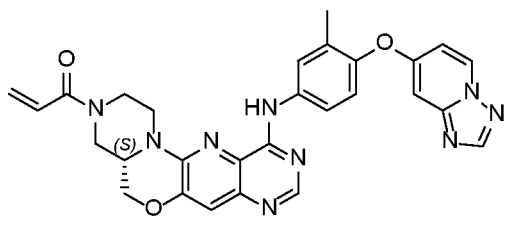
$R^1$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, each of which is independently optionally substituted by 3-6 membered heterocycle or -$NR^{1a}R^{1b}$, wherein each $R^{1a}$ and $R^{1b}$ are independently $C_1$-$C_3$ alkyl, and wherein the 3-6 membered heterocycle is optionally substituted by halogen or $C_1$-$C_6$ alkyl;

$R^2$ is $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, each of which is independently optionally substituted by 1 to 4 fluoro;

$R^3$ is -H, $C_1$-$C_6$ alkyl, $-CD_3$, or $C_3$-$C_6$ cycloalkyl; and

$R^4$, $R^5$, and $R^6$ are each independently -H or halogen.

Claim 38. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

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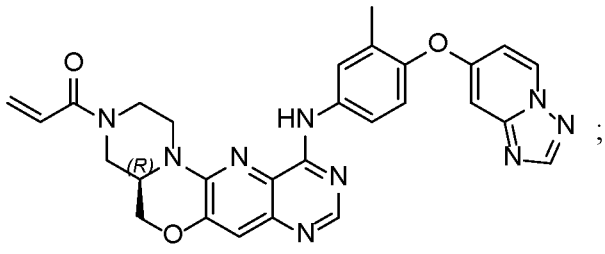


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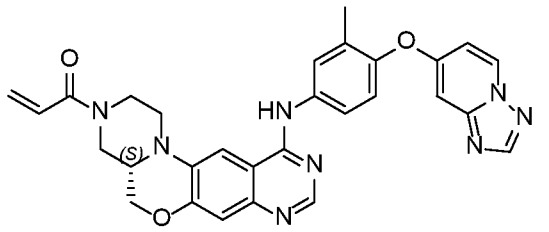
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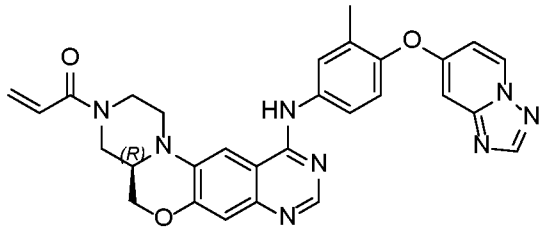
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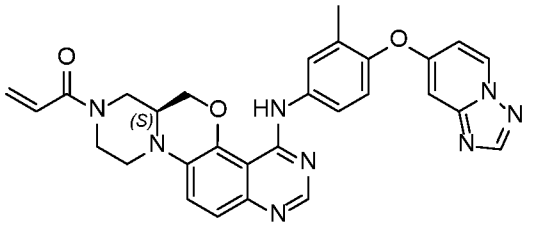
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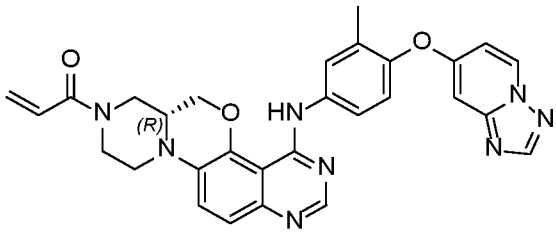
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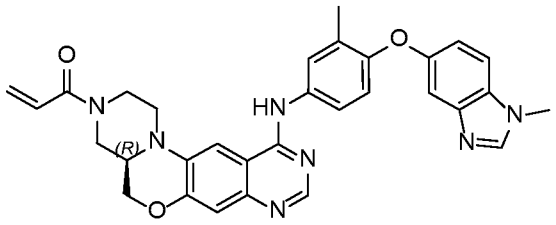
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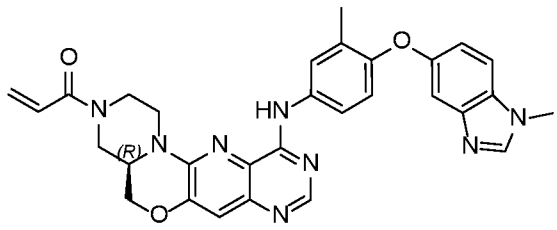
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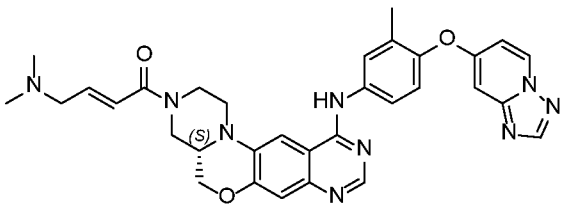
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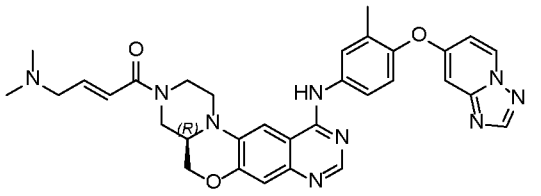
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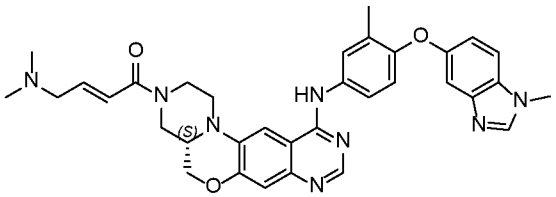
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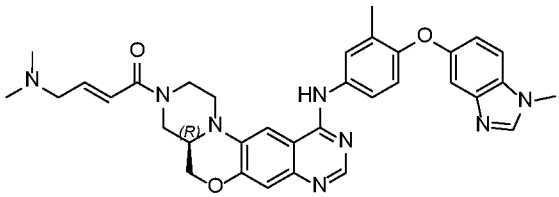
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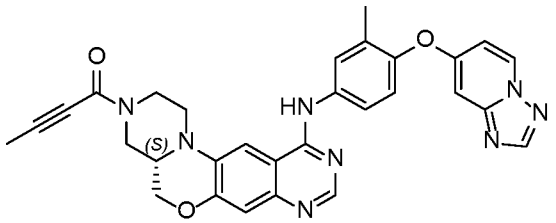
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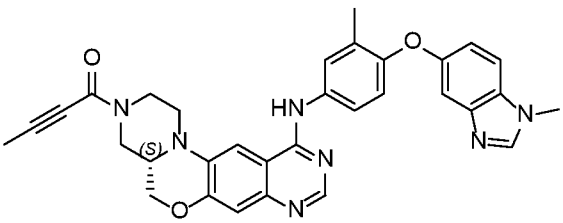
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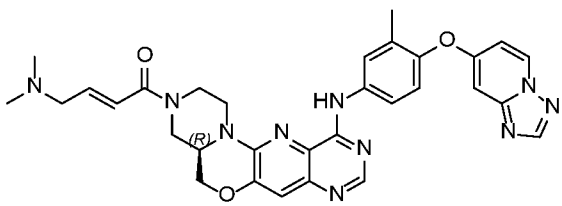
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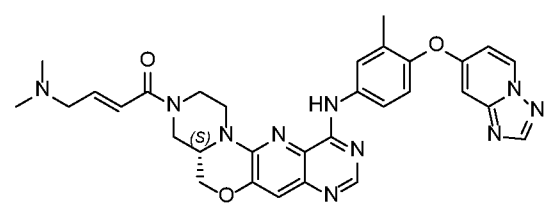
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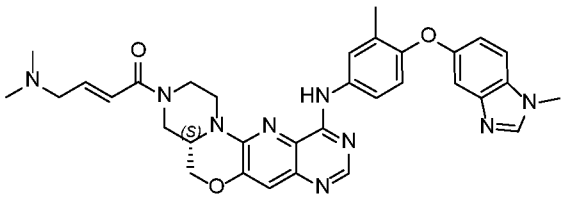
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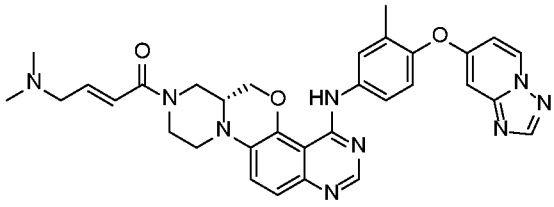
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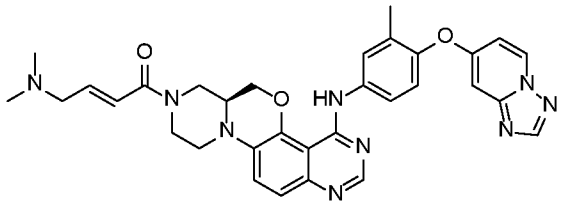
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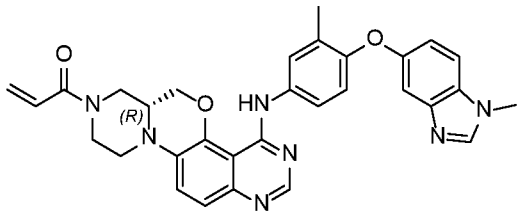
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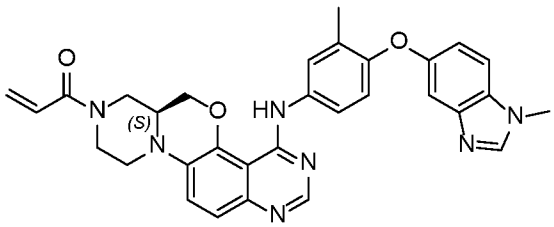
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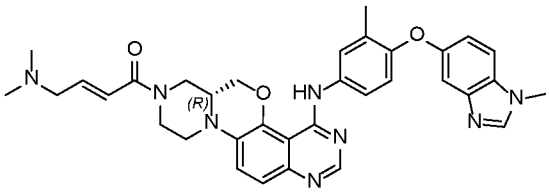
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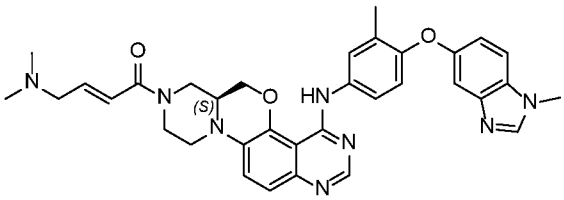
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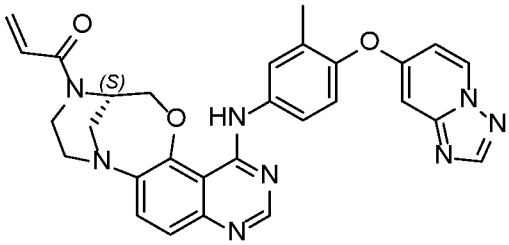
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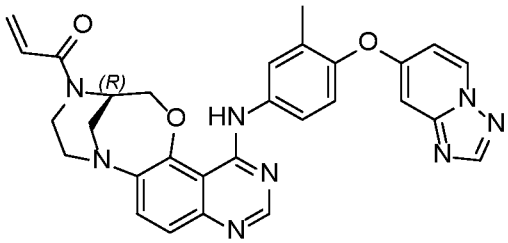
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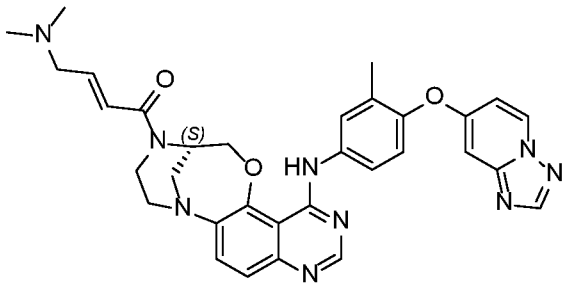
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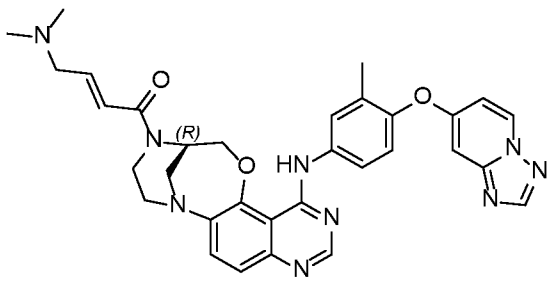
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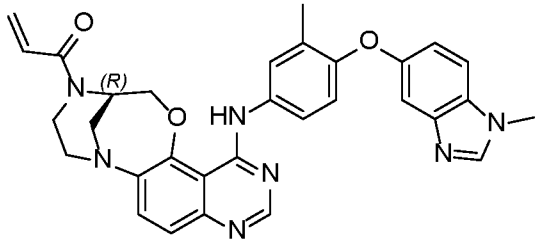
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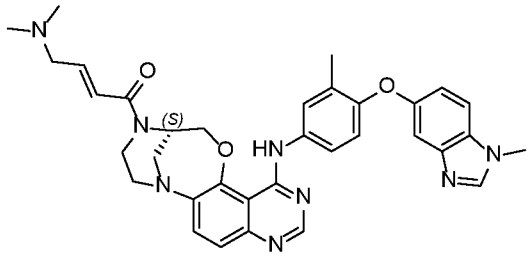
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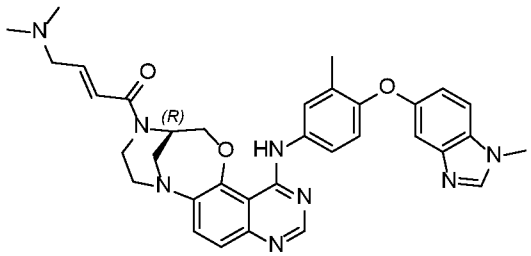
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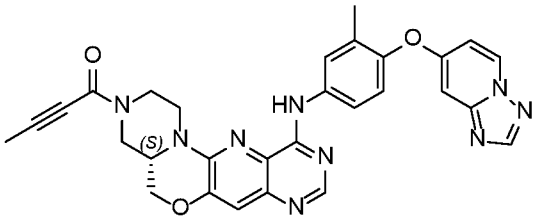
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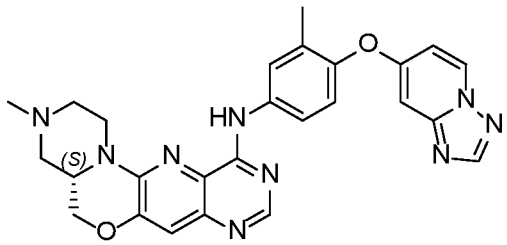
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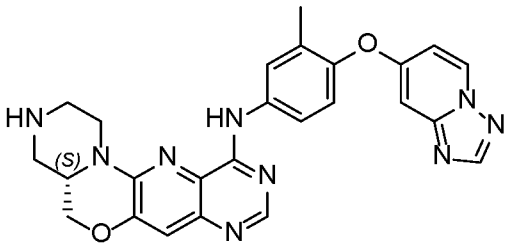
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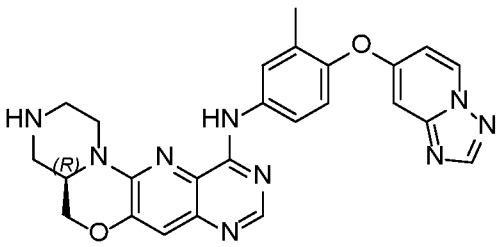
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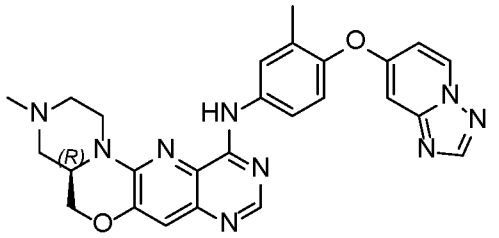
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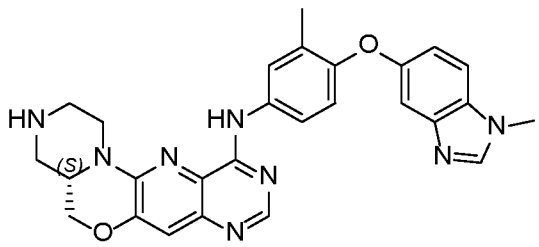
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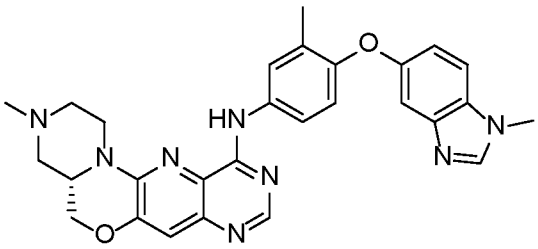
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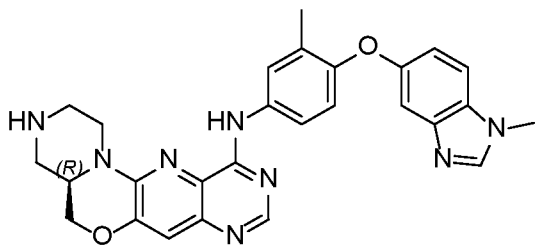
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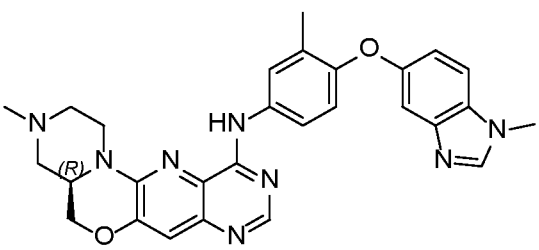
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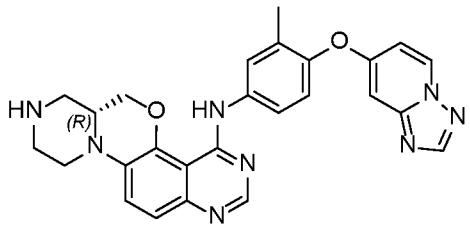
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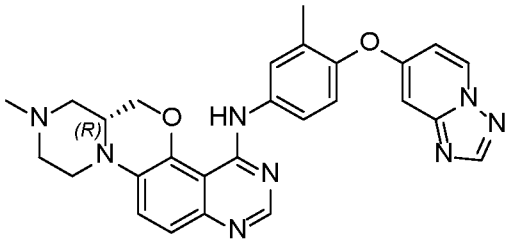
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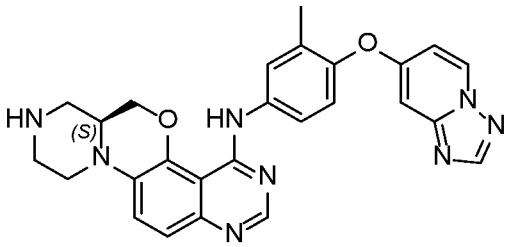
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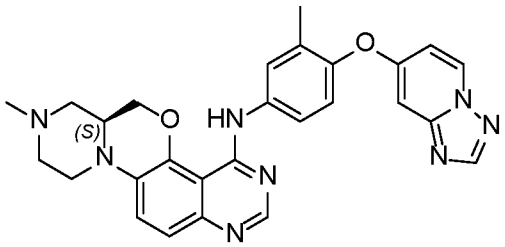
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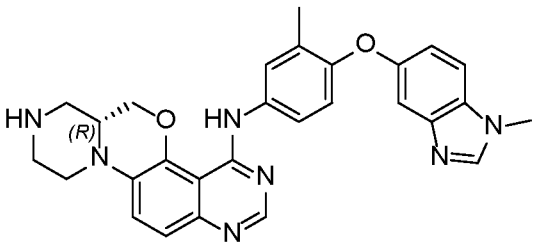
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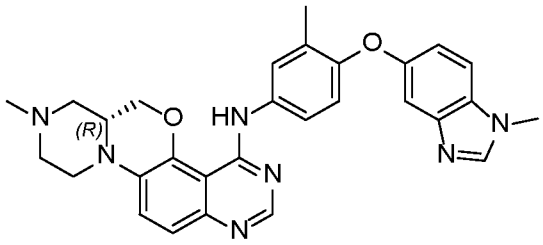
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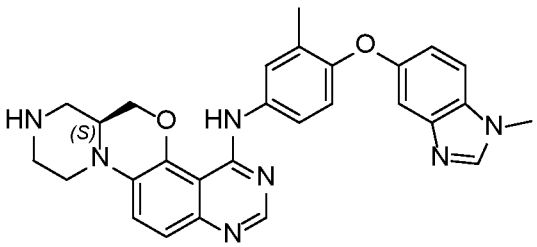
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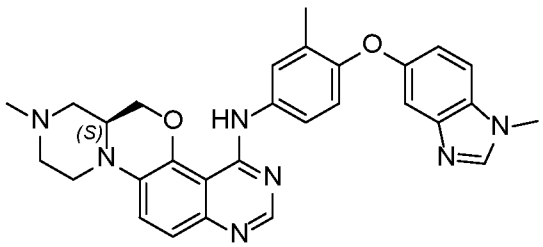
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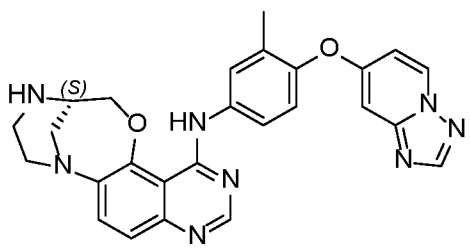
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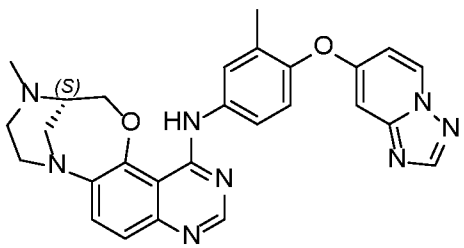
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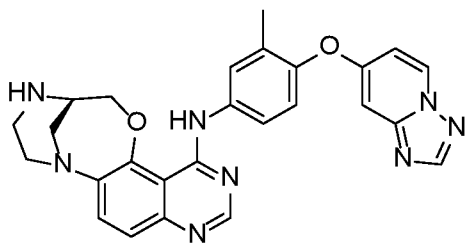
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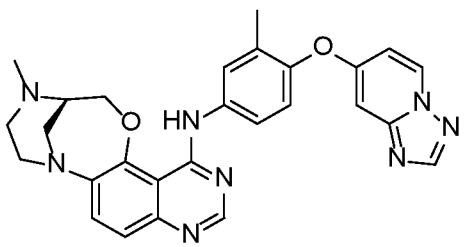
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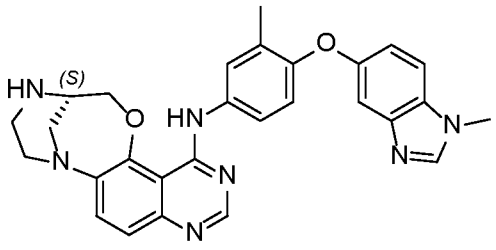
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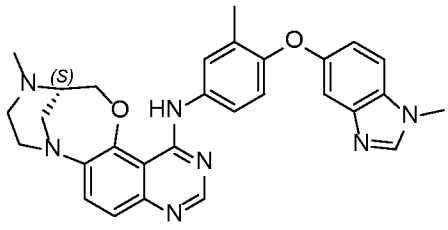
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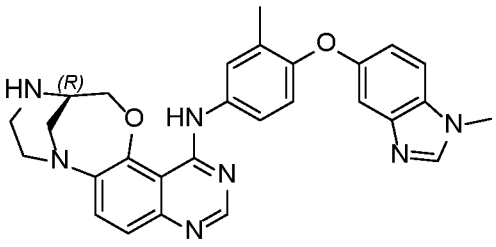
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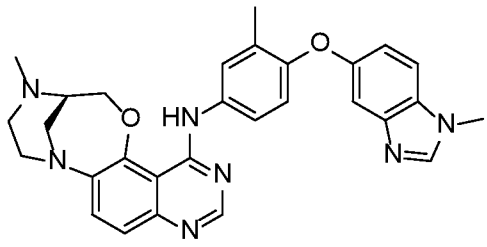
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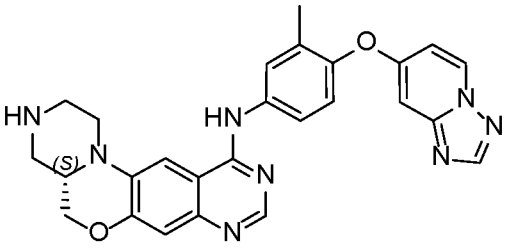
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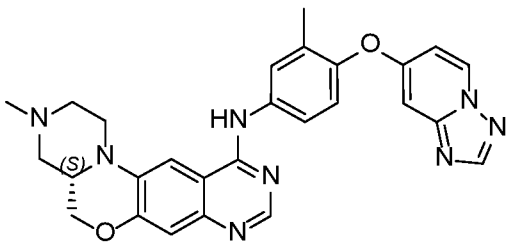
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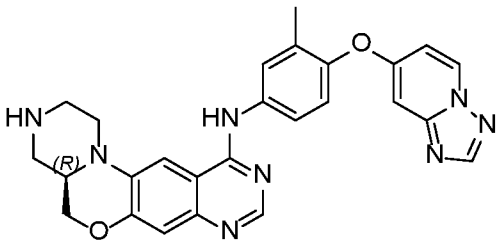
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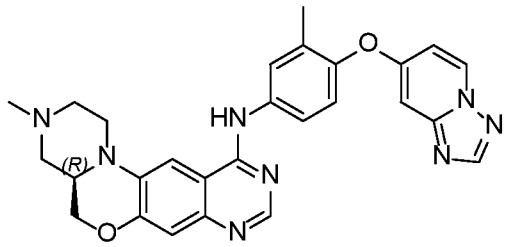
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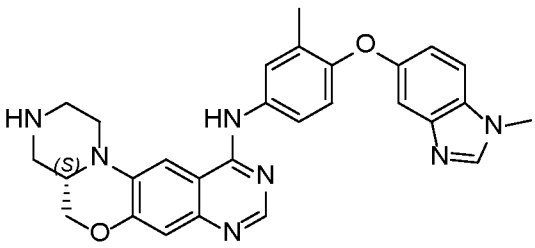
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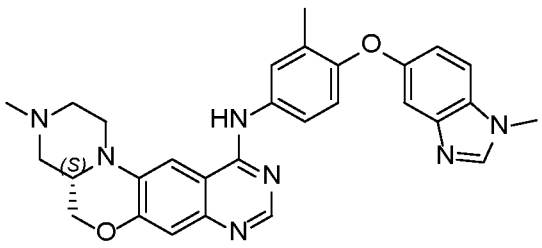
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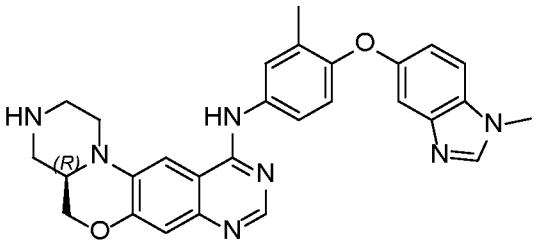
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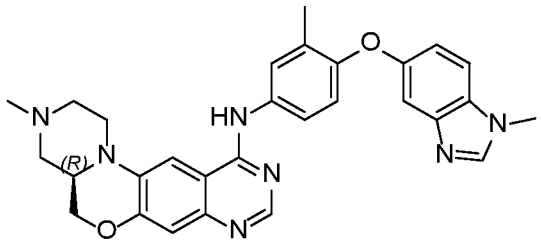
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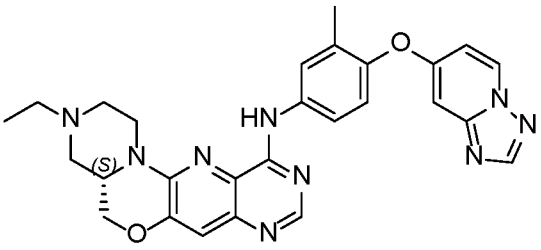
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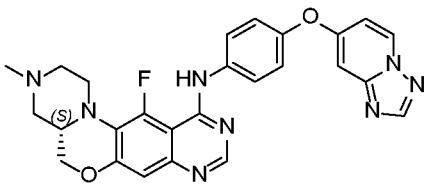
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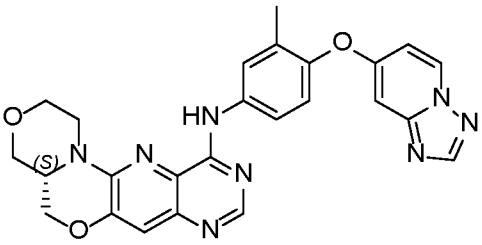
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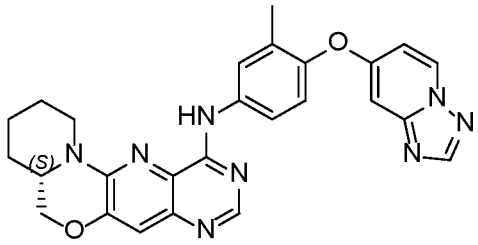
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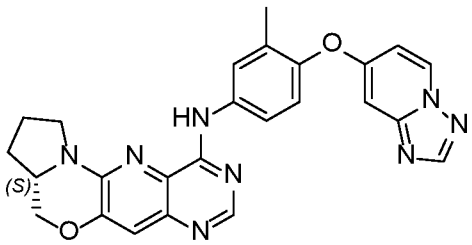
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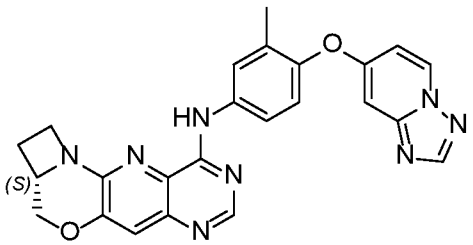
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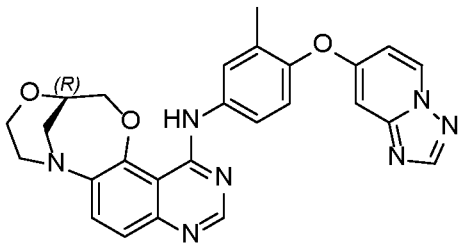
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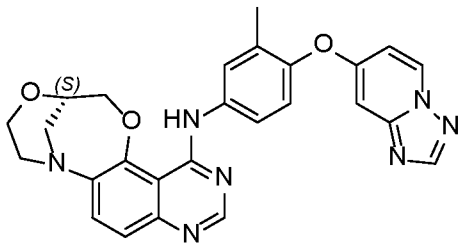
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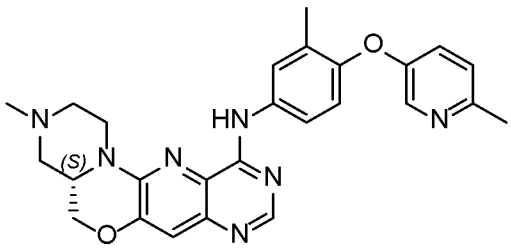
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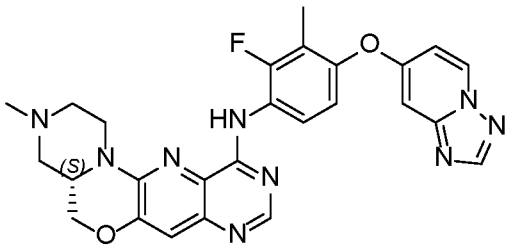
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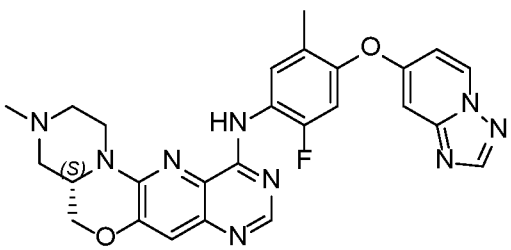
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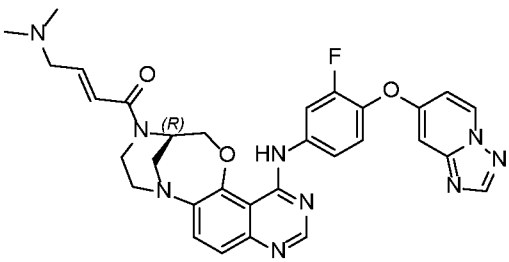
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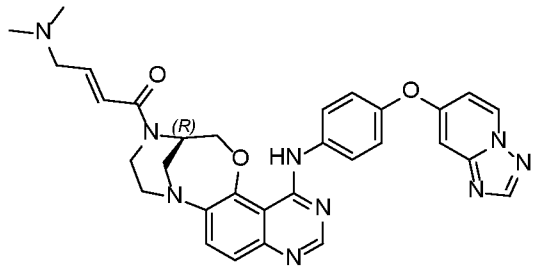
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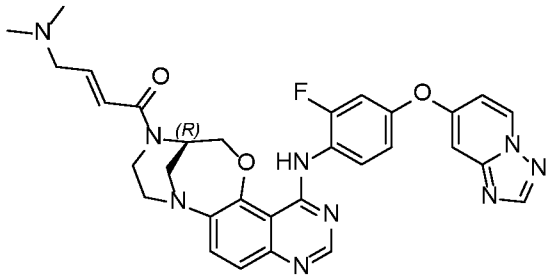
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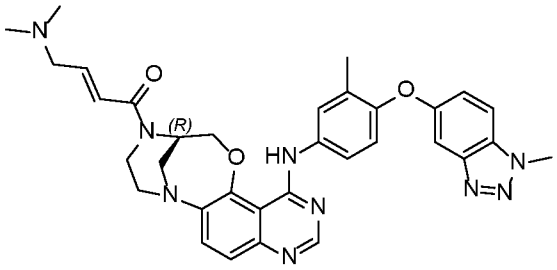
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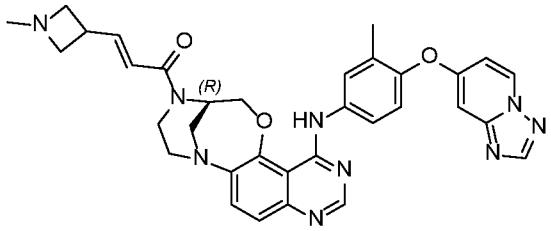
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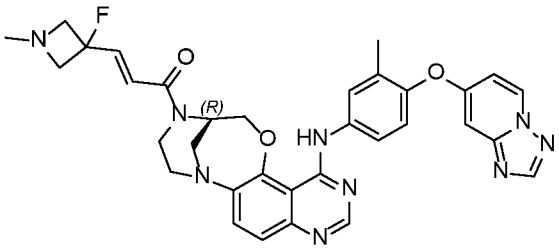
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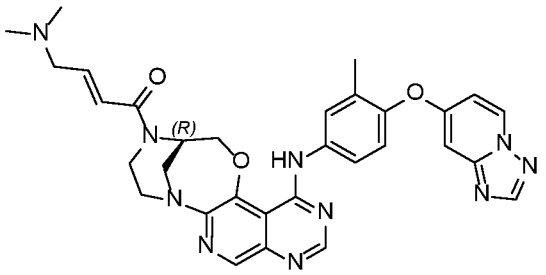
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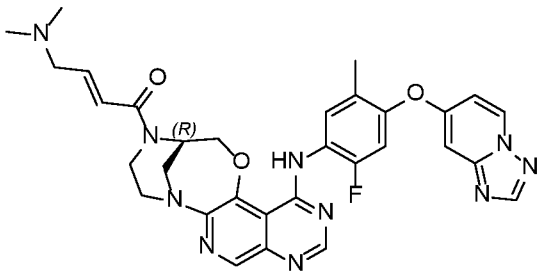
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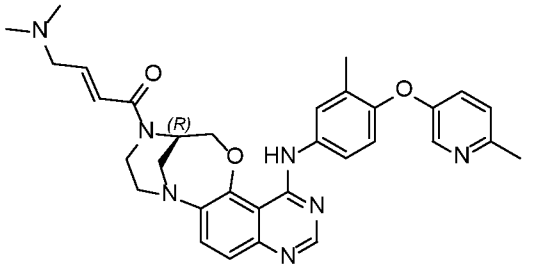
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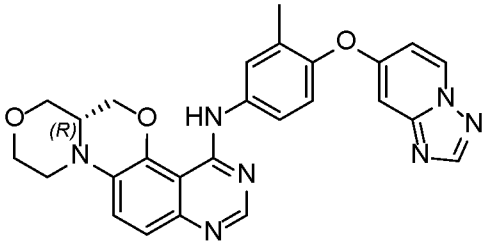
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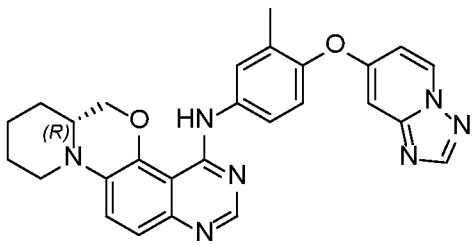
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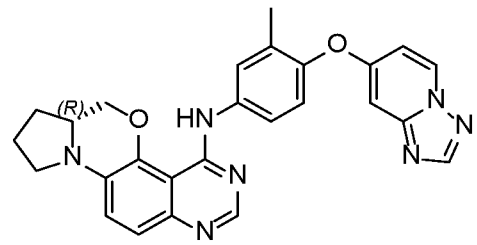
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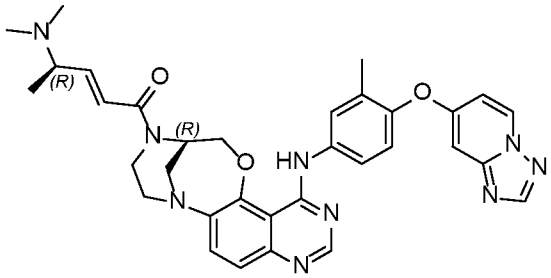
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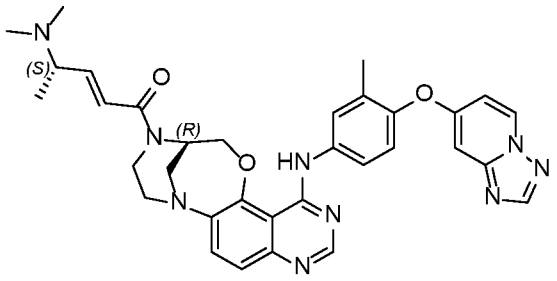
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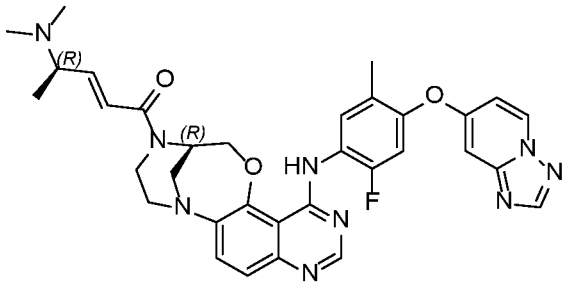
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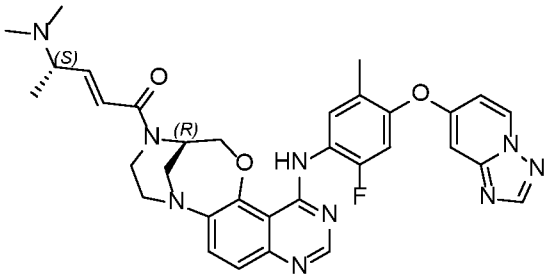
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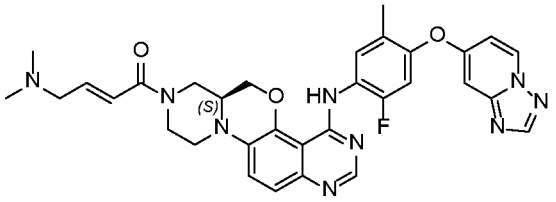
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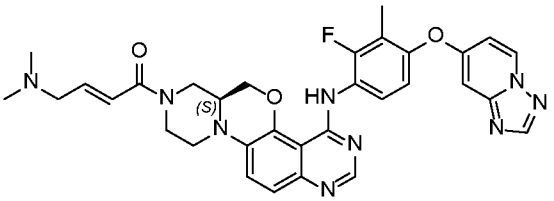
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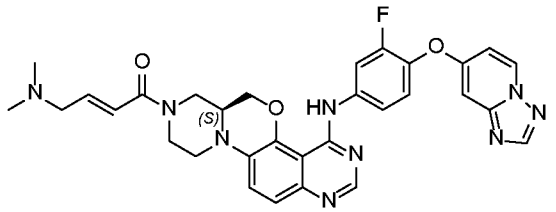
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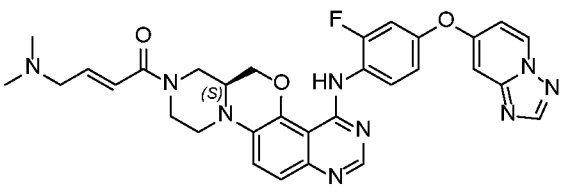
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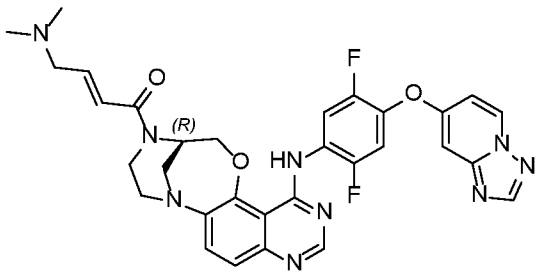
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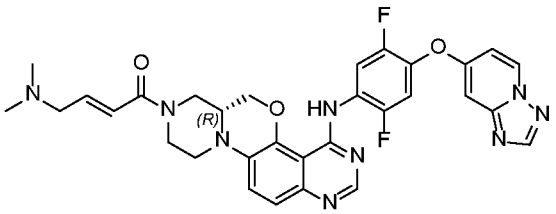
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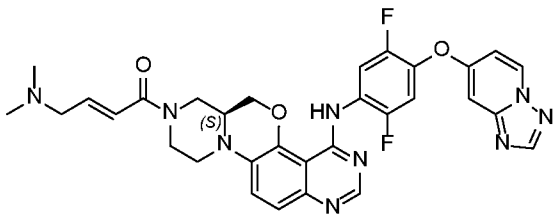
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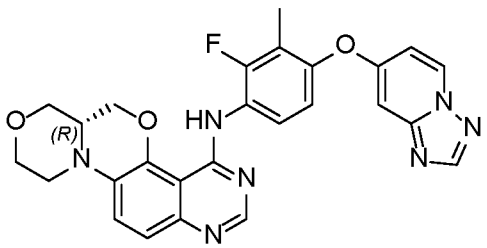
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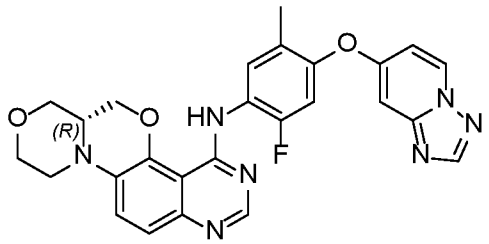
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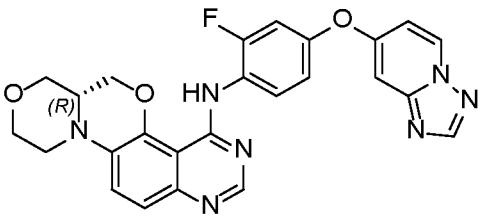
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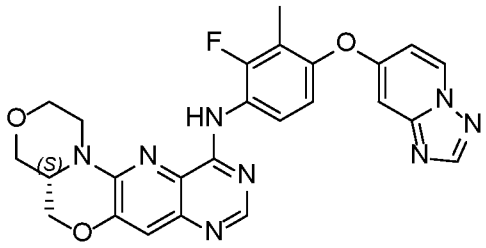
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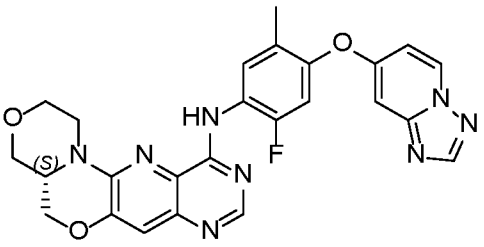
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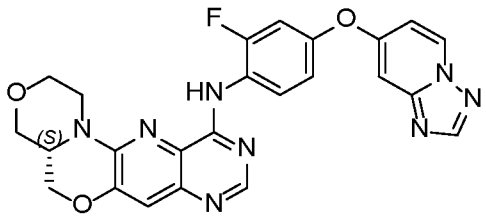
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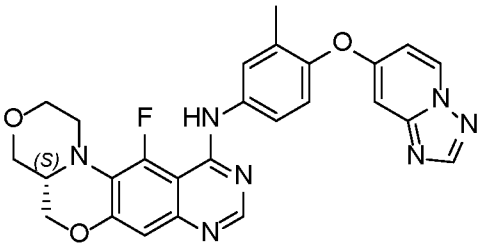
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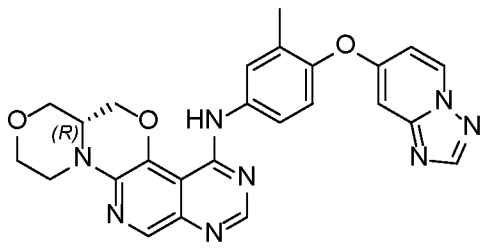
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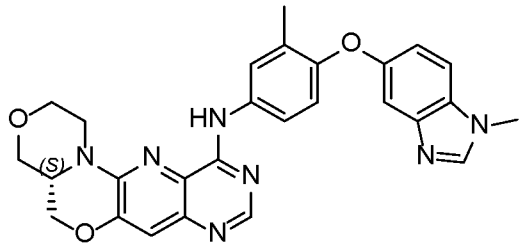
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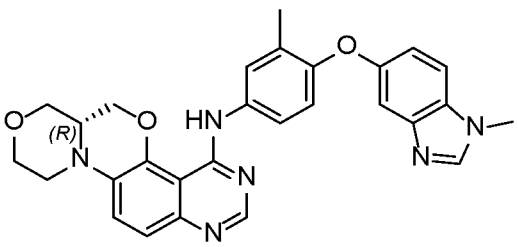
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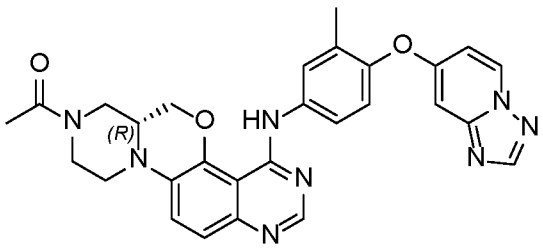
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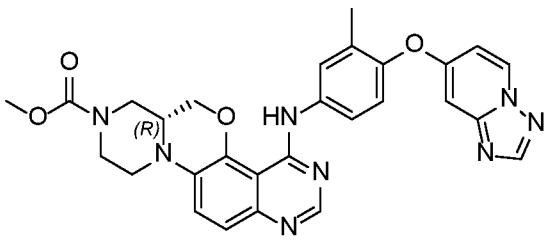
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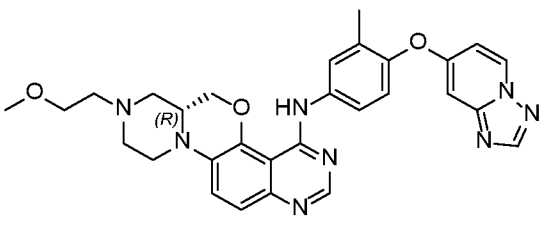
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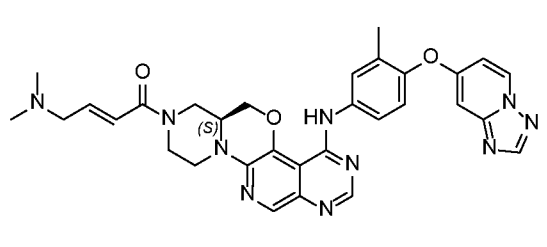
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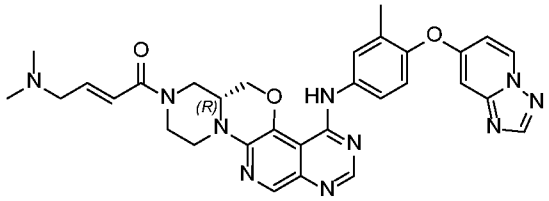
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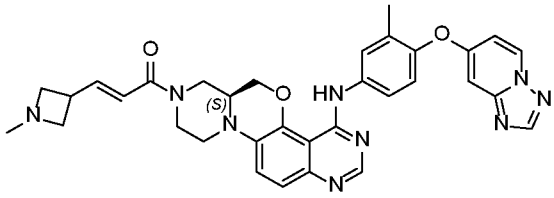
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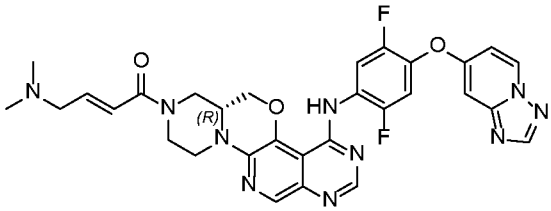
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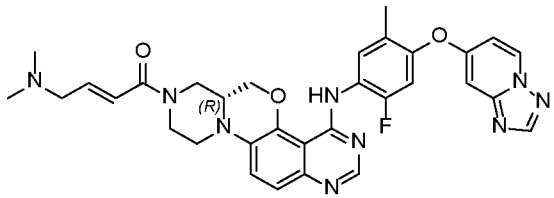
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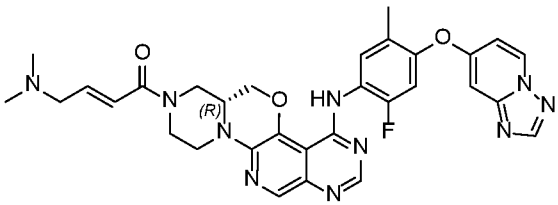
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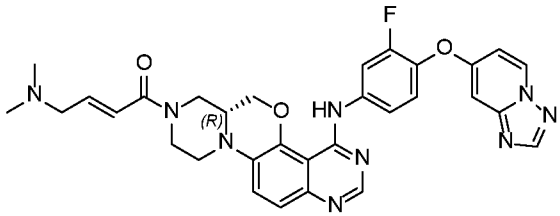
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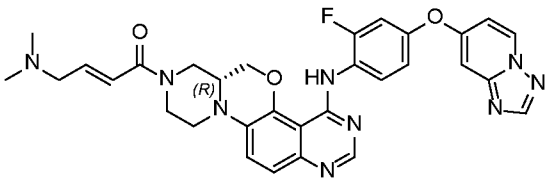
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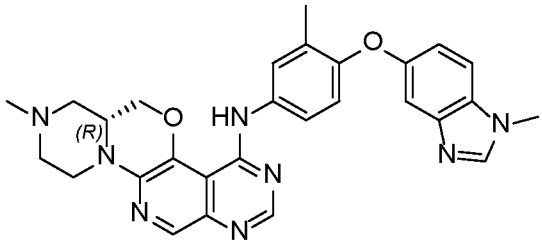
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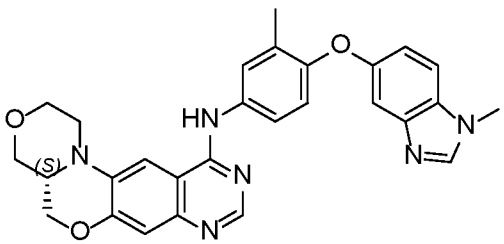
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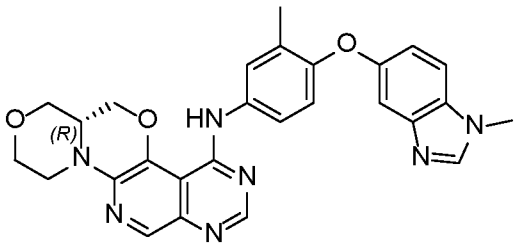
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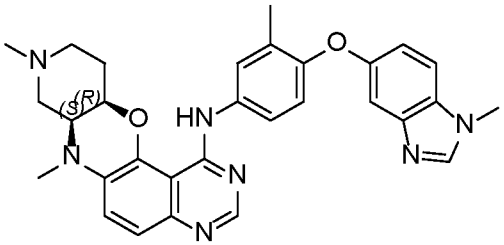
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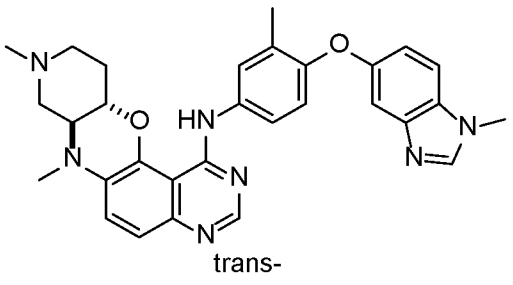
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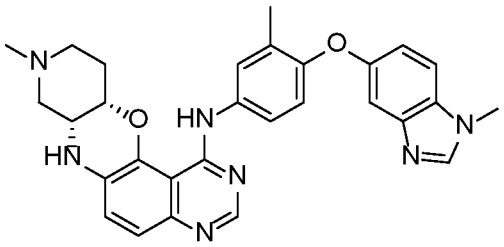
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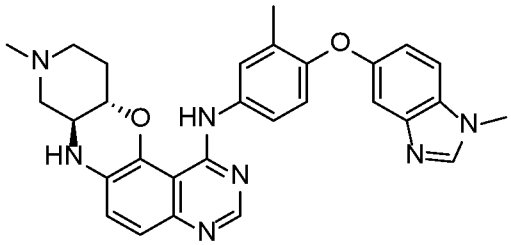
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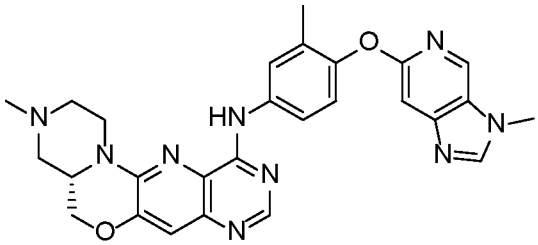
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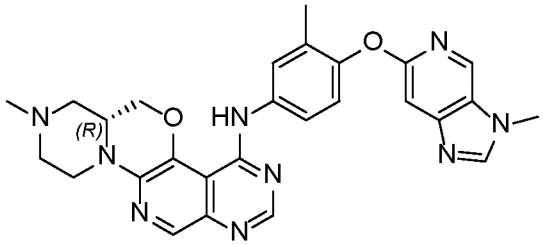
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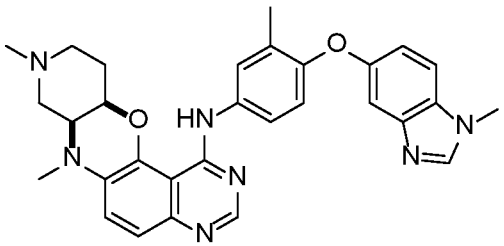
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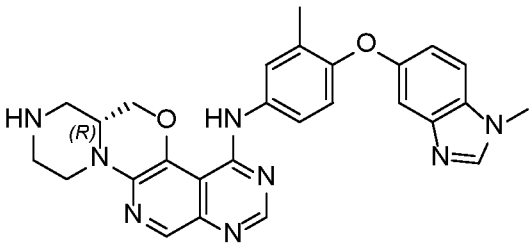
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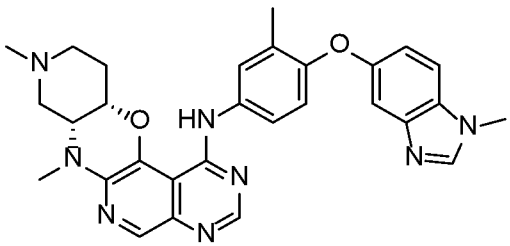
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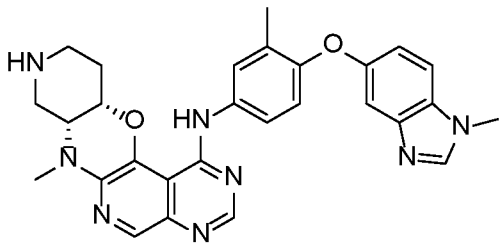
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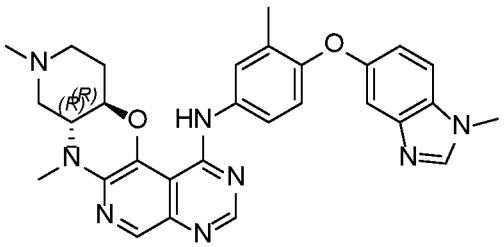
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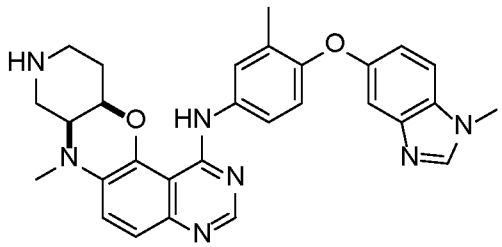
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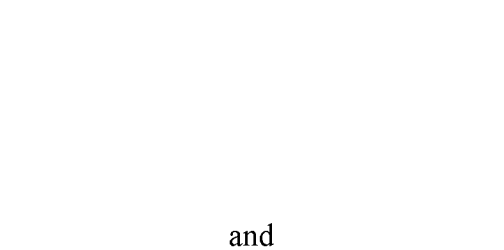
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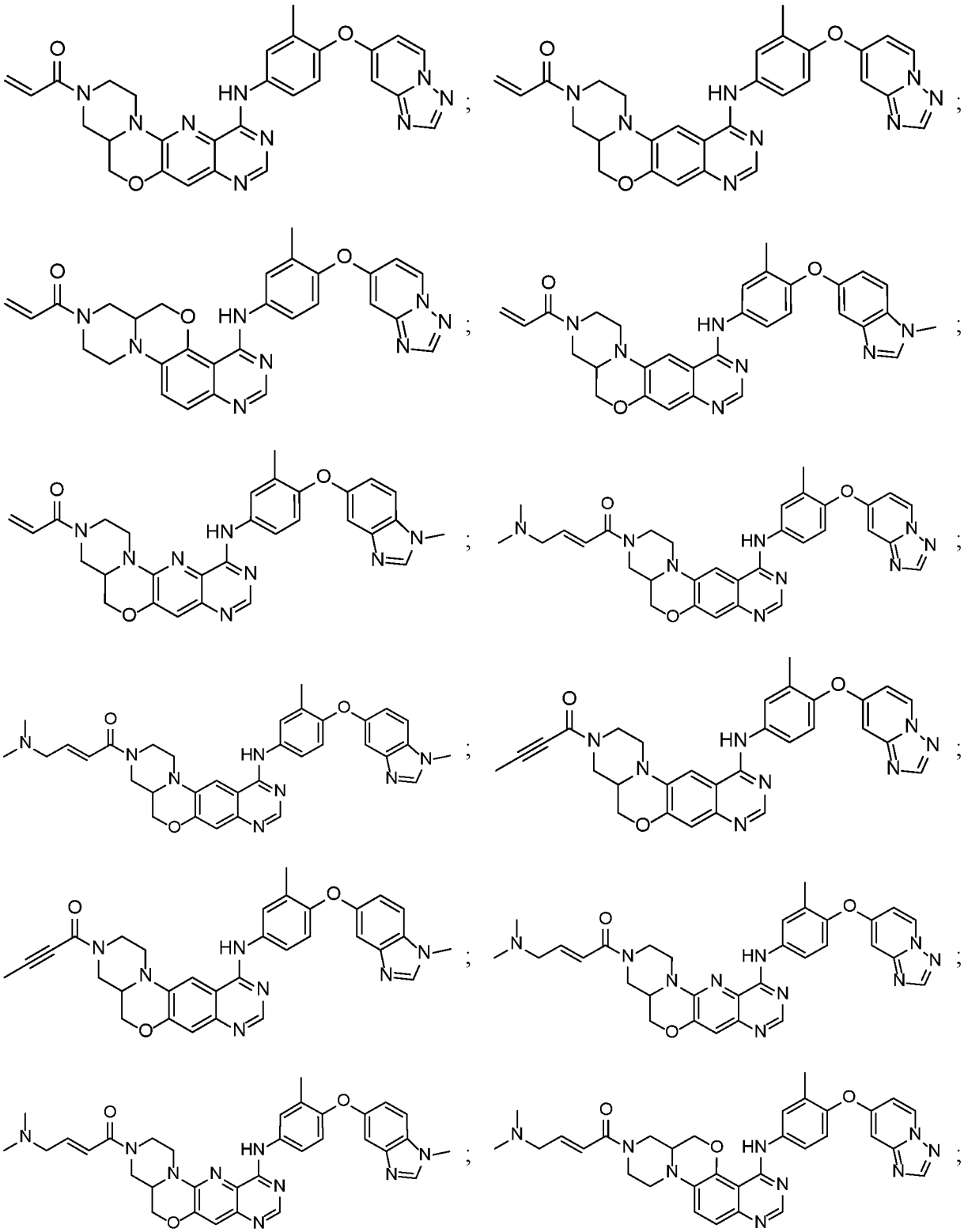
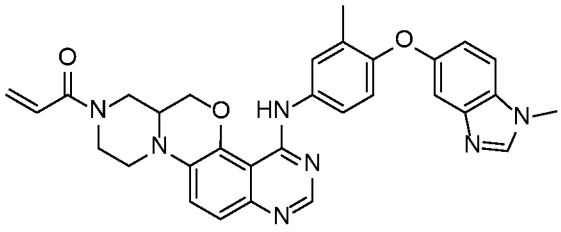
and

Claim 39. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

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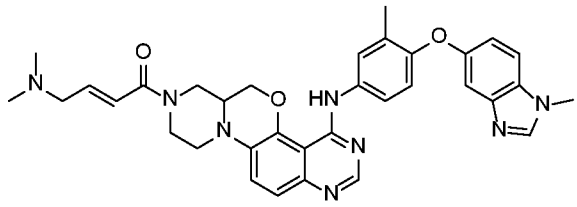
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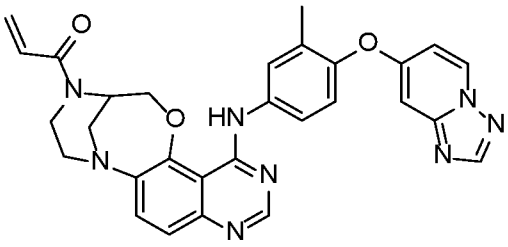
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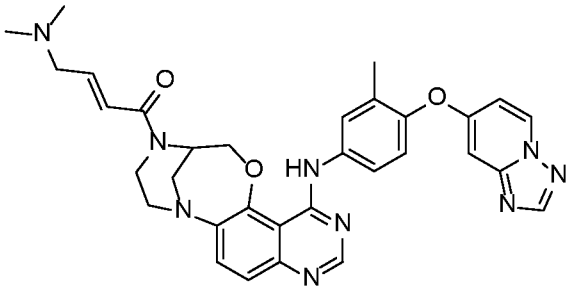
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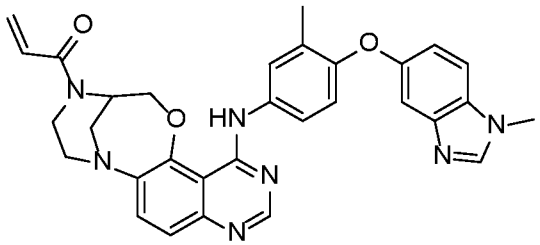
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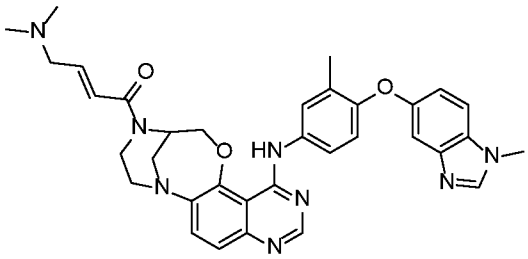
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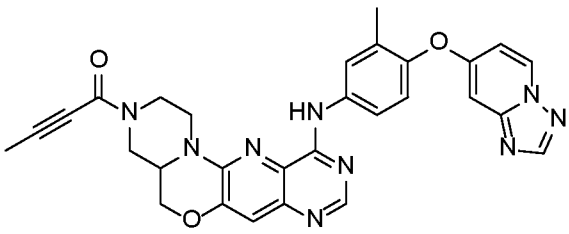
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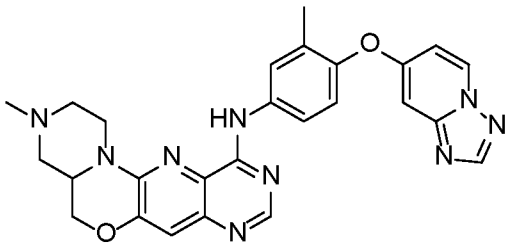
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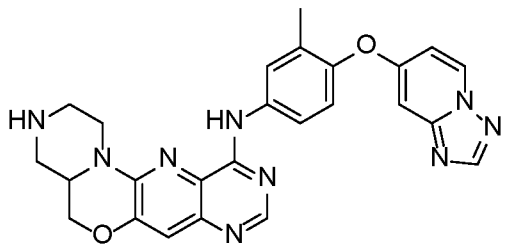
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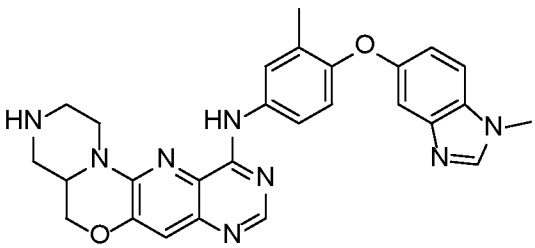
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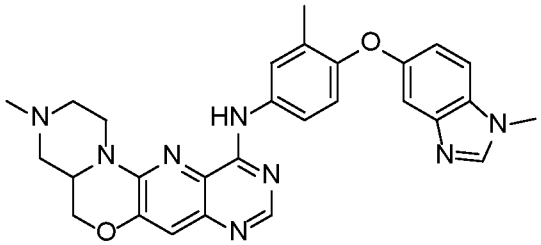
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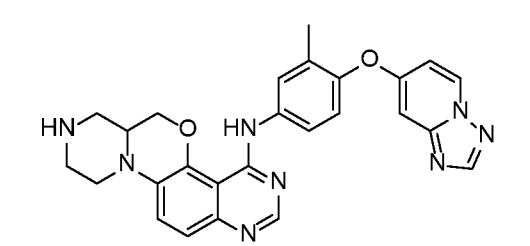
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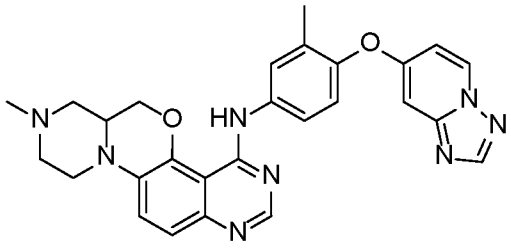
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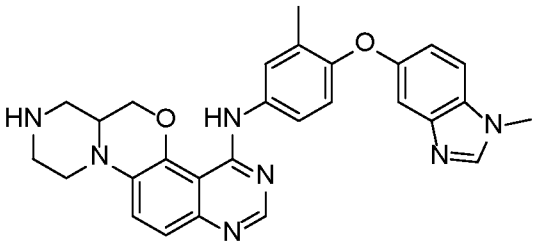
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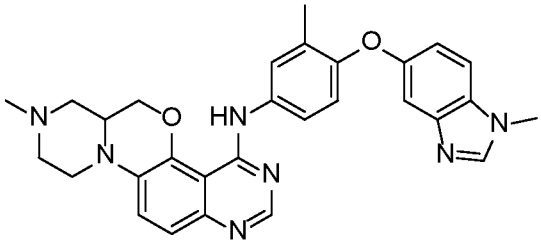
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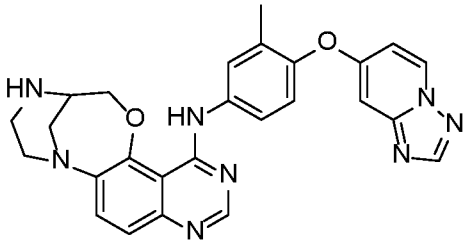
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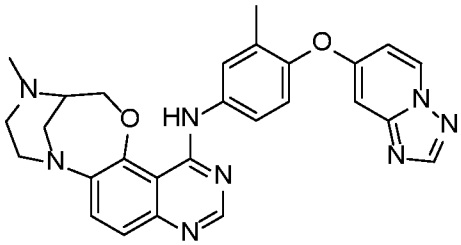
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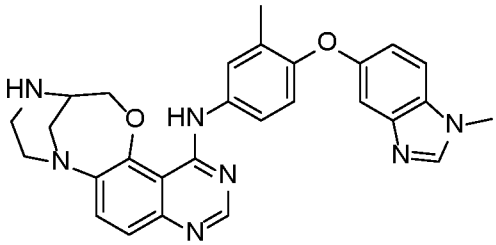
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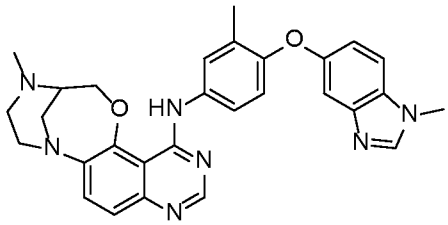
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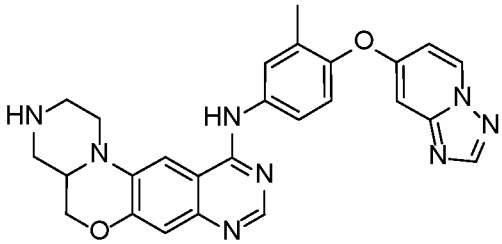
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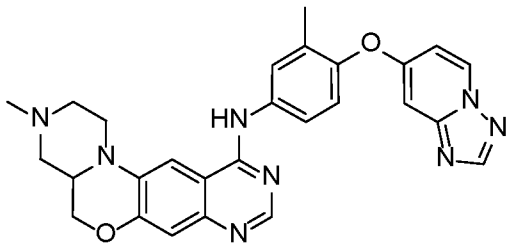
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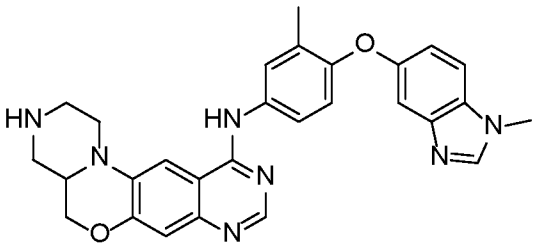
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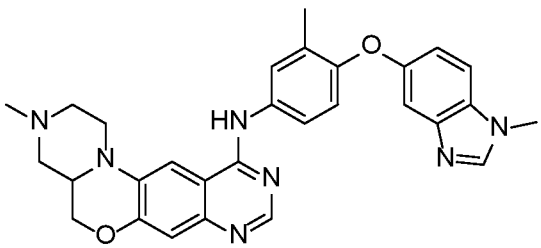
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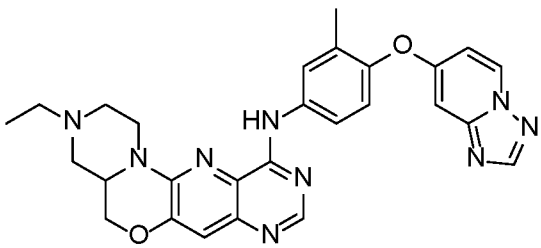
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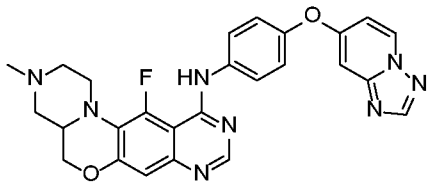
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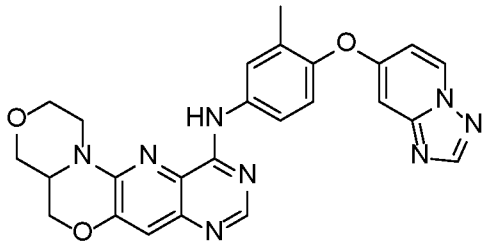
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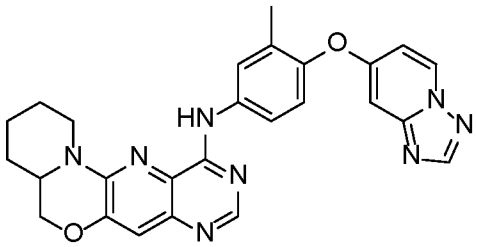
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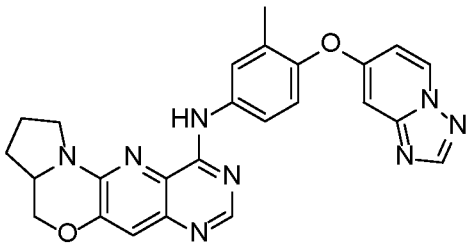
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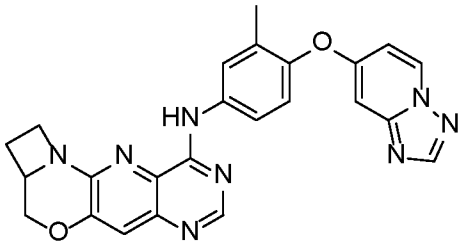
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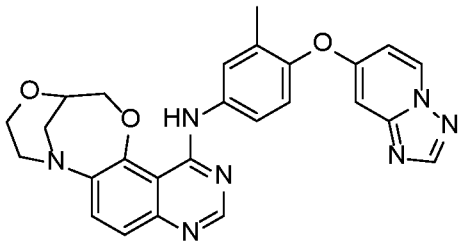
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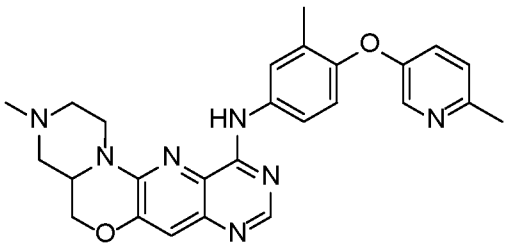
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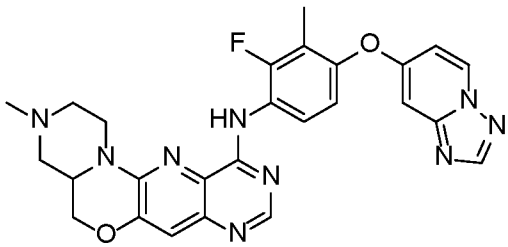
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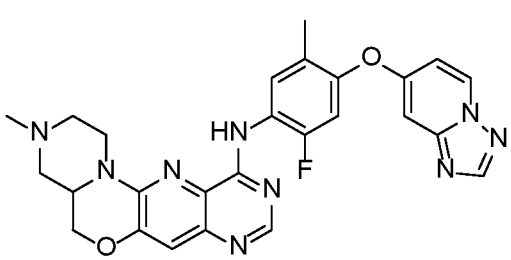
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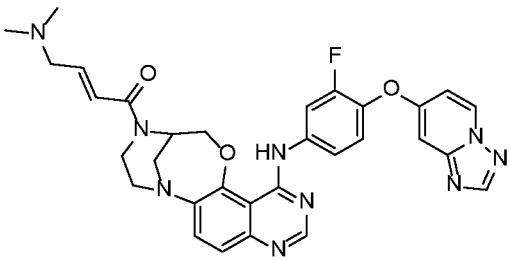
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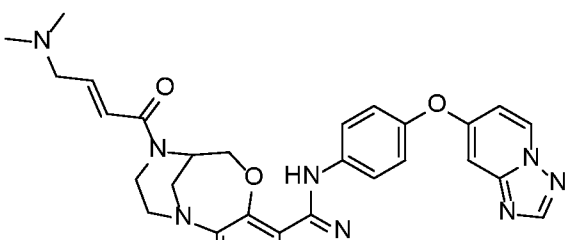
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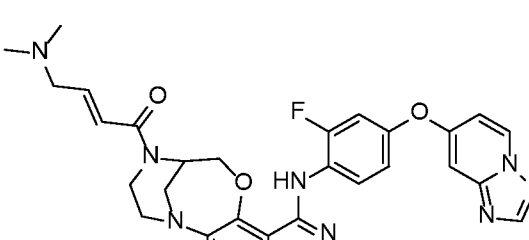
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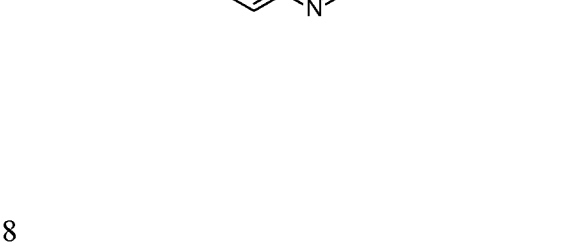
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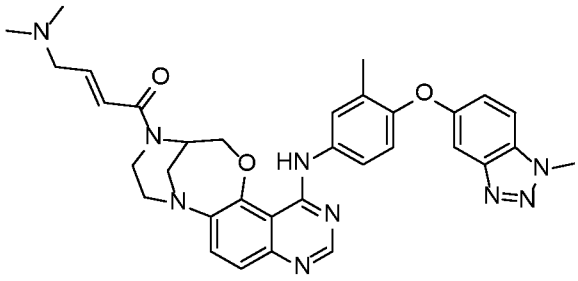
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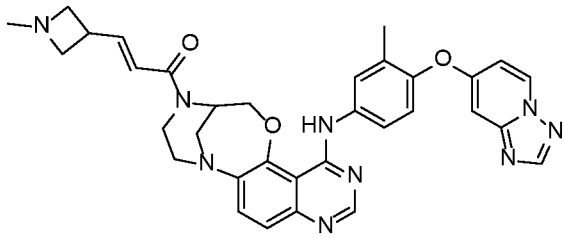
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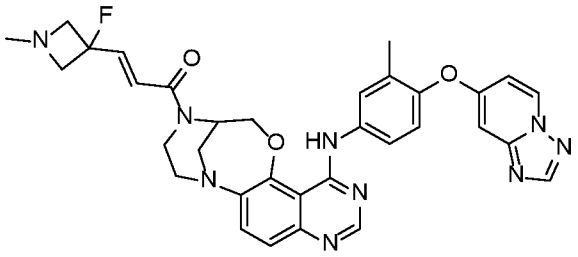
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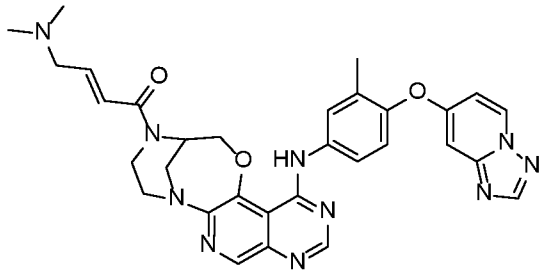
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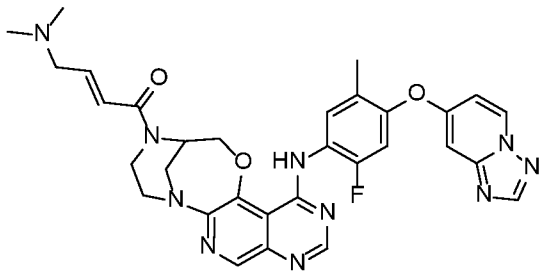
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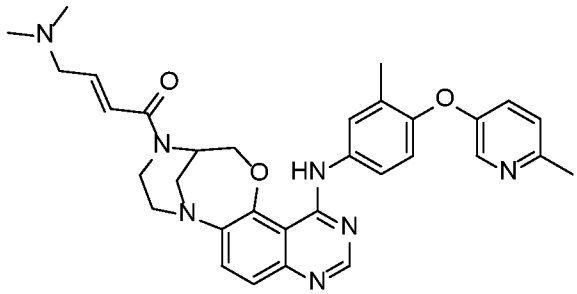
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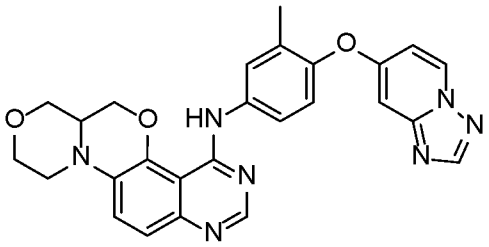
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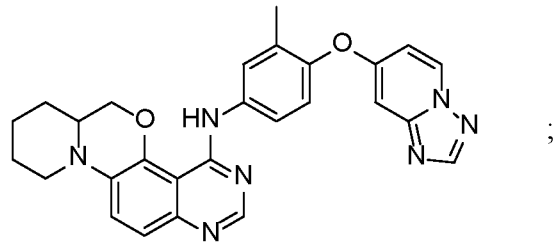
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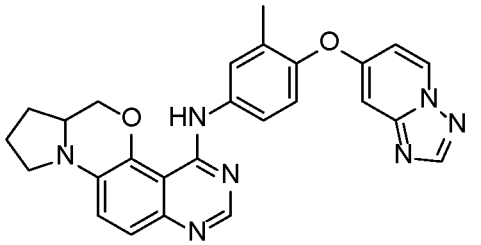
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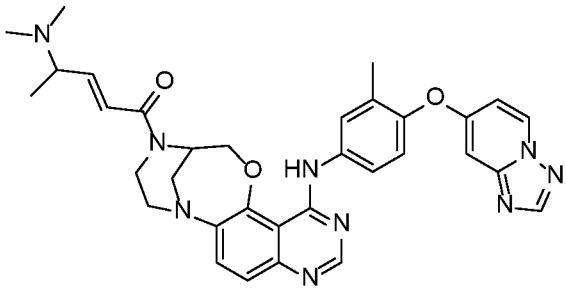
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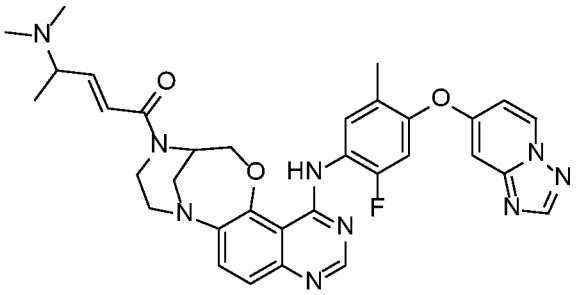
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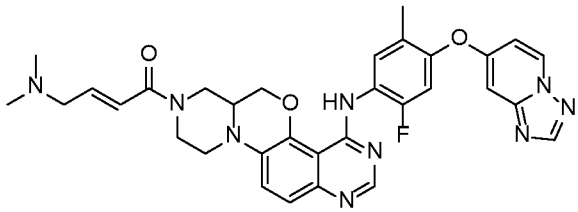
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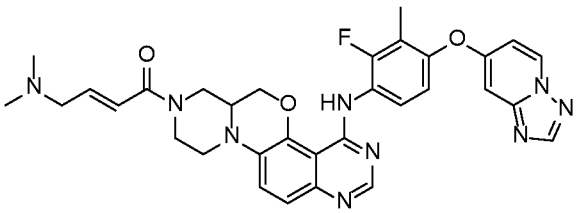
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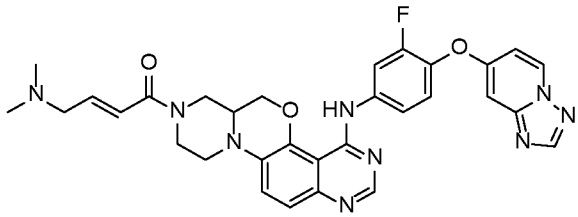
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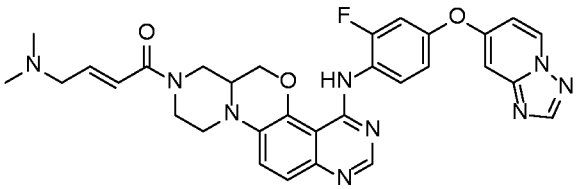
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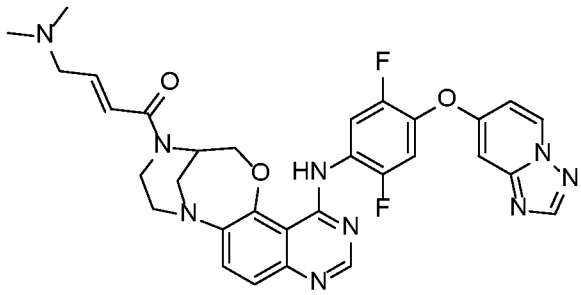
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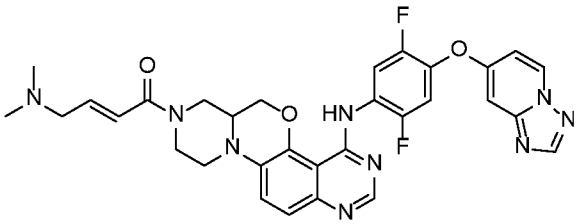
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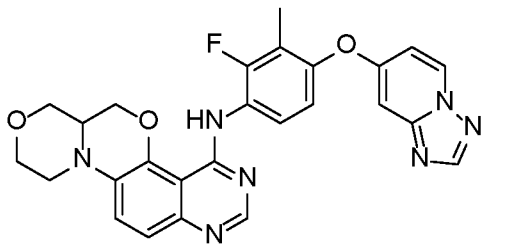
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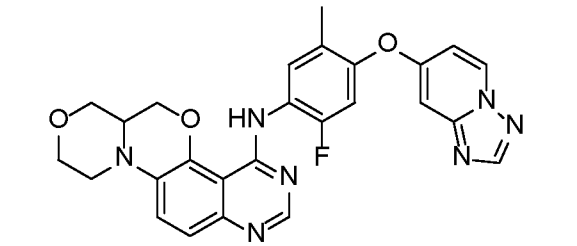
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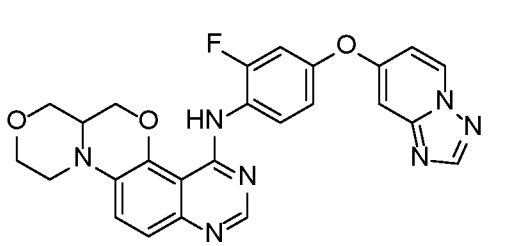
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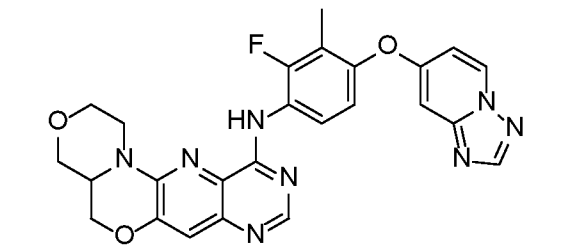
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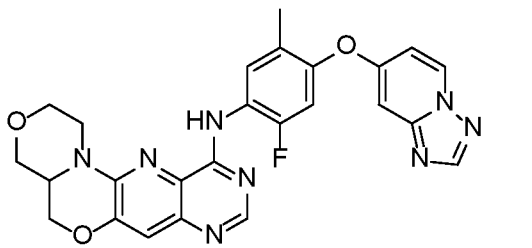
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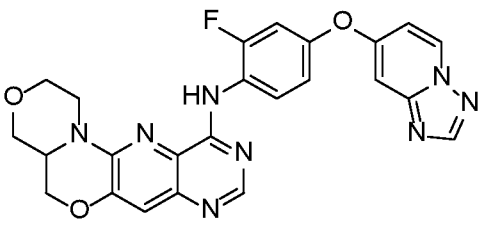
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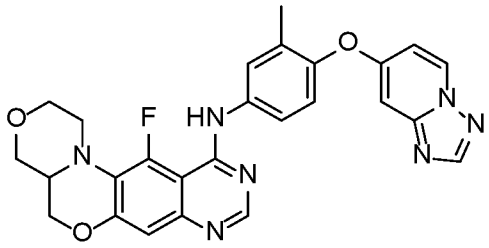
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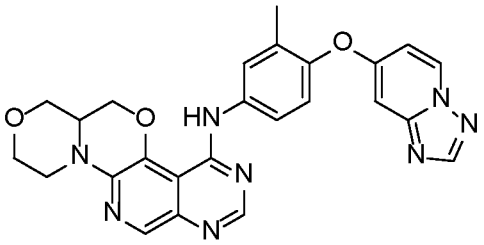
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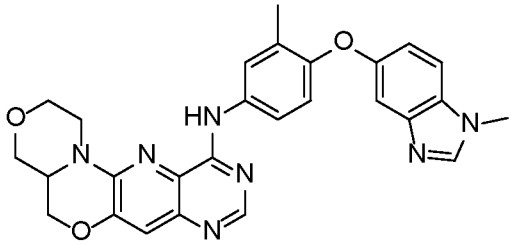
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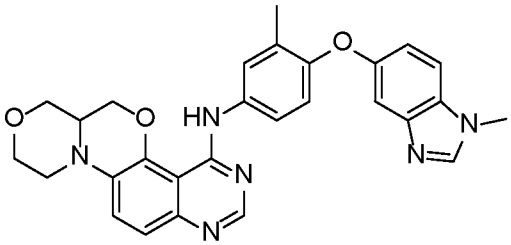
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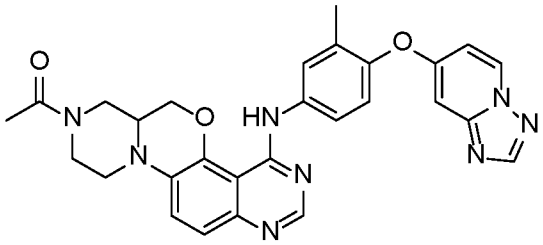
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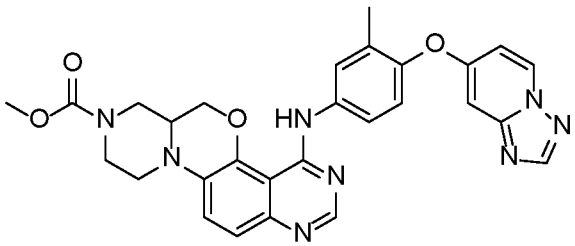
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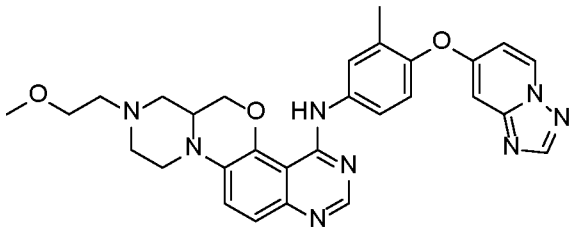
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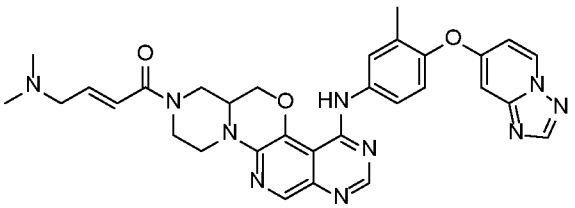
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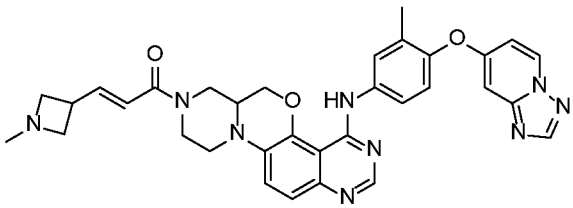
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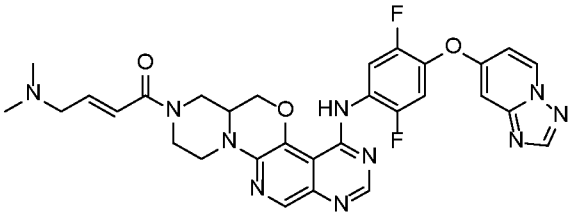
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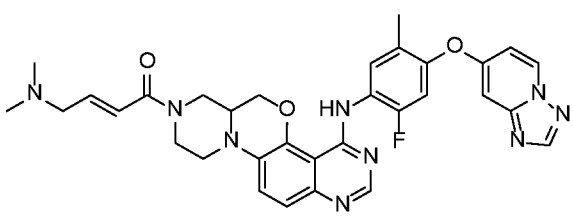
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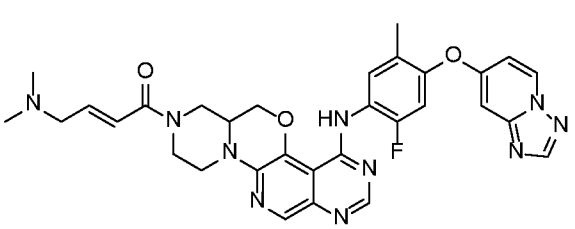
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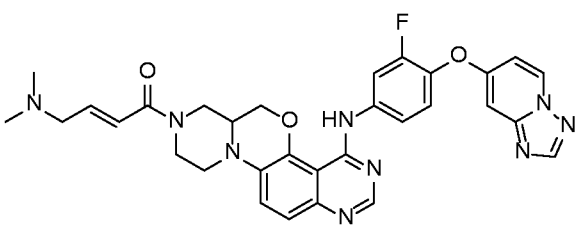
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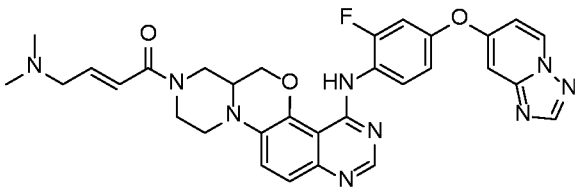
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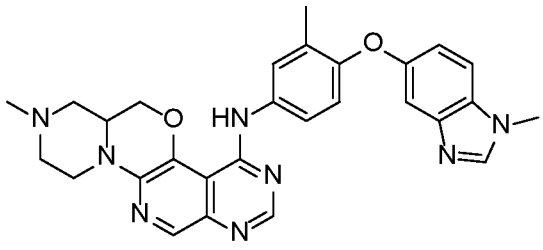
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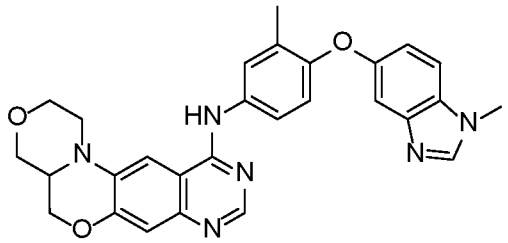
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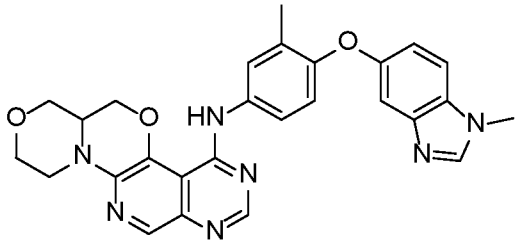
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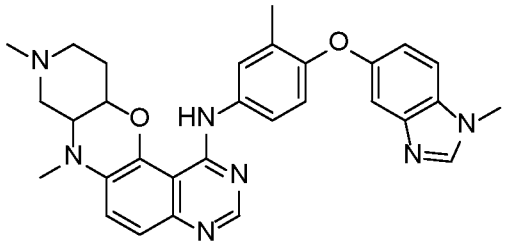
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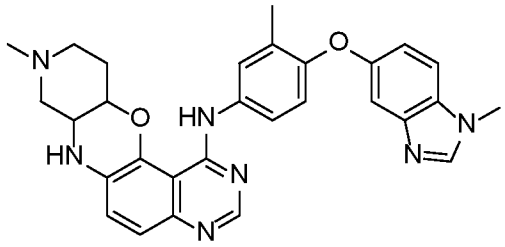
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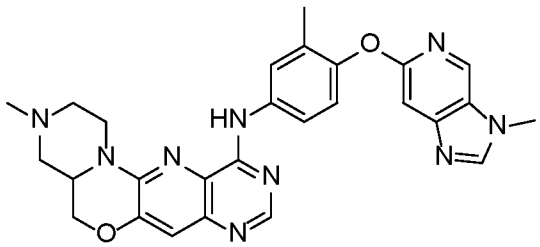
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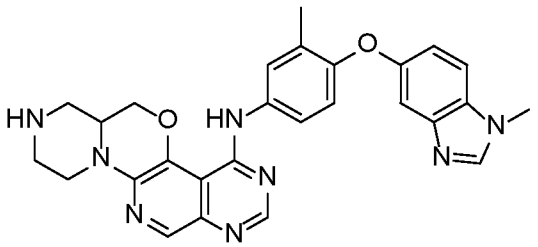
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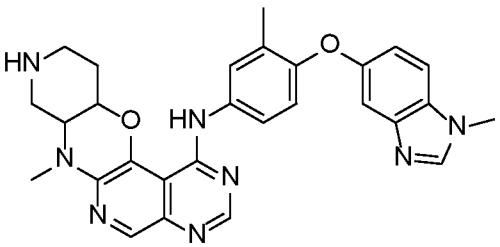
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and

Claim 40. A pharmaceutical composition comprising the compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Claim 41. A method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2 comprising contacting the ErbB2 or the mutant form with a therapeutically effective amount of the compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of claim 40.

Claim 42. The method of claim 41, wherein the mutant form of human ErbB2 comprises a mutation in Exon 20.

Claim 43. The method of claim 41 or claim 42, wherein the mutant form of human ErbB2 comprises one or more mutations that introduce amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP.

Claim 44. The method of claim 41, wherein the mutant form of human ErbB2 comprises a disease-associated point mutation in ErbB2.

Claim 45. The method of claim 41 or 44, wherein the mutant form of human ErbB2 comprises one or more point mutations in ErbB2 that introduce:

(a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or

(b) a frameshift at A1232.

Claim 46. A method of treating a patient having a cancer, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of claim 40.

Claim 47. The method of claim 46, wherein the cancer comprises cells or cell tissue having increased ErbB2 kinase activity as compared to a control.

Claim 48. The method of claim 46 or claim 47, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2.

Claim 49. The method of any one of claims 46 to 48, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2 that introduce amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP.

Claim 50. The method of claim 46 or claim 47, wherein the cancer comprises cells or cell tissue having one or more disease-associated point mutations in ErbB2.

Claim 51. The method of any one of claims 46 to 47 and 50, wherein the cancer comprises cells or cell tissue having one or more point mutations that introduce:

(a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y, H470Q, I655V, V659E, G660D, R678Q/C, L755R/S/P, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, and N1219S; or

(b) a frameshift at A1232.

Claim 52. The method of any one of claims 46 to 51, wherein the cancer is lung, glioma, skin, head and neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal, bladder, prostate, or ovarian cancer.

Claim 53. The method of any one of claims 46 to 52, wherein the cancer is non-small cell lung cancer.

Claim 54. The method of any one of claims 46 to 53, wherein the patient has received at least one, at least two, or at least three prior therapies for the cancer.

Claim 55. The method of claim 54, wherein one or more of the prior therapies selected from the group consisting of lapatinib, neratinib, afatinib, pyrotinib, poziotinib, TAK-788, and tucatinib.

Claim 56. The method of any one of claims 46 to 55, wherein the method further comprises administering one or more additional anti-cancer agents.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/073968

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D498/22 C07D519/00 A61K31/5365
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)
A61P C07D 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, 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. |
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| A | WO 2022/140769 A1 (ENLIVEN THERAPEUTICS INC [US]) 30 June 2022 (2022-06-30) claims 1-72 | 1-56 |
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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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 |
|---|---|
| 4 December 2023 | 22/12/2023 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Marzi, Elena |

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