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(54) Title: SUBSTITUTED FUSED BICYCLIC COMPOUNDS AND RELATED METHODS OF TREATMENT

(57) Abstract: The present invention provides compounds useful for the treatment of narcolepsy or cataplexy in a subject in need thereof. Also provided related pharmaceutical compositions and methods of treating narcolepsy or cataplexy in a subject in need thereof comprising administering to the subject a compound or a pharmaceutically acceptable salt thereof, or a composition.

SUBSTITUTED FUSED BICYCLIC COMPOUNDS AND RELATED METHODS OF TREATMENT

RELATED APPLICATION

This application claims the benefit of U.S. Provisional patent application serial No.: 63/353,998, filed on June 21, 2022. The entire contents of the above-identified application are herein incorporated by reference.

TECHNICAL FIELD

The present invention relates to substituted bicyclic compounds, particularly, substituted fused bicyclic compounds having agonist activity.

BACKGROUND OF THE INVENTION

Orexin is a neuropeptide synthesized and released by a subpopulation of neurons within the lateral hypothalamus and its surrounding regions. It consists of two subtypes: orexin A and orexin B. Orexin A and orexin B bind to orexin receptors. Orexin receptors are G protein-coupled receptors expressed preferentially in the brain. There are two subtypes (type 1 and type 2) of orexin receptors (Cell, Vol. 92, 573-585, 1998). Activation of orexin receptors is known to be important for a variety of central nervous system functions, such as maintenance of wakefulness, energy homeostasis, reward processing and motivation (Saper *et al.*, TRENDS in Neuroscience 2001; Yamanaka *et al.*, Neuron 2003; Sakurai, Nature Reviews Neuroscience 2014).

Narcolepsy is a neurological disease that results in excessive daytime sleepiness, sudden bouts of muscular paralysis (cataplexy), and disrupted sleep patterns (Mahoney *et al.*, Nature Reviews Neuroscience, 2019). It is known that narcolepsy is caused by the degeneration of orexin neurons. Narcoleptic symptoms can be modeled in transgenic mice engineered to degenerate orexin neurons, and their symptoms can be reversed by intraventricular administration of orexin peptides (Proc. Natl. Acad. Sci. USA, Vol. 101, 4649-4654, 2004). Studies of orexin-2 receptor knockout mice have suggested that the orexin-2 receptor plays a preferential role in maintaining wakefulness (Cell, Vol. 98, 437-451, 1999, Neuron, Vol. 38, 715-730, 2003). As such, orexin-2 receptor agonists can be therapeutic agents for narcolepsy or other disorders exhibiting excessive daytime sleepiness, such as Parkinson's disease (CNS Drugs, Vol. 27, 83-90, 2013; Brain, Vol. 130, 2007, 1586-1595).

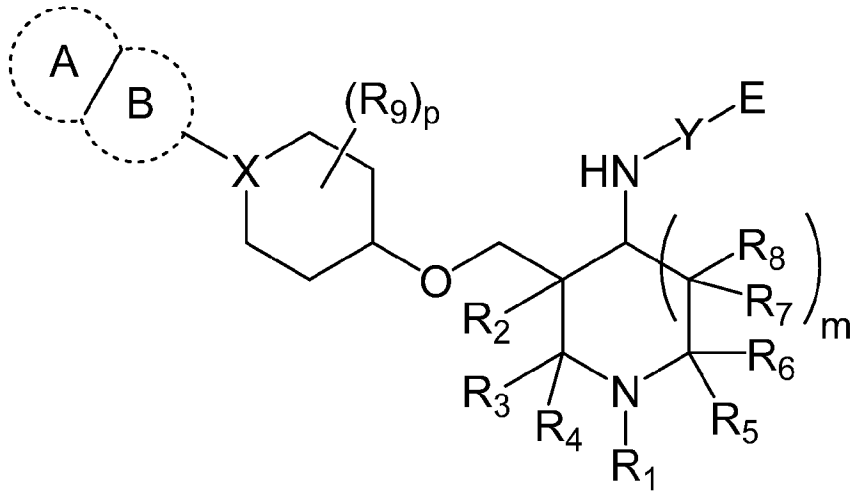
A compound having agonist activity at the orexin-2 receptor is hypothesized to be useful as a novel therapeutic agent for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, disturbance of consciousness such as coma and the like, narcolepsy syndrome, hypersomnolence syndrome characterized by hypersomnia (e.g., in Parkinson's disease, Guillain-Barre syndrome or Kleine Levin syndrome), Alzheimer's disease, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, or sepsis and the like. (Cell Metabolism, Vol. 9, 64-76, 2009; Neuroscience, Vol. 121, 855-863, 2003; Respiration, Vol. 71, 575-579, 2004; Peptides, Vol. 23, 1683-1688, 2002; WO 2015/073707; Journal of the American College of Cardiology, Vol. 66, 2015, pages 2522-2533; WO 2015/048091; WO 2015/147240).

Some compounds having orexin-2 receptor agonist activity have been reported (U.S. Pat. No. 8,258,163; WO 2015/088000; WO 2014/198880; Journal of Medicinal Chemistry, Vol. 58, pages 7931-7937; US 20190040010; US 20190031611; US 20170226137). However, it is considered that these compounds are not satisfactory, for example, in terms of activity, pharmacokinetics, permeability into the brain/central nervous system or safety, and the development of an improved compound having orexin-2 receptor agonist activity is desired.

SUMMARY OF THE INVENTION

The present invention aims to provide fused bicyclic compounds having orexin-2 receptor agonist activity.

Accordingly, in an initial aspect, the present invention provides a compound represented by Formula I-A or a pharmaceutically acceptable salt thereof:



(I-A)

wherein:

ring A is fused to ring B;

ring A is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

ring B is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

X is N or CH;

Y is $S(=O)_2$, C(=O), or $S(=O)(=NR_e)$;

R_e is selected from the group consisting of H, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl;

E is selected from the group consisting of NR_aR_b, C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl and C_1-C_3 alkylene-(5- to 7-membered heteroaryl), wherein the C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

R_a and R_b are each, independently, selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_5 cycloalkyl, and 4- to 7-membered heterocyclyl, wherein the C_1-C_3 alkyl, C_3-C_5 cycloalkyl, or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

or, alternatively, R_a and R_b, together with the N atom to which they are attached, form a 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, C_1-C_3 alkyl, C_1-C_3 alkoxyl, or C_1-C_3 alkyl substituted with 1-3 halogen;

R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), $(CR_cR_d)_n$-(C_6-C_{10} aryl) and $(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

R_c and R_d are each, independently, H, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

n is 0, 1, or 2;

each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

or, alternatively, R_3 and R_6, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

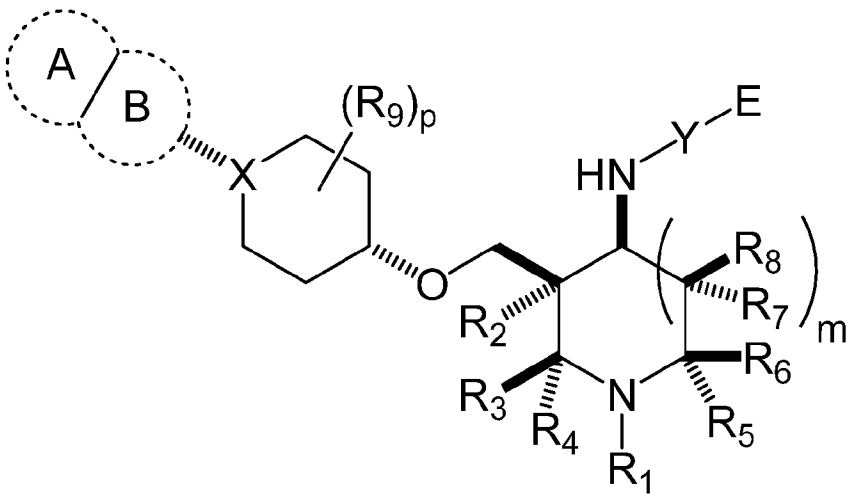
or, alternatively, R_4 and R_5, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

m is 0 or 1;

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

each R_9 is, independently, selected from the group consisting of deuterium, halogen, hydroxyl, and cyano.

In one embodiment, provided herein are compounds of Formula I-A having the structure of Formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

ring A is fused to ring B;

ring A is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

ring B is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

X is N or CH;

Y is $S(=O)_2$, C(=O), or $S(=O)(=NR_e)$;

R_e is selected from the group consisting of H, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl;

E is selected from the group consisting of NR_aR_b, C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl and C_1-C_3 alkylene-(5- to 7-membered heteroaryl), wherein the C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

R_a and R_b are each, independently, selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_5 cycloalkyl, and 4- to 7-membered heterocyclyl, wherein the C_1-C_3 alkyl, C_3-C_5 cycloalkyl, or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

or, alternatively, R_a and R_b, together with the N atom to which they are attached, form a 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, C_1-C_3 alkyl, C_1-C_3 alkoxyl, or C_1-C_3 alkyl substituted with 1-3 halogen;

R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), $(CR_cR_d)_n$-(C_6-C_{10} aryl) and $(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

R_c and R_d are each, independently, H, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

n is 0, 1, or 2;

each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

or, alternatively, R_3 and R_6, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

or, alternatively, R_4 and R_5, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

m is 0 or 1;

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

each R_9 is, independently, selected from the group consisting of deuterium, halogen, hydroxyl, and cyano.

Also provided herein is a pharmaceutical composition comprising a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, provided herein is a method of treating narcolepsy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of treating cataplexy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are compounds, e.g., the compounds of Formula I-A, or I, or pharmaceutically acceptable salts thereof, that are useful in the treatment of narcolepsy or cataplexy in a subject.

In a non-limiting aspect, these compounds may modulate the orexin-2 receptor. In a particular embodiment, the compounds provided herein are considered orexin-2 agonists. As such, in one aspect, the compounds provided herein are useful in treatment of narcolepsy in a subject by acting as an agonist of the orexin-2 receptor.

Definitions

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

As used herein, the articles "a" and "an" refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element. Furthermore, use of the term "including" as well as other forms, such as "include," "includes," and "included," is not limiting.

As used herein, the term "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term "about" is meant to encompass variations of ±20% or ±10%, including ±5%, ±1%, and ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

As used to herein, the term "EC_{50}" refers to the concentration of a compound required to achieve an effect that is 50% of the maximal observed effect of a compound.

The term "agonist," as used herein, refers to a compound that, when contacted with a target of interest (e.g., the orexin-2 receptor), causes an increase in the magnitude of a certain activity or function of the target compared to the magnitude of the activity or function

observed in the absence of the agonist.

The term "treat," "treated," "treating," or "treatment" includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises bringing into contact with the orexin-2 receptor an effective amount of a compound of the invention for conditions related to narcolepsy or cataplexy.

As used herein, the term "prevent" or "prevention" means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term "patient," "individual" or "subject" refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals. Preferably, the patient, subject, or individual is human.

As used herein, the terms "effective amount," "pharmaceutically effective amount," and "therapeutically effective amount" refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical

methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. The phrase "pharmaceutically acceptable salt" is not limited to a mono, or 1:1, salt. For example, "pharmaceutically acceptable salt" also includes bis-salts, such as a bis-hydrochloride salt. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term "composition" or "pharmaceutical composition" refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the patient such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the invention, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer

solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

As used herein, "pharmaceutically acceptable carrier" also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the invention and are physiologically acceptable to the patient. Supplementary active compounds may also be incorporated into the compositions. The "pharmaceutically acceptable carrier" may further include a pharmaceutically acceptable salt of the compound useful within the invention. Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the term "alkyl," by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (*i.e.*, C_{1-6} alkyl means an alkyl having one to six carbon atoms) and includes straight and branched chains. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, neopentyl, and hexyl. Other examples of C_1-C_6-alkyl include ethyl, methyl, isopropyl, isobutyl, n-pentyl, and n-hexyl.

As used herein, the term "halo" or "halogen" alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term "alkylene" refers to divalent aliphatic hydrocarbyl groups, for example, having from 1 to 4 carbon atoms that are either straight-chained or branched. This term includes, by way of example, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), n-propylene ($-CH_2CH_2CH_2-$), iso-propylene ($-CH_2CH(CH_3)-$), and the like.

As used herein, the term "alkenyl" denotes a monovalent group derived from a hydrocarbon moiety containing at least two carbon atoms and at least one carbon-carbon double bond. The double bond may or may not be the point of attachment to another group. Alkenyl groups (*e.g.*, C_2-C_8-alkenyl) include, but are not limited to, for example, ethenyl, propenyl, prop-1-en-2-yl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

As used herein, the term "alkynyl" denotes a monovalent group derived from a hydrocarbon moiety containing at least two carbon atoms and at least one carbon-carbon triple bond. The triple bond may or may not be the point of attachment to another group.

Alkynyl groups (*e.g.*, C_2-C_8-alkynyl) include, but are not limited to, for example, ethynyl, propynyl, prop-1-yn-2-yl, butynyl, 1-methyl-2-butyn-1-yl, heptynyl, octynyl and the like.

As used herein, the term "alkoxy," refers to the group –O-alkyl, wherein alkyl is as defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, t-butoxy and the like.

As used herein, the term "cycloalkyl" means a non-aromatic carbocyclic system that is partially or fully saturated having 1, 2 or 3 rings wherein such rings may be fused. The term "fused" means that a second ring is present (*i.e.*, attached or formed) by having two adjacent atoms in common (*i.e.*, shared) with the first ring. Cycloalkyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms. The term "cycloalkyl" includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[3.1.0]hexyl, spiro[3.3]heptanyl, and bicyclo[1.1.1]pentyl.

As used herein, the term "heterocyclyl" means a non-aromatic carbocyclic system containing 1, 2, 3 or 4 heteroatoms selected independently from N, O, and S and having 1, 2 or 3 rings wherein such rings may be fused, wherein fused is defined above. Heterocyclyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms, and containing 0, 1, or 2 N, O, or S atoms. The term "heterocyclyl" includes cyclic esters (*i.e.*, lactones) and cyclic amides (*i.e.*, lactams) and also specifically includes, but is not limited to, epoxidyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl (*i.e.*, oxanyl), pyranyl, dioxanyl, aziridinyl, azetidinyl, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, oxazolidinyl, thiazolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, and the like. For example, the term "heterocyclyl" can include 4- to 10-membered heterocyclyl, 4- to 7-membered heterocyclyl, 5- to 10-membered heterocyclyl, 6- to 10-membered heterocyclyl, 4- to 6-membered heterocyclyl, 4-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7-membered heterocyclyl, 8-membered heterocyclyl, 9-membered heterocyclyl, or 10-membered heterocyclyl.

As used herein, the term "aromatic" refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, *i.e.*, having $(4n + 2)$ delocalized π (pi) electrons, where n is an integer.

As used herein, the term "aryl" means an aromatic carbocyclic system containing 1, 2 or 3 rings, wherein such rings may be fused, wherein fused is defined above. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) may be fully saturated,

partially unsaturated or fully unsaturated. The term "aryl" includes, but is not limited to, phenyl, naphthyl, indanyl, and 1,2,3,4-tetrahydronaphthalenyl. For example, the term "aryl" can include C_6-C_{10} aryl, C_6-C_8 aryl, or C_6 aryl (*i.e.*, phenyl).

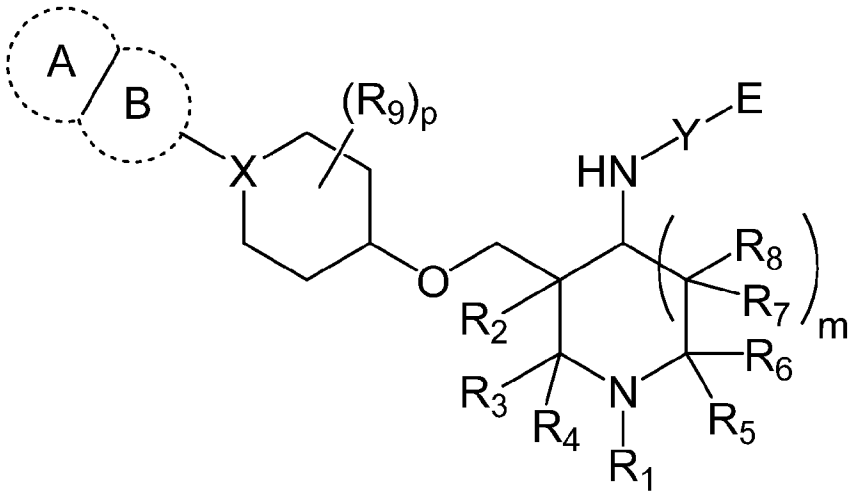
As used herein, the term "heteroaryl" means an aromatic carbocyclic system containing 1, 2, 3, or 4 heteroatoms selected independently from N, O, and S and having 1, 2, or 3 rings wherein such rings may be fused, wherein fused is defined above. The term "heteroaryl" includes, but is not limited to, furanyl, thiophenyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and the like. For example, the term "heteroaryl" can include 5- to 10-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 6-membered heteroaryl, 6- to 10-membered heteroaryl, 6- to 8-membered heteroaryl, 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, or 10-membered heteroaryl.

It is to be understood that if an aryl, heteroaryl, cycloalkyl, or heterocyclyl moiety may be bonded or otherwise attached to a designated moiety through differing ring atoms (*i.e.*, shown or described without denotation of a specific point of attachment), then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridinyl" means 2-, 3- or 4-pyridinyl, the term "thiophenyl" means 2- or 3-thiophenyl, and so forth.

As used herein, the term "substituted" means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

Compounds of the Invention

Accordingly, in an initial aspect, the present invention provides a compound represented by Formula I-A or a pharmaceutically acceptable salt thereof:



(I-A)

wherein:

ring A is fused to ring B;

ring A is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

ring B is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

X is N or CH;

Y is $S(=O)_2$, C(=O), or $S(=O)(=NR_e)$;

R_e is selected from the group consisting of H, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl;

E is selected from the group consisting of NR_aR_b, C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl and C_1-C_3 alkylene-(5- to 7-membered heteroaryl), wherein the C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) is unsubstituted or

substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

R_a and R_b are each, independently, selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_5 cycloalkyl, and 4- to 7-membered heterocyclyl, wherein the C_1-C_3 alkyl, C_3-C_5 cycloalkyl, or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

or, alternatively, R_a and R_b, together with the N atom to which they are attached, form a 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, C_1-C_3 alkyl, C_1-C_3 alkoxyl, or C_1-C_3 alkyl substituted with 1-3 halogen;

R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), $(CR_cR_d)_n$-(C_6-C_{10} aryl) and $(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

R_c and R_d are each, independently, H, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

n is 0, 1, or 2;

each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

or, alternatively, R_3 and R_6, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

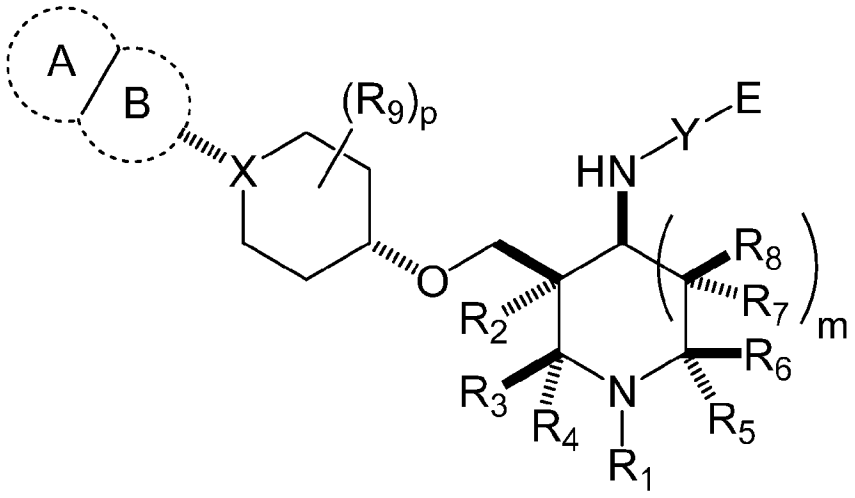
or, alternatively, R_4 and R_5, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

m is 0 or 1;

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

each R_9 is, independently, selected from the group consisting of deuterium, halogen, hydroxyl, and cyano.

In one embodiment, provided herein are compounds of Formula I-A having the structure of Formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

ring A is fused to ring B;

ring A is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

ring B is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

X is N or CH;

Y is $S(=O)_2$, C(=O), or $S(=O)(=NR_e)$;

R_e is selected from the group consisting of H, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl;

E is selected from the group consisting of NR_aR_b, C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl and C_1-C_3 alkylene-(5- to 7-membered heteroaryl), wherein the C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) is unsubstituted or

substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

R_a and R_b are each, independently, selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_5 cycloalkyl, and 4- to 7-membered heterocyclyl, wherein the C_1-C_3 alkyl, C_3-C_5 cycloalkyl, or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

or, alternatively, R_a and R_b, together with the N atom to which they are attached, form a 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, C_1-C_3 alkyl, C_1-C_3 alkoxyl, or C_1-C_3 alkyl substituted with 1-3 halogen;

R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), $(CR_cR_d)_n$-(C_6-C_{10} aryl) and $(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

R_c and R_d are each, independently, H, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

n is 0, 1, or 2;

each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

or, alternatively, R_3 and R_6, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

or, alternatively, R_4 and R_5, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

m is 0 or 1;

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

each R_9 is, independently, selected from the group consisting of deuterium, halogen, hydroxyl, and cyano.

In one embodiment of Formula (I), ring A is selected from the group consisting of: 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the 4- to

7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: C_3-C_8 cycloalkyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: C_3-C_8 cycloalkyl and 4- to 7-membered heterocyclyl, wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: C_3-C_8 cycloalkyl and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: 4- to 7-membered heterocyclyl and C_6-C_{10} aryl, wherein the 4- to 7-membered

heterocyclyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is selected from the group consisting of: 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is 4- to 7-membered heterocyclyl, wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is C_6-C_{10} aryl, wherein the C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is 5- to 7-membered heteroaryl wherein the 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: C_3-C_8 cycloalkyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and 5- to 7-membered heteroaryl,

wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: C_3-C_8 cycloalkyl and 4- to 7-membered heterocyclyl, wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: C_3-C_8 cycloalkyl and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: 4- to 7-membered heterocyclyl and C_6-C_{10} aryl, wherein the 4- to 7-membered heterocyclyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is selected from the group consisting of: 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is 4- to 7-membered heterocyclyl, wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is C_6-C_{10} aryl, wherein the C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring B is 5- to 7-membered heteroaryl wherein the 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl is

unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl and 4- to 7-membered heterocyclyl, wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: 4- to 7-membered heterocyclyl and C_6-C_{10} aryl, wherein the 4- to 7-membered heterocyclyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A and ring B are each, independently, selected from the group consisting of: 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is 5- to 7-membered heteroaryl and ring B is C_6-C_{10} aryl, wherein the 5- to 7-membered heteroaryl and C_6-C_{10} aryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is 5- to 7-membered heteroaryl and ring B is 5- to 7-membered heteroaryl, wherein each 5- to 7-membered heteroaryl, independently,

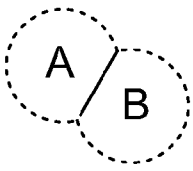
is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is 4- to 7-membered heterocyclyl and ring B is C_6-C_{10} aryl, wherein the 4- to 7-membered heterocyclyl and C_6-C_{10} aryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is 4- to 7-membered heterocyclyl and ring B is 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

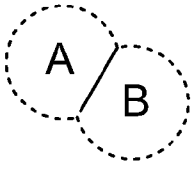
In another embodiment of Formula (I), ring A is C_3-C_8 cycloalkyl and ring B is C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl and C_6-C_{10} aryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), ring A is C_3-C_8 cycloalkyl and ring B is 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl and 5- to 7-membered heteroaryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

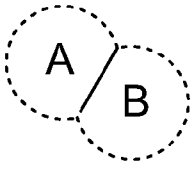
In another embodiment of Formula (I), 

is selected from the group consisting of benzoimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, imidazo[1,5-*a*]pyridinyl, indolyl, isoindolyl, indolinyl, indazolyl, isoindazolyl, benzothiazolyl, purinyl, benzofuranyl, benzoisoxazolyl, benzoisothiazolyl, isobenzofuranyl, benzothiofuranyl, indoleninyl, pyrano[3,4-*b*]-pyrrolyl, indoxazinyl, benzoxazolyl, anthranilyl, and indolizinyl, wherein the benzoimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, imidazo[1,5-*a*]pyridinyl, indolyl, isoindolyl, indolinyl, indazolyl, isoindazolyl, benzothiazolyl, purinyl, benzofuranyl, benzoisoxazolyl, benzoisothiazolyl, isobenzofuranyl, benzothiofuranyl, indoleninyl, pyrano[3,4-*b*]-pyrrolyl, indoxazinyl, benzoxazolyl, anthranilyl, and indolizinyl is unsubstituted or substituted with 1-

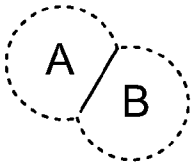
3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



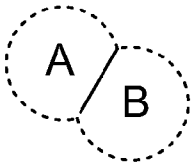
In another embodiment of Formula (I), is benzoimidazolyl, wherein the benzoimidazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



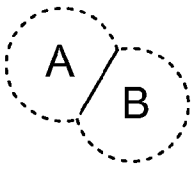
In another embodiment of Formula (I), is 1*H*-pyrazolo[3,4-*c*]pyridinyl, wherein the 1*H*-pyrazolo[3,4-*c*]pyridinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



In another embodiment of Formula (I), is imidazo[1,5-*a*]pyridinyl, wherein the imidazo[1,5-*a*]pyridinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

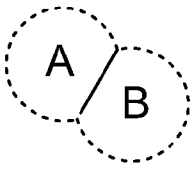


In another embodiment of Formula (I), is indolyl, wherein the indolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

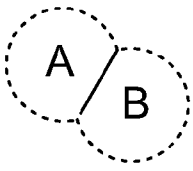


In another embodiment of Formula (I), is isoindolyl, wherein the isoindolyl is unsubstituted or substituted with 1-3 substituents selected from halogen,

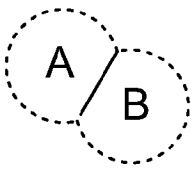
hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



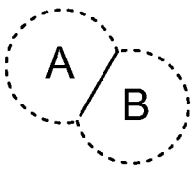
In another embodiment of Formula (I), is indolinyl, wherein the indolinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



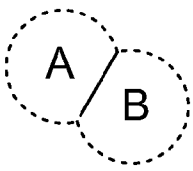
In another embodiment of Formula (I), is indazolyl, wherein the indazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



In another embodiment of Formula (I), is isoindazolyl, wherein the isoindazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

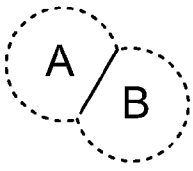


In another embodiment of Formula (I), is benzothiazolyl, wherein the benzothiazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

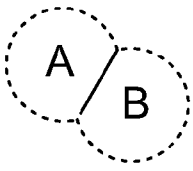


In another embodiment of Formula (I), is purinyl, wherein the purinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl,

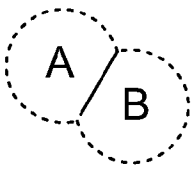
C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

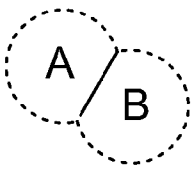
is benzofuranyl, wherein the benzofuranyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

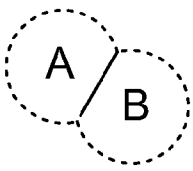
is benzoisoxazolyl, wherein the benzoisoxazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

is benzoisothiazolyl, wherein the benzoisothiazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

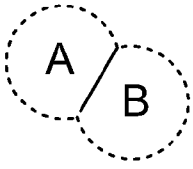
In another embodiment of Formula (I), 

is isobenzofuranyl, wherein the isobenzofuranyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

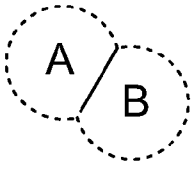
In another embodiment of Formula (I), 

is benzothiofuranyl, wherein the benzothiofuranyl is unsubstituted or substituted with 1-3 substituents selected from

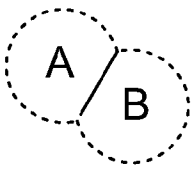
halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

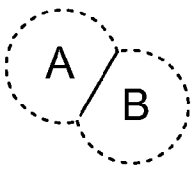
is indoleninyl, wherein the indoleninyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

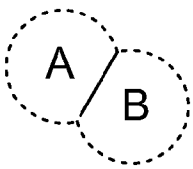
is pyrano[3,4-*b*]-pyrrolyl, wherein the pyrano[3,4-*b*]-pyrrolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

is indoxazinyl, wherein the indoxazinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

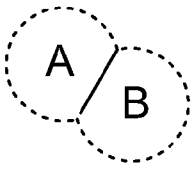
In another embodiment of Formula (I), 

is benzoxazolyl, wherein the benzoxazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

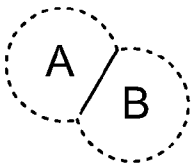
In another embodiment of Formula (I), 

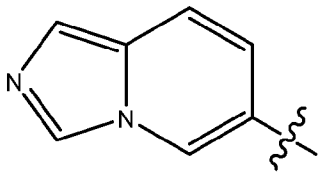
is anthranilyl, wherein the anthranilyl is unsubstituted or substituted with 1-3 substituents selected from halogen,

hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

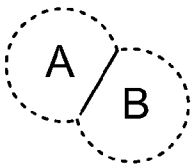
In another embodiment of Formula (I), 

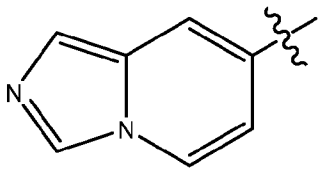
is indolizinyl, wherein the indolizinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

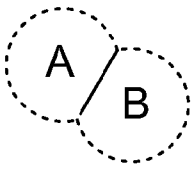
is 

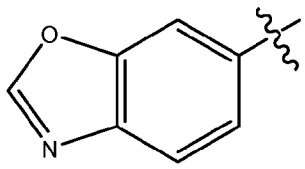
, which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

is 

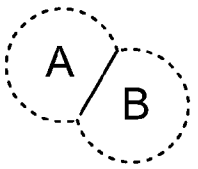
, which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

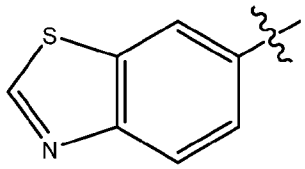
In another embodiment of Formula (I), 

is 

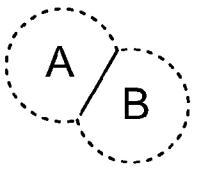
, which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl,

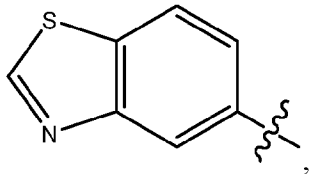
C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

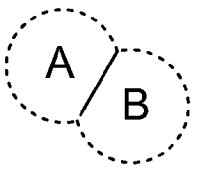
is 

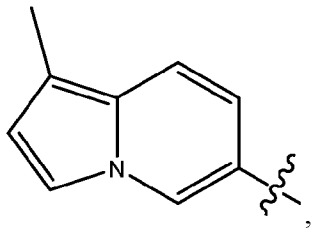
, which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

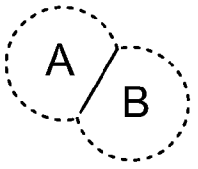
is 

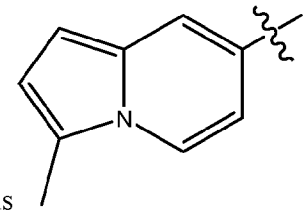
, which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

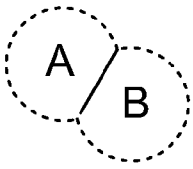
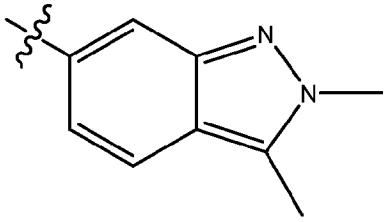
is 

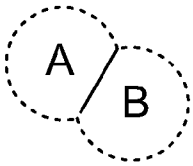
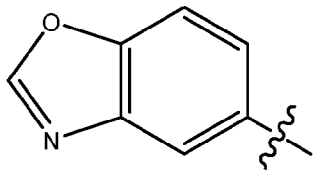
, which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

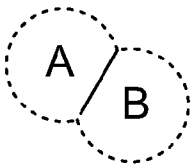
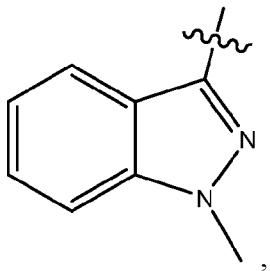
In another embodiment of Formula (I), 

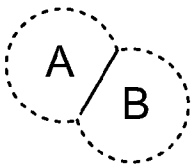
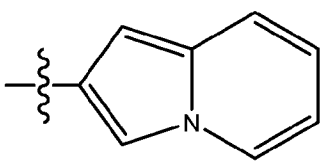
is 

, which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

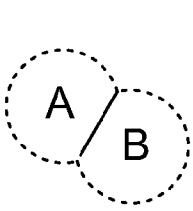
In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1 substituent selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

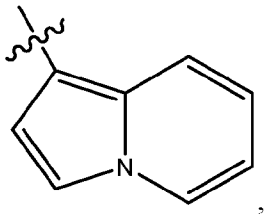
In another embodiment of Formula (I),  is  , which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

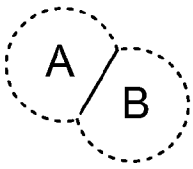
In another embodiment of Formula (I),  is  , which is unsubstituted or substituted with 1-3 substituents

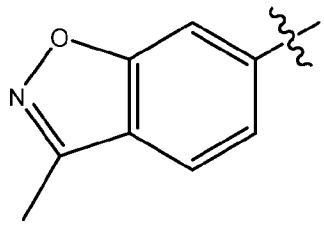
selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

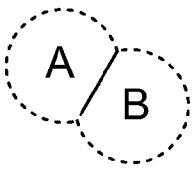
is 

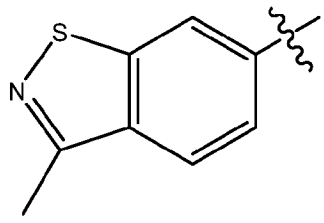
, which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), 

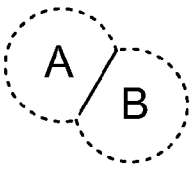
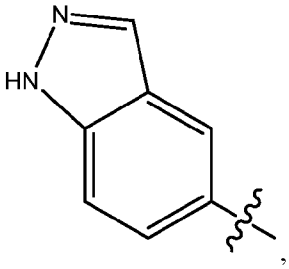
is 

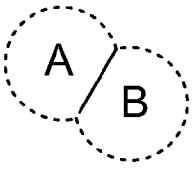
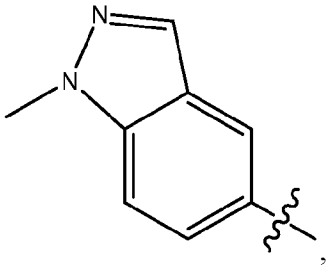
, which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

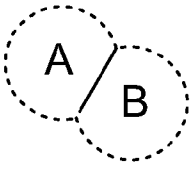
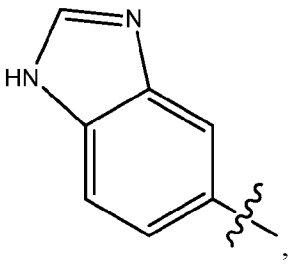
In another embodiment of Formula (I), 

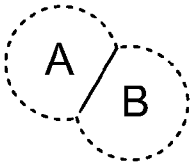
is 

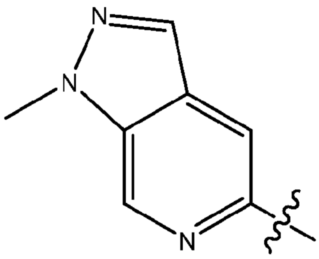
, which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

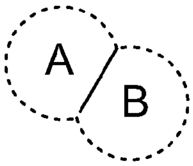
In another embodiment of Formula (I),  is  , which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

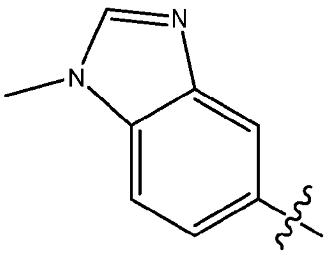
In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

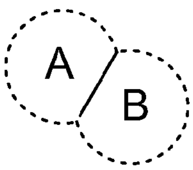
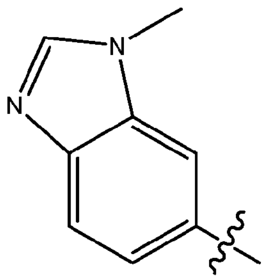
In another embodiment of Formula (I),  is  , which is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

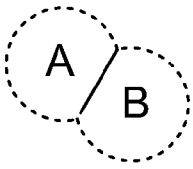
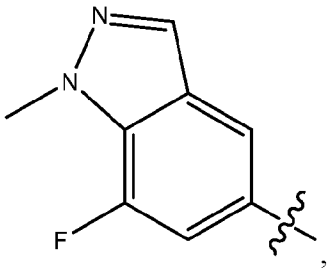
In another embodiment of Formula (I),  is

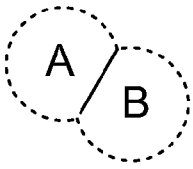
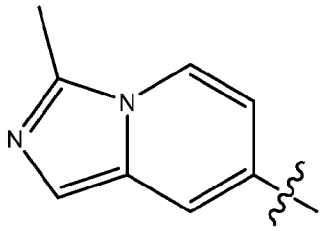
 , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

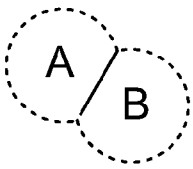
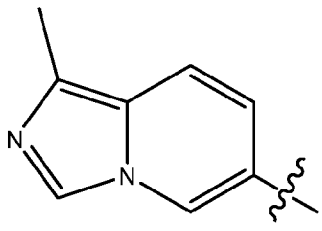
In another embodiment of Formula (I),  is

 , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1 substituent selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I),  is  , which is unsubstituted or further substituted with 1-2 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

In another embodiment of Formula (I), p is 0. In another embodiment of Formula (I), p is 1. In another embodiment of Formula (I), p is 2. In another embodiment of Formula (I), p is 3. In another embodiment of Formula (I), p is 4. In another embodiment of Formula (I), p is 0, 1 or 2. In another embodiment of Formula (I), p is 0 or 1.

In another embodiment of Formula (I), p is 1 and R_9 is deuterium. In another embodiment of Formula (I), p is 1 and R_9 is halogen. In another embodiment of Formula (I), p is 1 and R_9 is fluorine. In another embodiment of Formula (I), p is 1 and R_9 is hydroxyl. In another embodiment of Formula (I), p is 1 and R_9 is cyano. In another embodiment of Formula (I), p is 2 and each R_9 is hydroxyl. In another embodiment of Formula (I), p is 2 and each R_9 is halogen. In another embodiment of Formula (I), p is 2 and each R_9 is fluorine.

In another embodiment of Formula (I), E is NR_aR_b. In another embodiment of Formula (I), E is C_1-C_3 alkylene-NR_aR_b. In another embodiment of Formula (I), E is unsubstituted C_1-C_3 alkyl, unsubstituted C_2-C_4 alkenyl or unsubstituted C_2-C_4 alkynyl. In another embodiment of Formula (I), E is C_1-C_3 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), E is C_1-C_3 alkyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_3-C_8 cycloalkyl. In another embodiment of Formula (I), E is C_3-C_8 cycloalkyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_1-C_3 alkylene-(C_3-C_8 cycloalkyl). In another embodiment of Formula (I), E is C_1-C_3 alkylene-(C_3-C_8 cycloalkyl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted 4- to 10-membered heterocyclyl. In another embodiment of Formula (I), E is 4- to 10-membered heterocyclyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_1-C_3 alkylene-(4- to 10-membered heterocyclyl). In another embodiment of Formula (I), E is C_1-C_3 alkylene-(4- to 10-membered heterocyclyl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_6-C_{10} aryl. In another embodiment of Formula (I), E is C_6-C_{10} aryl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_1-C_3 alkylene-(C_6-C_{10} aryl). In another embodiment of Formula (I), E is C_1-C_3 alkylene-(C_6-C_{10}

aryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted 5- to 7-membered heteroaryl. In another embodiment of Formula (I), E is 5- to 7-membered heteroaryl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is unsubstituted C_1-C_3 alkylene-(5- to 7-membered heteroaryl). In another embodiment of Formula (I), E is C_1-C_3 alkylene-(5- to 7-membered heteroaryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

In another embodiment of Formula (I), E is C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), wherein the C_1-C_3alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

In another embodiment of Formula (I), E is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), wherein the C_1-C_3alkyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

In another embodiment of Formula (I), E is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, or C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), wherein the C_1-C_3alkyl, C_3-C_8 cycloalkyl, or C_1-C_3 alkylene-(C_3-C_8 cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

In another embodiment of Formula (I), E is methyl. In another embodiment of Formula (I), E is methyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl. In another embodiment of Formula (I), E is CF_3. In another embodiment of Formula (I), E is CHF_2. In another embodiment of Formula (I), E is CH_2F. In another embodiment of Formula (I), E is $NH(CH_3)$. In another embodiment of Formula (I), E is $N(CH_3)_2$.

In another embodiment of Formula (I), E is C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl). In another embodiment of Formula (I), E is unsubstituted C_6-C_{10} aryl or C_1-C_3 alkylene-(C_6-C_{10} aryl). In

another embodiment of Formula (I), E is C_6-C_{10} aryl or C_1-C_3 alkylene-(C_6-C_{10} aryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

In another embodiment of Formula (I), E is 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl). In another embodiment of Formula (I), E is unsubstituted 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl). In another embodiment of Formula (I), E is 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

In another embodiment of Formula (I), Y is $S(=O)_2$. In another embodiment of Formula (I), Y is C(=O). In another embodiment of Formula (I), Y is $S(=O)(=NR_e)$.

In another embodiment of Formula (I), X is N. In another embodiment of Formula (I), X is CH.

In another embodiment of Formula (I), R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), and C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, and C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, or C_3-C_8 cycloalkyl, is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is selected from the group consisting of C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), and C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkoxyl, wherein the C_1-C_4 alkoxyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), wherein the C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heterocyclyl), wherein the 5- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 6-membered heterocyclyl), wherein the 5- to 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heterocyclyl), wherein the 5-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heterocyclyl), wherein the 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), wherein the C_6 aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_8 aryl), wherein the C_8 aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_{10} aryl), wherein the C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(5- to 6-membered heteroaryl), wherein the 5- to 6-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(5-membered heteroaryl), wherein the 5-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heteroaryl), wherein the 6-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(7-membered heteroaryl), wherein the 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl or C(=O)-O-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl), wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl), wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with

one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_5 cycloalkyl, wherein the C_3-C_5 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5- to 6-membered heterocyclyl), wherein the 5- to 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), wherein the 5-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(6-membered heterocyclyl), wherein the 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl,

unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is

substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium. In another embodiment of Formula (I), R_1 is pyridazinyl. In another embodiment of Formula (I), R_1 is 3-pyridazinyl.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is unsubstituted. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is unsubstituted and further wherein n is 0. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is unsubstituted and further wherein n is 1. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-

membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

In another embodiment of Formula (I), each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium. In another embodiment of Formula (I), each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H or halogen. In another embodiment of Formula (I), each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H or fluorine. In another embodiment of Formula (I), each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H or C_1-C_3 alkyl. In another embodiment of Formula (I), each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

In another embodiment of Formula (I), R_3 and R_6, together, form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen. In another embodiment of Formula (I), R_3 and R_6, together, form an unsubstituted C_2 alkylene or a C_2 alkylene substituted with one or more halogen. In another embodiment of Formula (I), R_3 and R_6, together, form an azabicyclo[3.2.1]octanyl bridged bicyclic heterocyclyl.

In another embodiment of Formula (I), R_4 and R_5, together, form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen. In another embodiment of Formula (I), R_4 and R_5, together, form an unsubstituted C_2 alkylene or a C_2 alkylene substituted with one or more halogen. In another embodiment of Formula (I), R_4 and R_5, together, form an azabicyclo[3.2.1]octanyl bridged bicyclic heterocyclyl.

In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkoxyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkoxyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkoxyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-C_1-C_4 alkoxyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is

$C(=O)$-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $C(=O)$-$(CR_cR_d)_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of

Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6-C_{10} aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-(CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another

embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1

or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-$(CR_cR_d)_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is C(=O)-O-(CR_cR_d)$_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 10-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 10-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 10-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 10-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is (CR_cR_d)$_n$-(6-

membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4,

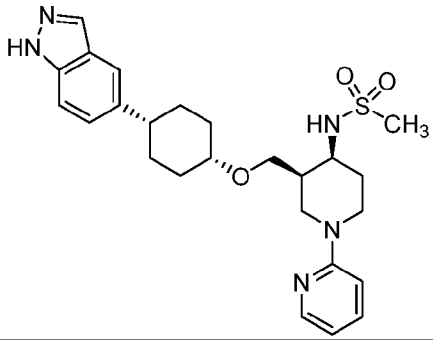
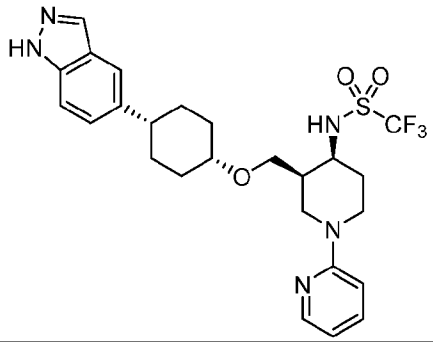
R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

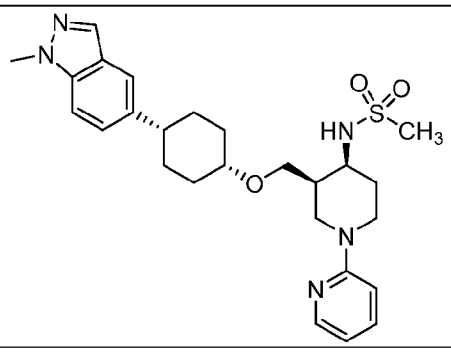
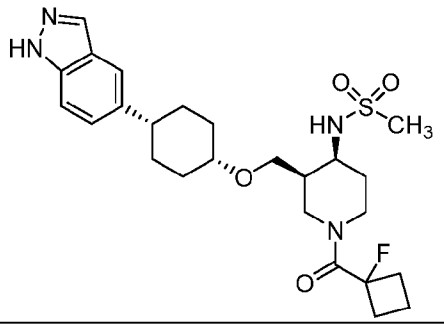
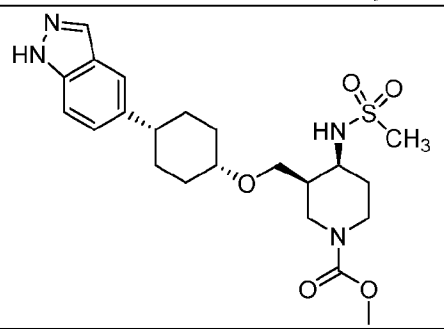
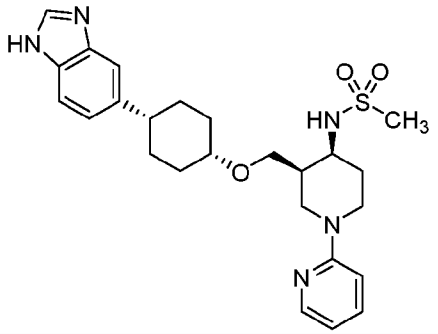
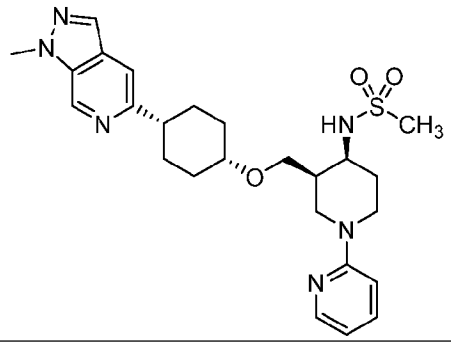
In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or halogen. In another embodiment of Formula (I), R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or fluorine.

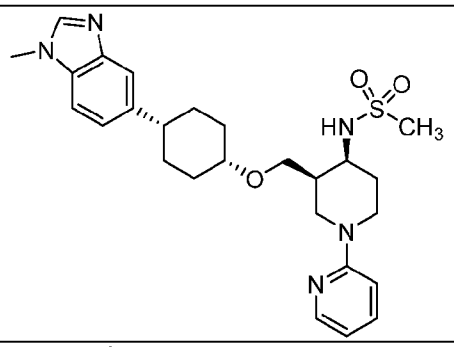
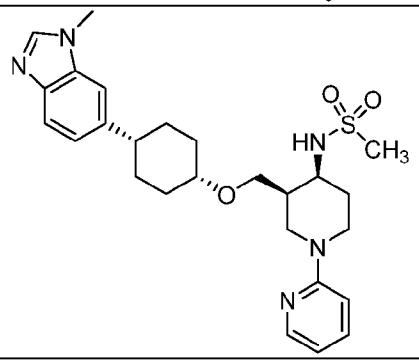
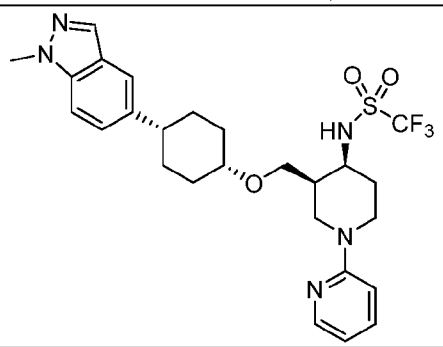
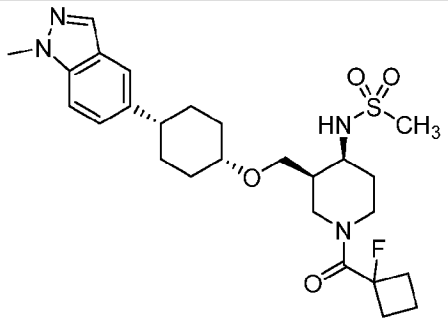
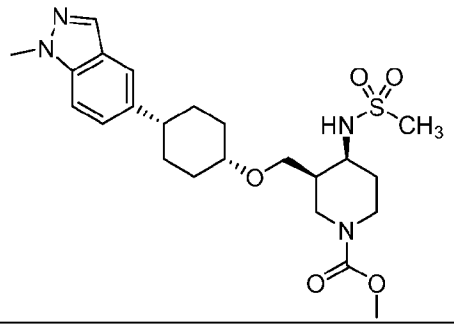
Each of the embodiments described herein with respect to compounds of Formula I also applies to compounds of Formula I-A.

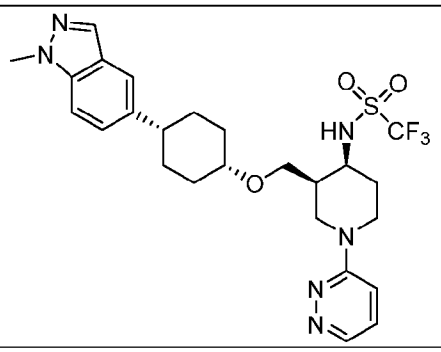
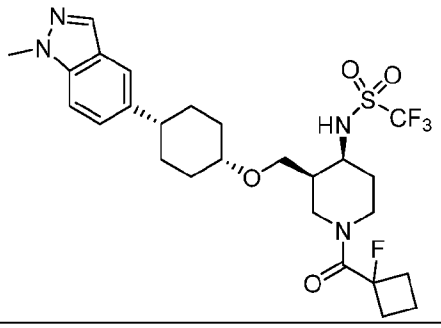
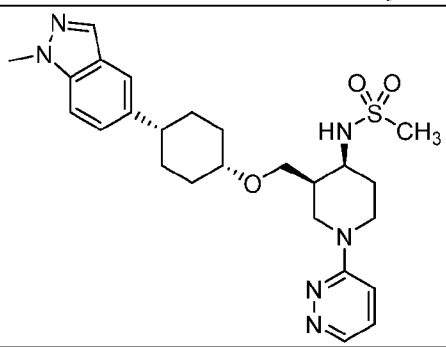
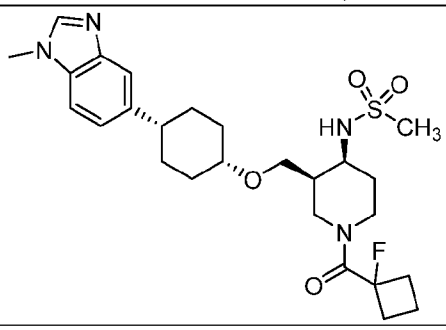
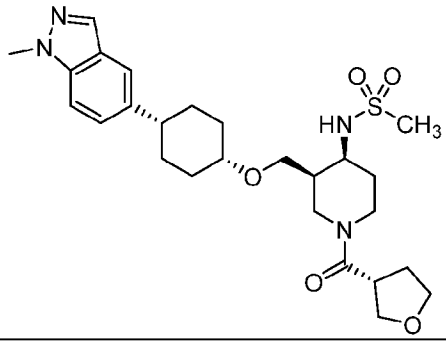
Certain embodiments of compounds of Formula I-A, or I, or pharmaceutically acceptable salts thereof, are shown below in Table 1. Compounds of Formula I-A, or I, or pharmaceutically acceptable salts thereof, and compounds of Table 1, or pharmaceutically acceptable salts thereof, collectively or individually are sometimes referred to herein as "compounds of the invention" or "compounds provided herein".

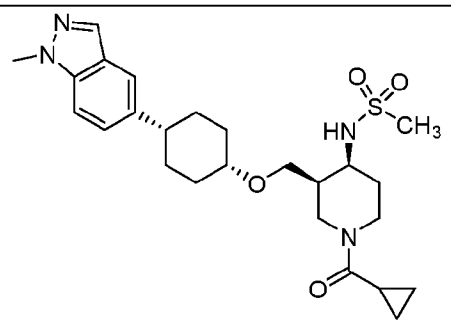
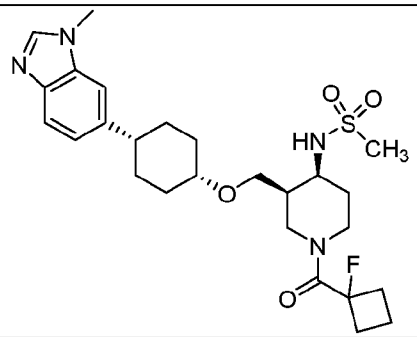
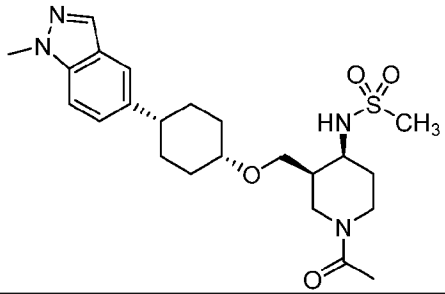
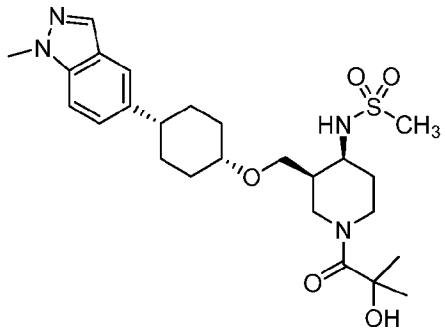
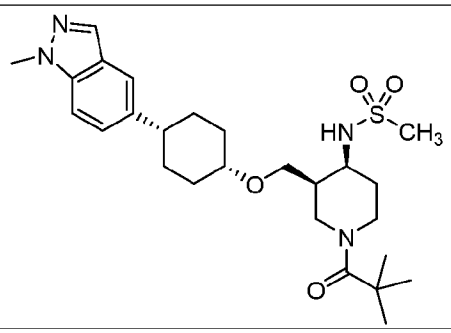
Table 1

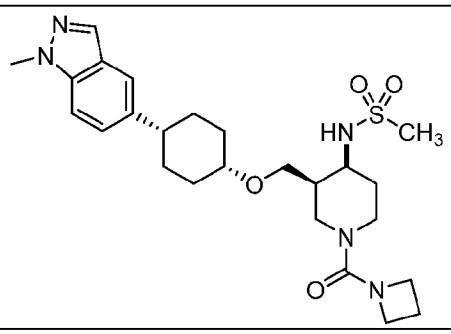
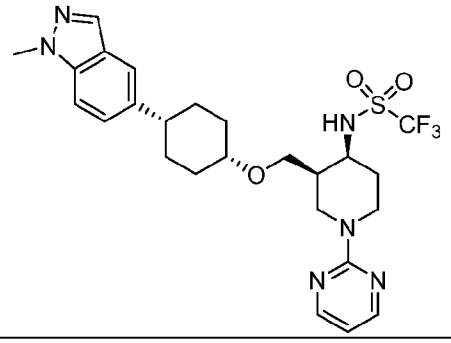
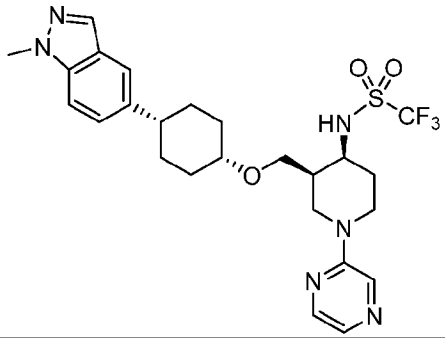
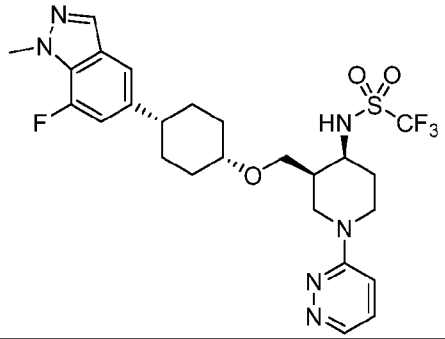
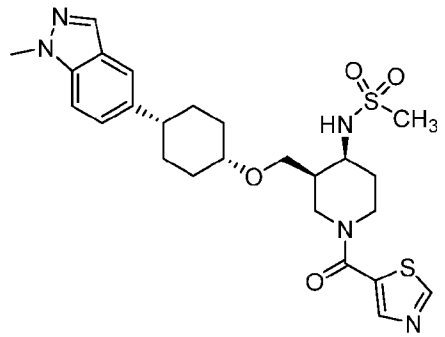
Structure	Compound No.
	1
	2

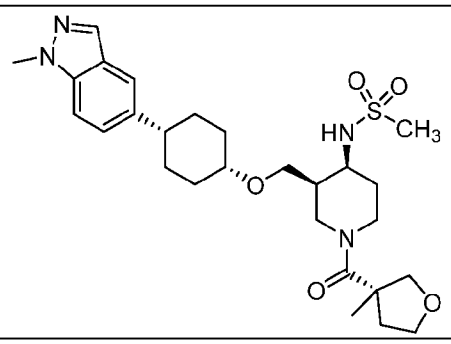
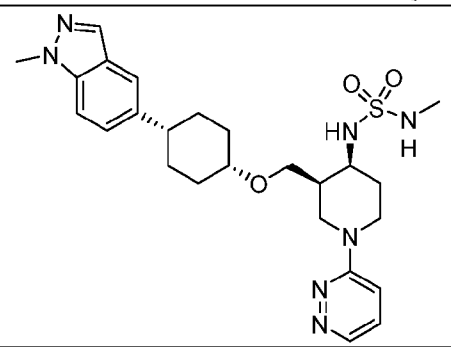
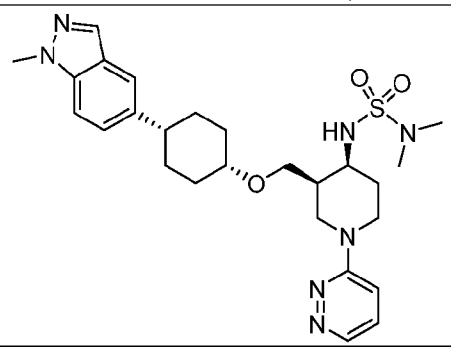
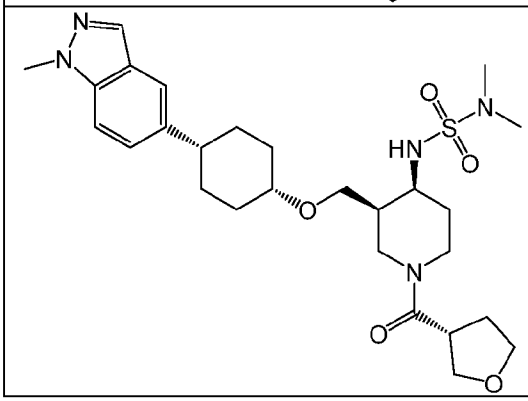
	3
	4
	5
	6
	7

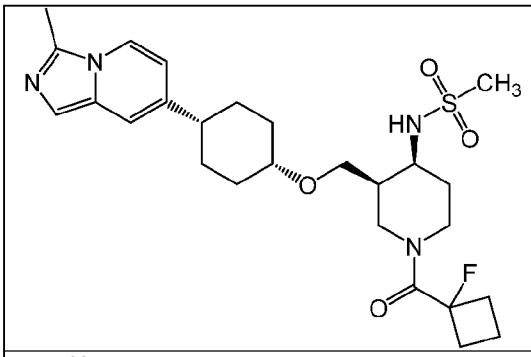
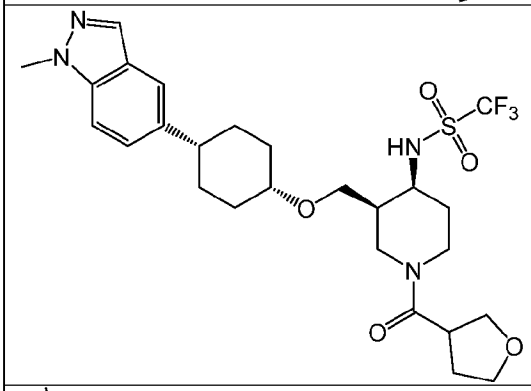
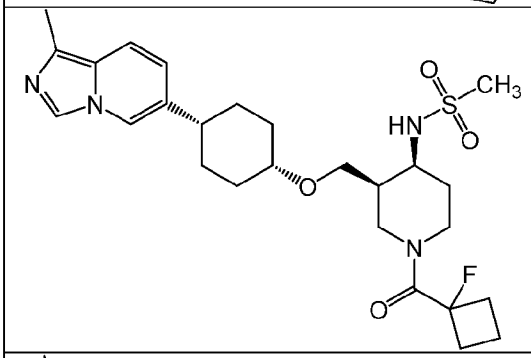
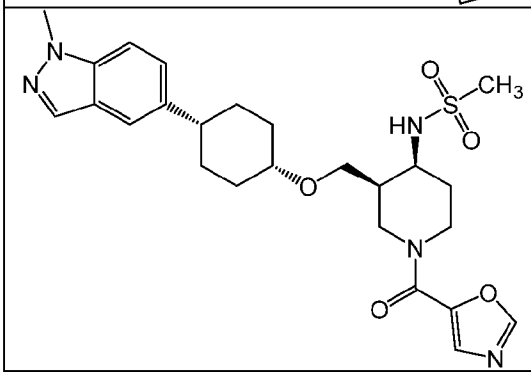
	8
	9
	10
	11
	12

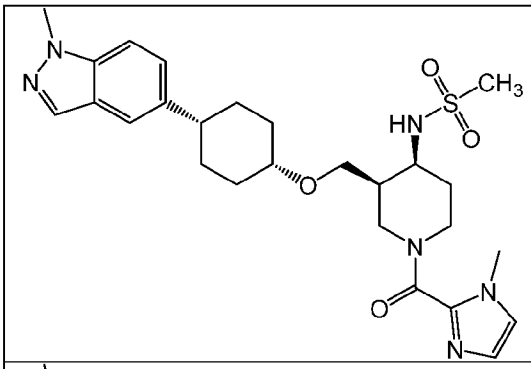
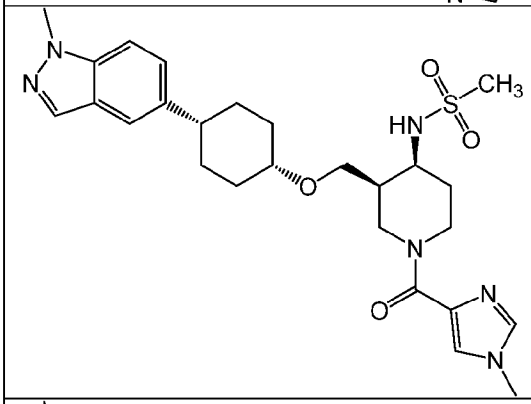
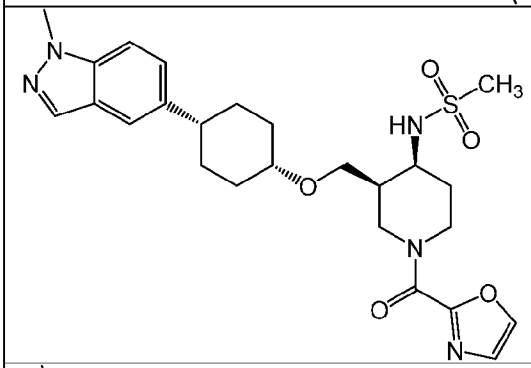
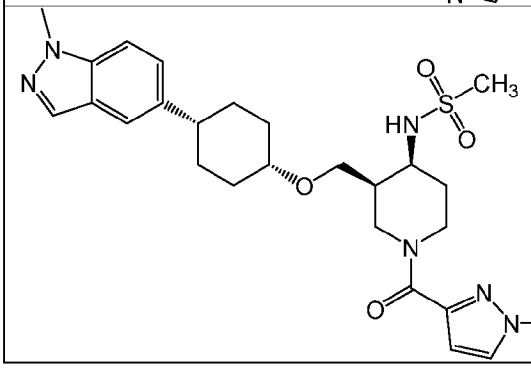
	13
	14
	15
	16
	17

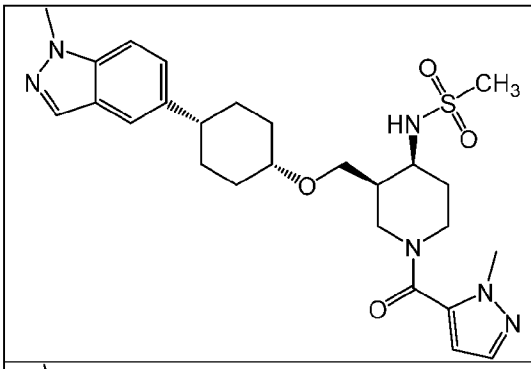
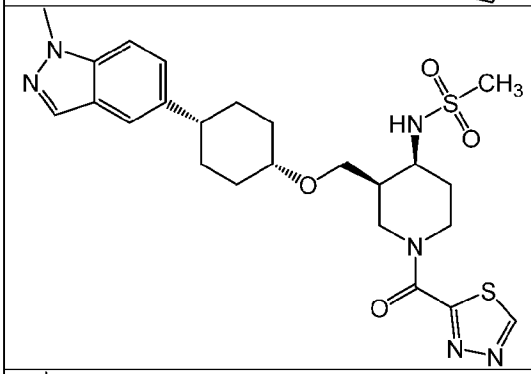
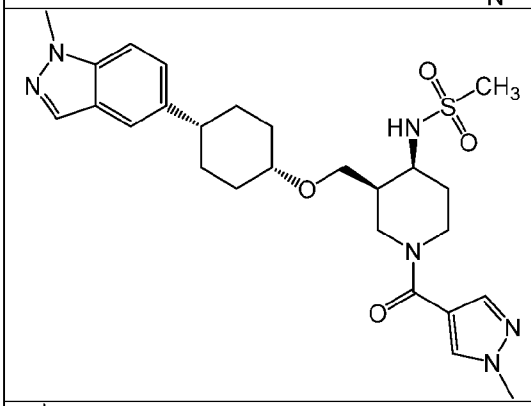
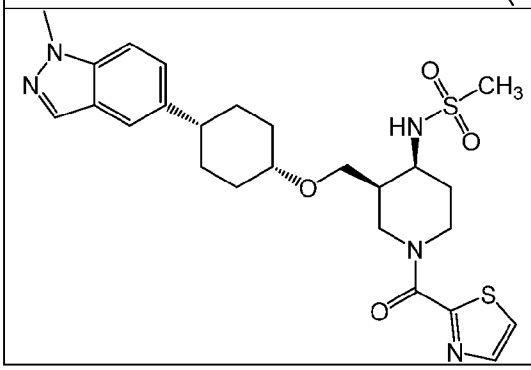
	18
	19
	20
	21
	22

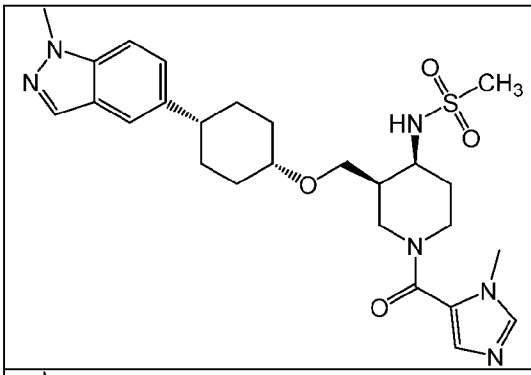
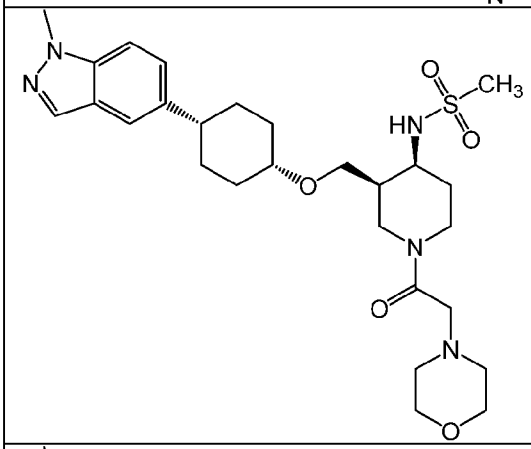
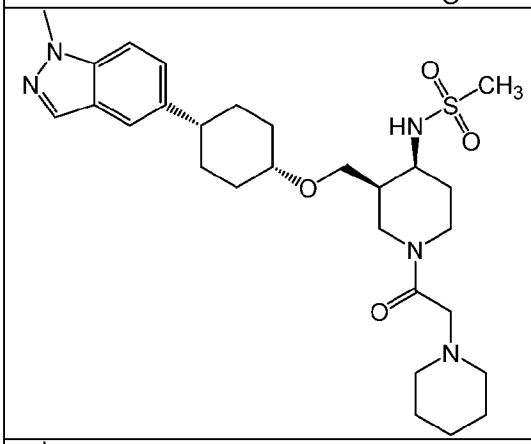
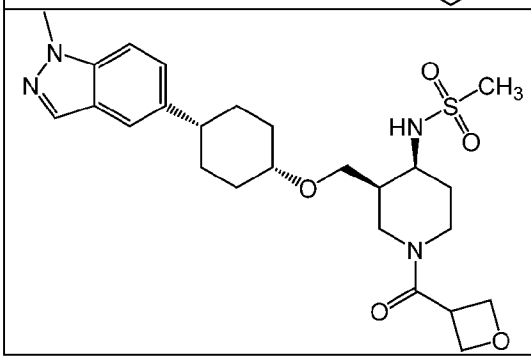
	23
	24
	25
	26
	27

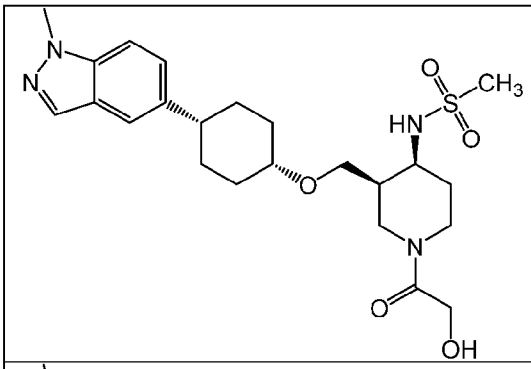
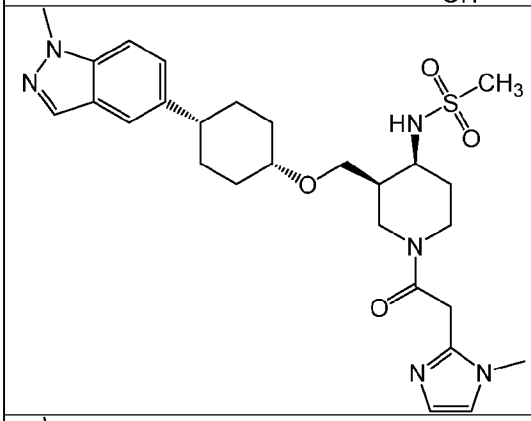
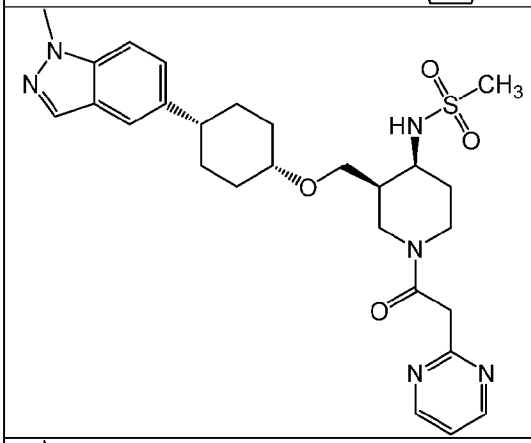
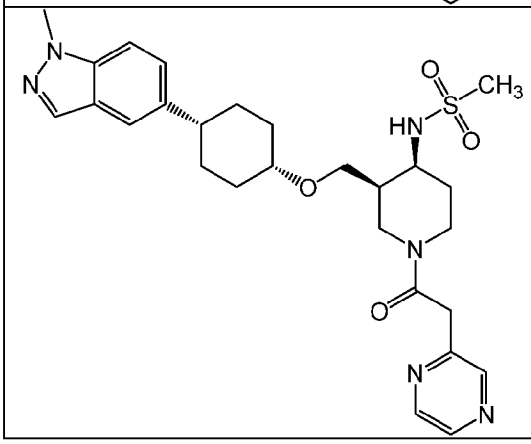
	28
	29
	30
	31

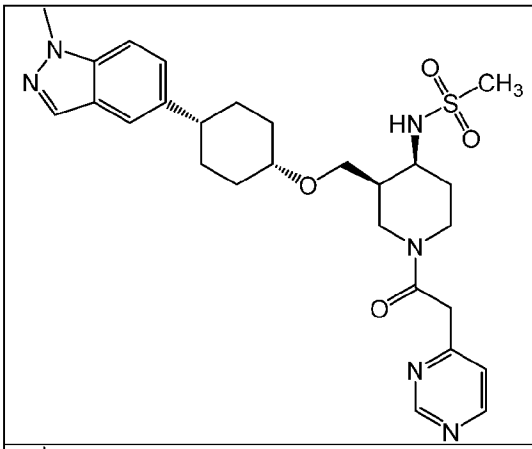
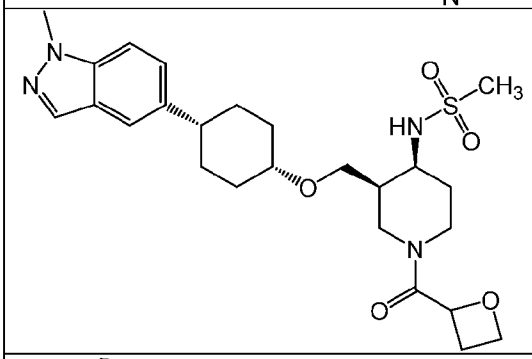
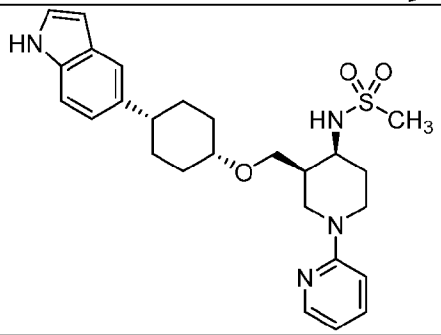
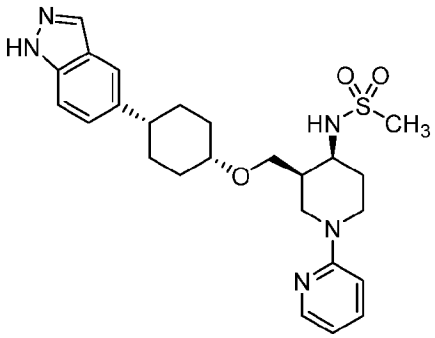
	32
	33
	34
	35

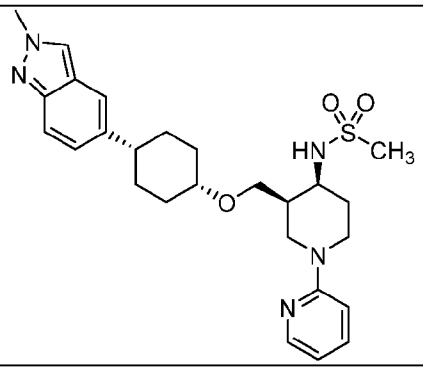
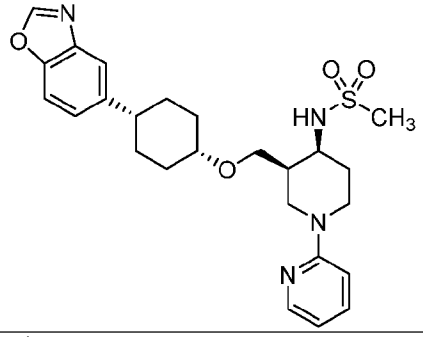
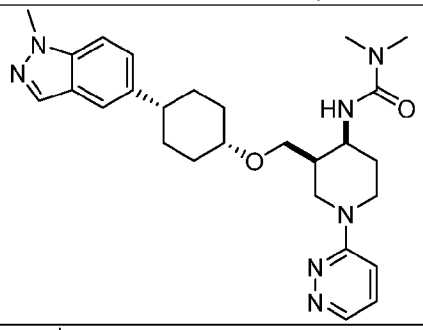
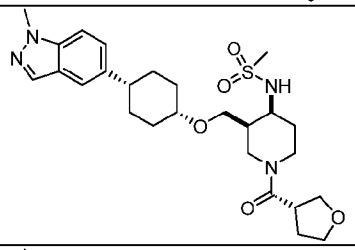
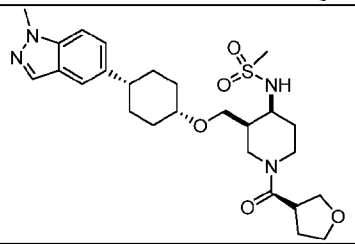
	36
	37
	38
	39

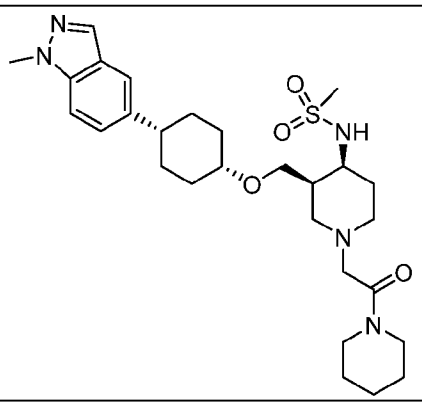
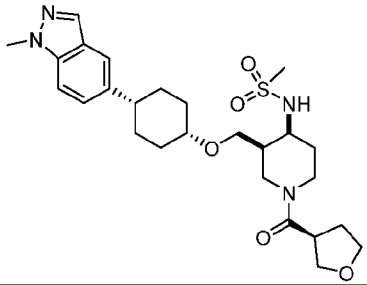
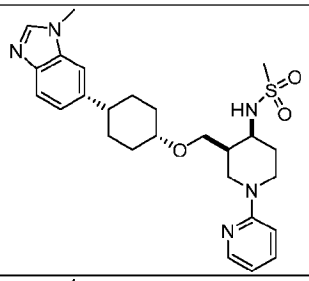
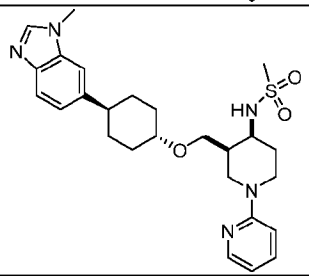
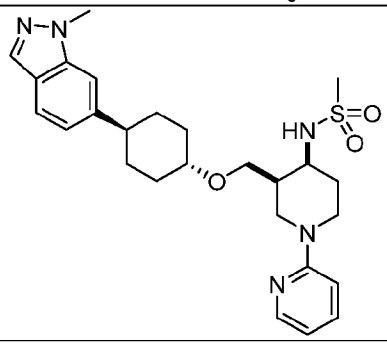
	40
	41
	42
	43

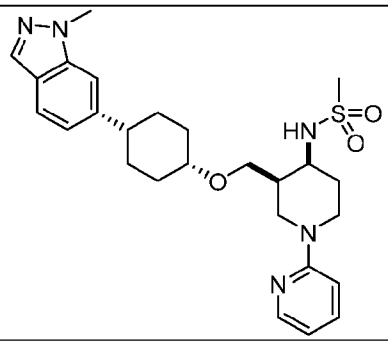
	44
	45
	46
	47

	48
	49
	50
	51

	52
	53
	54
	55

	56
	57
	58
	59
	60

	61
	62
	63
	64
	65

	66

The disclosed compounds possess one or more stereocenters, and each stereocenter may exist independently in either the R or S configuration. In one embodiment, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds described herein encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein.

Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In one embodiment, a mixture of two or more isomers is utilized as the disclosed compound described herein. In another embodiment, a pure isomer is utilized as the disclosed compound described herein. In another embodiment, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis or separation of a mixture of enantiomers or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

In one embodiment, the disclosed compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

Compounds described herein also include isotopically-labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{36}Cl, ^{18}F, ^{123}I, ^{125}I, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, and ^{35}S. In one embodiment, isotopically-labeled compounds are useful in drug or substrate tissue

distribution studies. In another embodiment, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements). In another embodiment, the compounds described herein include a ^{2}H (*i.e.*, deuterium) isotope.

In yet another embodiment, substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The specific compounds described herein, and other compounds encompassed by one or more of the Formulas described herein having different substituents are synthesized using techniques and materials described herein and as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey and Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compounds as described herein are modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the Formulas as provided herein.

Compounds described herein are synthesized using any suitable procedures starting from compounds that are available from commercial sources or are prepared using procedures described herein.

Methods of Treatment

The compounds of the invention can be used in a method of treating a disease or condition in a subject, said method comprising administering to the subject a compound of the invention, or a pharmaceutical composition comprising a compound of the invention. In one embodiment of the methods described herein, the subject is human. In one aspect, the compounds provided herein are useful in treatment of a disease or condition by acting as an agonist of the orexin-2 receptor.

The compounds of the invention can be used to treat a disease or condition selected from the group consisting of narcolepsy, cataplexy, or hypersomnia in a subject in need thereof.

In one embodiment, the compounds of the invention can be used to treat narcolepsy in a subject. In one embodiment, the compounds of the invention can be used to treat cataplexy in a subject. In one embodiment, the compounds of the invention can be used to treat hypersomnia in a subject.

Orexin-2 receptors are important in a wide range of biological functions. This suggests that orexin-2 receptors play a role in diverse disease processes in humans or other species. The compound of the present invention is useful for treating, preventing, or ameliorating the risk of one or more of the following symptoms or diseases of various neurological and psychiatric diseases associated with alterations in sleep/wake function. That is, narcolepsy, narcolepsy with cataplexy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome, hypersomnolence syndrome characterized by hypersomnia (e.g., in subjects with Kleine Levin syndrome, major depression with hypersomnia, Lewy body dementia, Parkinson's disease, progressive supranuclear paralysis, Prader-Willi syndrome, Mobius syndrome, hypoventilation syndrome, Niemann-Pick disease type C, brain contusion, cerebral infarction, brain tumor, muscular dystrophy, multiple sclerosis, multiple systems atrophy, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's encephalitis, limbic encephalitis, or Hashimoto's encephalopathy), coma, loss of consciousness, obesity (e.g., malignant mastocytosis, exogenous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypop hyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, or central obesity), insulin resistance syndrome, Alzheimer's disease, disturbance of consciousness such as coma and the like, side effects and complications due to anesthesia, sleep disturbance, excessive daytime sleepiness, sleep problem, insomnia, intermittent sleep, nocturnal myoclonus, REM sleep interruption, jet lag, jet lag syndrome, sleep disorder of alternating worker, sleep disorder, night terror, depression, major depression, sleepwalking disease, enuresis, sleep disorder, Alzheimer's dusk, sundowning, diseases associated with circadian rhythm, fibromyalgia, condition arising from decline in the quality of sleep, overeating, obsessive compulsive eating disorder, obesity-related disease, hypertension, diabetes, elevated plasma insulin concentration and insulin resistance, hyperlipidemia, hyperlipemia, endometrial cancer, breast cancer, prostate cancer,

colorectal cancer, cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, cardiac disease, abnormal heartbeat, arrhythmia, myocardial infarction, congestive cardiac failure, cardiac failure, coronary heart disease, cardiovascular disorder, polycysticovarian disease, craniopharingioma, Prader-Willi syndrome, Froelich's syndrome, growth hormone deficient, normal mutant short stature, Turner's syndrome, children suffering from acute lymphoblastic leukemia, syndrome X, reproductive hormone abnormality, declining fertility, infertility, male gonadal function decline, sexual and reproductive dysfunction such as female male hirsutism, fetal defects associated with pregnant women obesity, gastrointestinal motility disorders such as obesity-related gastroesophageal reflux, obesity hypoventilation syndrome (Pickwick syndrome), respiratory diseases such as dyspnea, inflammation such as systemic inflammation of the vascular system, arteriosclerosis, hypercholesterolemia, hyperuricemia, lower back pain, gall bladder disease, gout, kidney cancer, risk of secondary outcomes of obesity, such as lowering the risk of left ventricular hypertrophy, migraine pain, headache, neuropathic pain, Parkinson's disease, psychosis, autoimmune encephalitis, cancer related fatigue (such as excessive daytime sleepiness or fatigue associated with cancer and/or chemotherapy), cancer related nausea and vomiting, corticobasal degeneration, Huntington's disease, neuromyelitis optica, nociception, progressive supranuclear palsy, schizophrenia, systemic lupus erythematosus, traumatic brain injury, facial flushing, night sweats, diseases of the genital/urinary system, diseases related to sexual function or fertility, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive disorder, panic attack, panic disorder, post-traumatic stress disorder (PTSD), separation anxiety disorder, social phobia, anxiety disorder, acute neurological and psychiatric disorders such as cardiac bypass surgery and post-transplant cerebral deficit, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic nerve injury, Huntington's chorea, amyotrophic lateral sclerosis, eye damage, retinopathy, cognitive impairment, muscle spasm, tremor, epilepsy, disorders associated with muscle spasticity, delirium, amnestic disorder, age-related cognitive decline, schizoaffective disorder, delusional disorder, drug addiction, dyskinesia, chronic fatigue syndrome, fatigue, medication-induced Parkinsonism syndrome, Jill-do La Tourette's syndrome, chorea, myoclonus, tic, restless legs syndrome, dystonia, dyskinesia, attention deficit hyperactivity disorder (ADHD), behavior disorder, urinary incontinence, withdrawal symptoms, trigeminal neuralgia, hearing loss, tinnitus, nerve damage, retinopathy, macular degeneration, vomiting,

cerebral edema, pain, bone pain, arthralgia, toothache, cataplexy, and traumatic brain injury (TBI).

Particularly, the compound of the present invention is useful as a therapeutic or prophylactic drug for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome, hypersomnolence syndrome characterized by hypersomnia (e.g., in Parkinson's disease, Guillain-Barre syndrome or Kleine Levin syndrome), Alzheimer's disease, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma and the like, side effects and complications due to anesthesia, and the like, or anesthetic antagonist.

In one embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for narcolepsy.

In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy type-1. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy type-2. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy and excessive daytime sleepiness. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy, cataplexy, and excessive daytime sleepiness. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy and cataplexy. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for excessive daytime sleepiness. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for idiopathic hypersomnia. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for obstructive sleep apnea.

In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for hypersomnia in Parkinson's disease.

In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for hypersomnia. In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for excessive daytime sleepiness associated with Parkinson's disease.

In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for excessive daytime sleepiness or fatigue associated with cancer and/or chemotherapy.

In another embodiment, the present invention provides a method of treating narcolepsy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy type-1 in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy type-2 in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy and excessive daytime sleepiness in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy, cataplexy, and excessive daytime sleepiness in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy and cataplexy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating excessive daytime sleepiness in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating idiopathic hypersomnia in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating excessive daytime sleepiness and idiopathic hypersomnia in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating obstructive sleep apnea in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating excessive daytime sleepiness and obstructive sleep apnea in a subject in need thereof comprising administering to the subject a compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof.

In any of the methods as described herein, the subject is administered a compound of Formula I.

Each of the embodiments described herein with respect to the use of compounds of Formula I also applies to compounds of Formula I-A.

In any of the compositions or methods as described herein, the compound of Formula I-A, or I, or a pharmaceutically acceptable salt thereof, is present and/or administered in a therapeutically effective amount.

Administration / Dosage / Formulations

In another aspect, provided herein is a pharmaceutical composition comprising at least one compound of the invention, together with a pharmaceutically acceptable carrier.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well, known in the medical arts.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could begin administration of the pharmaceutical composition to dose the disclosed compound at levels lower than that

required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of the disclosed compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the disclosed compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a disclosed compound for the treatment of narcolepsy or cataplexy in a patient.

In one embodiment, the compounds of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

In some embodiments, the dose of a disclosed compound is from about 1 mg to about 1,000 mg. In some embodiments, a dose of a disclosed compound used in compositions described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 20 mg, or less than about 10 mg. For example, a dose is about 10 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 120 mg, 140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240, 260 mg, 280 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, or about 600 mg.

Routes of administration of any of the compositions of the invention include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds for use in the invention may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration. In one embodiment, the preferred route of administration is oral.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters,

lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For parenteral administration, the disclosed compounds may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing or dispersing agents may be used.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents are considered to be within the scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

Examples

The invention is further illustrated by the following examples, which should not be construed as further limiting. The practice of the present invention will employ, unless otherwise indicated, conventional techniques of organic synthesis, cell biology, cell culture, molecular biology, transgenic biology, microbiology and immunology, which are within the skill of the art.

General Procedures

Example 1: Synthesis Procedures

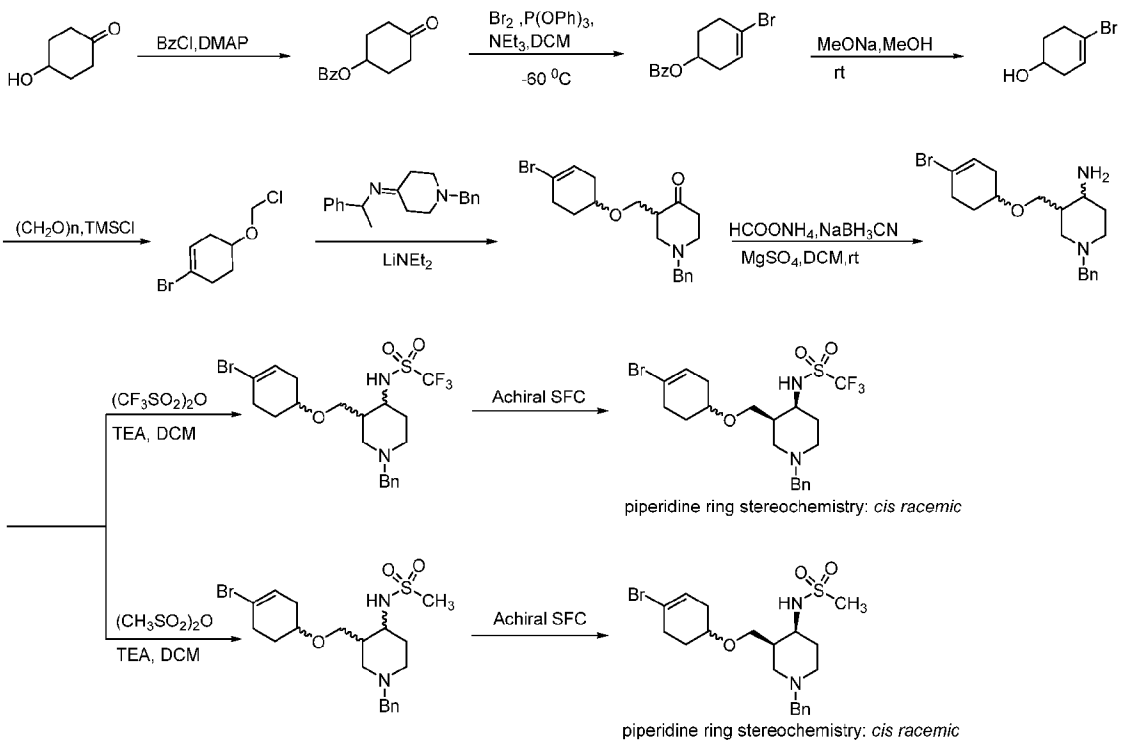
Synthesis procedures for preparation of the compounds of the invention are readily available to the ordinary skilled artisan. Unless otherwise indicated, starting materials were generally obtained from commercial sources. Synthetic procedures for other related compounds can be found, for example, in U.S. Application No.: 17/556,295, filed December 20, 2021 and in PCT Application No.: PCT/US21/64484, filed December 21, 2021; both of which are expressly incorporated by reference herein.

The following abbreviations may be used in the synthetic examples below:

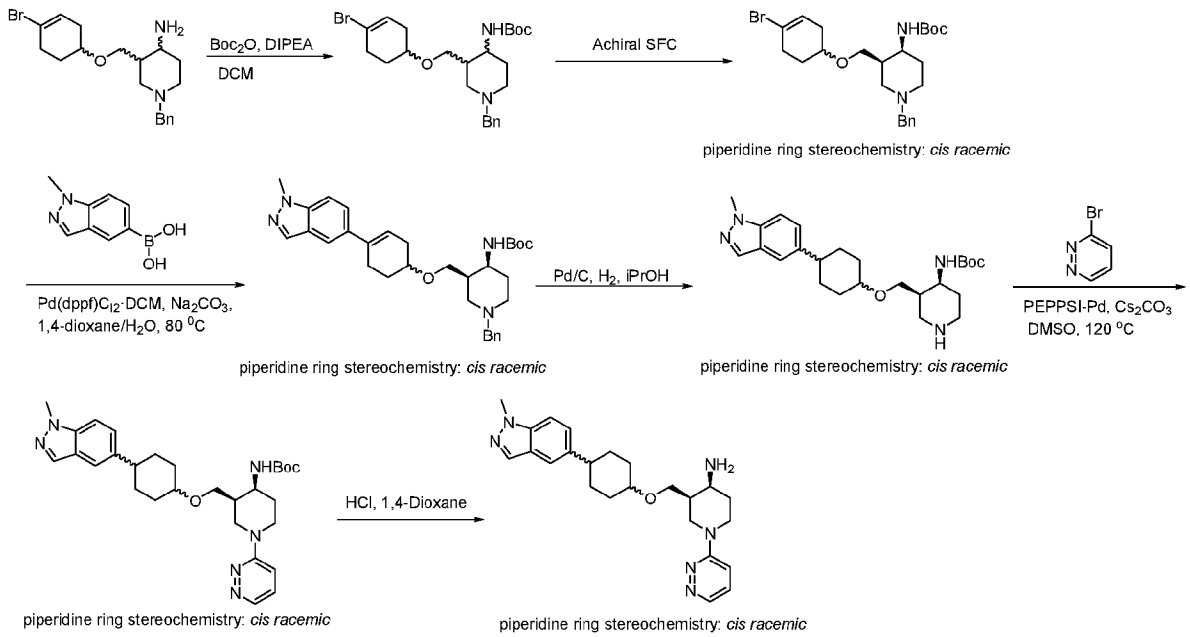
DCM = dichloromethane
MeOH = methanol
EtOH = ethanol
DIPEA or DIEA = *N,N*-diisopropylethylamine
ACN or MeCN = acetonitrile
PE = petroleum ether
EtOAc = ethyl acetate
TFA = trifluoroacetic acid
DMSO = dimethyl sulfoxide
i-PrOH = isopropanol
EA = ethyl acetate
Pd/C = palladium on carbon
Boc = *tert*-butyloxycarbonyl
Ms = methanesulfonyl
Bn = benzyl
Bz = benzoyl
$P(OPh)_3$ = Triphenyl phosphite
Et = ethyl
h = hours
min = minutes

$PdCl_2(dppf)$ = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
DMAP = 4-(dimethylamino)pyridine
KOAc = potassium acetate
Et_3N or TEA = triethylamine
TMS-Cl = trimethylsilyl chloride
$LiNEt_2$ = lithium diethylamide
SFC = supercritical fluid chromatography
PEPPSI = pyridine-enhanced precatalyst preparation stabilization initiation
$Pd(PPh_3)_4$ or $Pd(Ph_3P)_4$ = tetrakis(triphenylphosphine)palladium(0)
HOBt = 1-hydroxybenzotriazole
EDC = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.

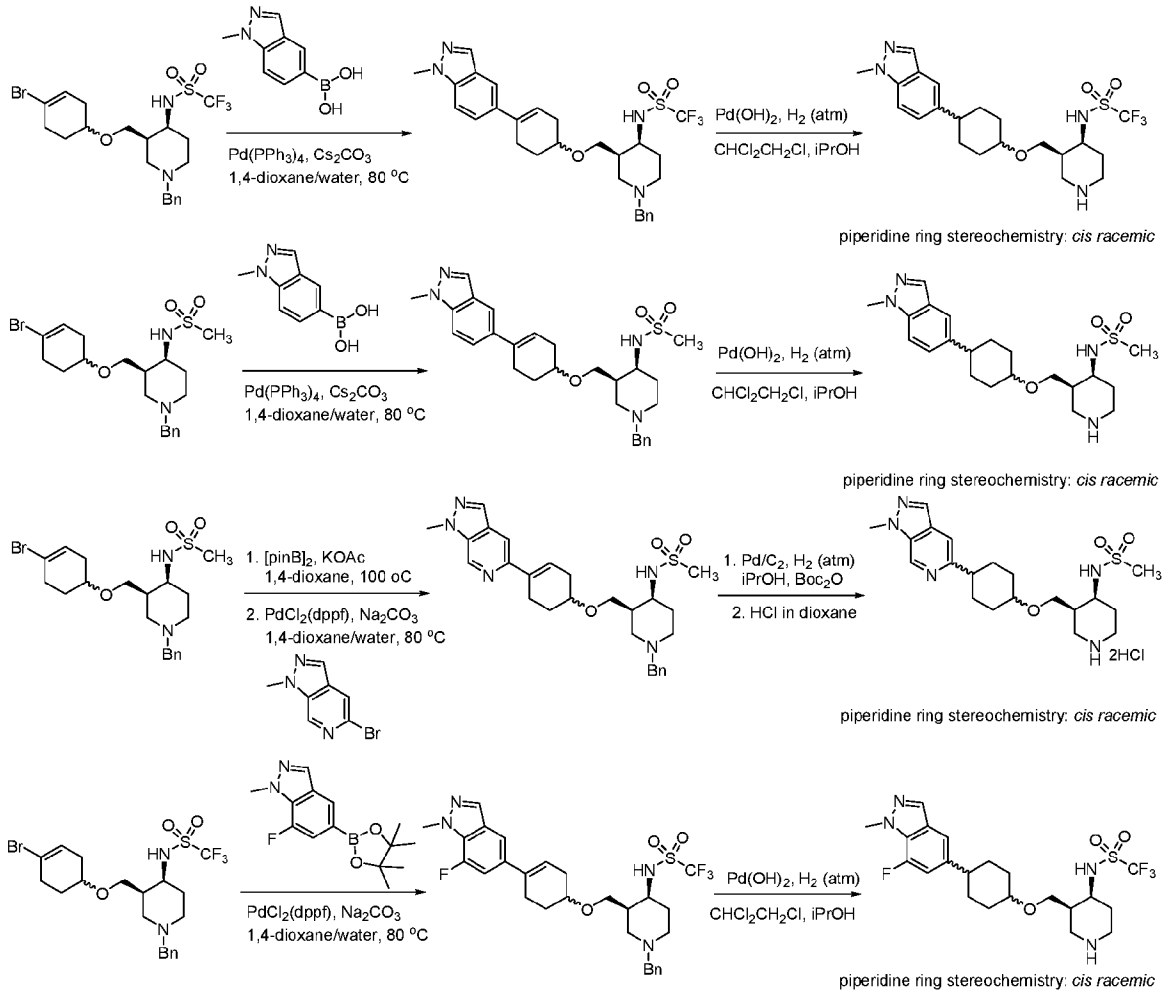
Scheme 1:



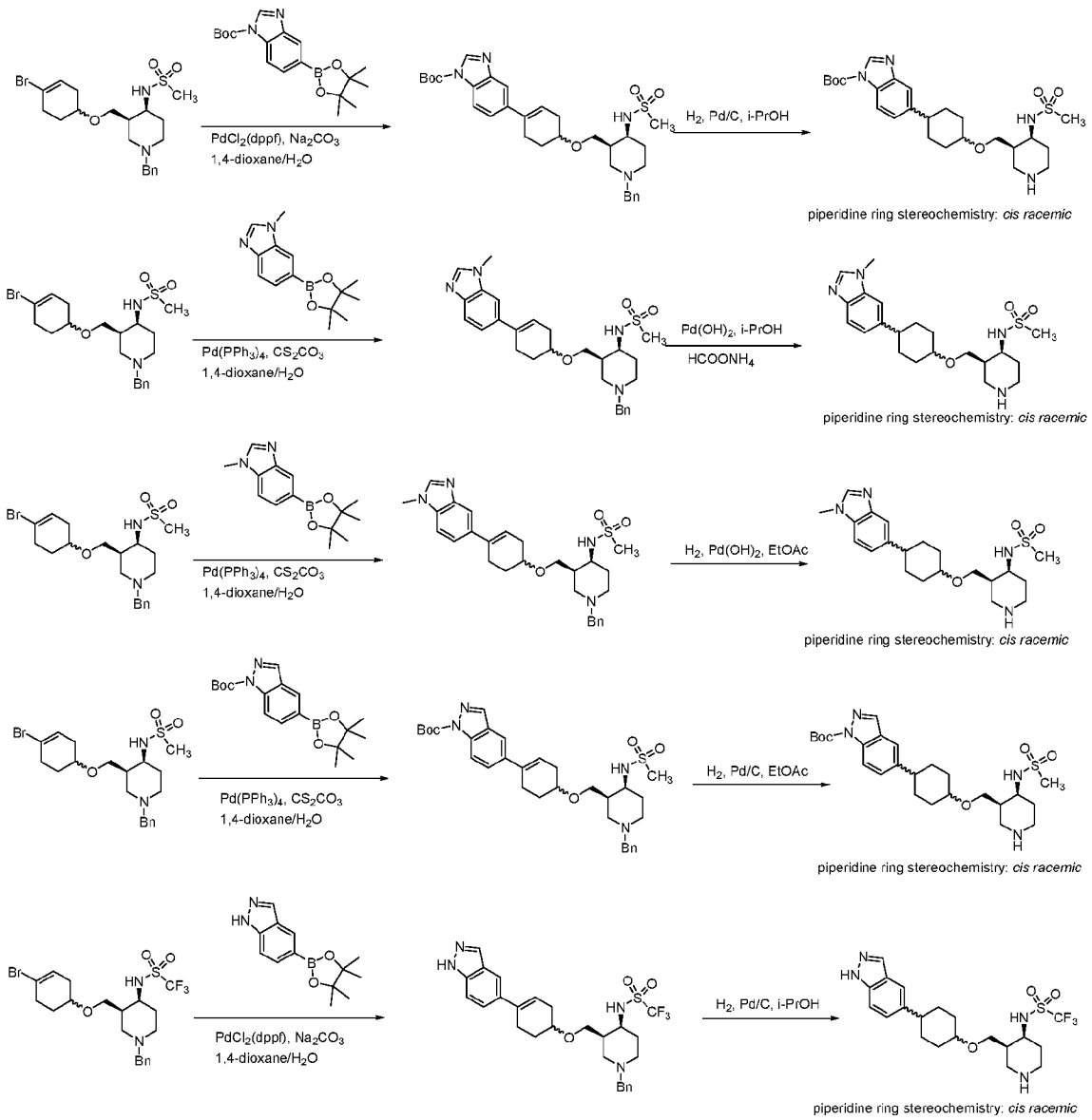
Scheme 2:


Boc2O, DIPEA
DCM
Achiral SFC
piperidine ring stereochemistry: cis racemic
Pd(dppf)Cl2·DCM, Na2CO3,
1,4-dioxane/H2O, 80 °C
piperidine ring stereochemistry: cis racemic
Pd/C, H2, iPrOH
piperidine ring stereochemistry: cis racemic
PEPPSI-Pd, Cs2CO3
DMSO, 120 °C
HCl, 1,4-Dioxane
piperidine ring stereochemistry: cis racemic
piperidine ring stereochemistry: cis racemic

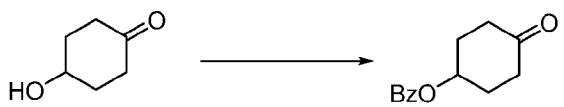
Scheme 3:


Pd(PPh3)4, Cs2CO3
1,4-dioxane/water, 80 °C
Pd(OH)2, H2 (atm)
CHCl2CH2Cl, iPrOH
piperidine ring stereochemistry: cis racemic
Pd(PPh3)4, Cs2CO3
1,4-dioxane/water, 80 °C
Pd(OH)2, H2 (atm)
CHCl2CH2Cl, iPrOH
piperidine ring stereochemistry: cis racemic
1. [pinB]2, KOAc
1,4-dioxane, 100 oC
2. PdCl2(dppf), Na2CO3
1,4-dioxane/water, 80 °C
1. Pd/C2, H2 (atm)
iPrOH, Boc2O
2. HCl in dioxane
2HCl
piperidine ring stereochemistry: cis racemic
PdCl2(dppf), Na2CO3
1,4-dioxane/water, 80 °C
Pd(OH)2, H2 (atm)
CHCl2CH2Cl, iPrOH
piperidine ring stereochemistry: cis racemic

Scheme 4:



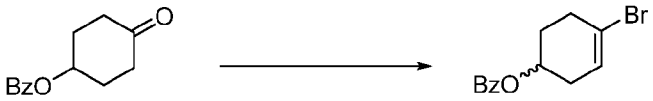
Scheme 1:



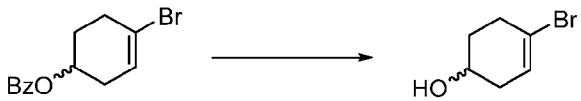
To a solution of 4-hydroxycyclohexan-1-one (10 g, 1 eq, 88 mmol) and DMAP (1.1 g, 0.1 eq, 8.8 mmol) in DCM (200 mL) was added benzoyl chloride (15 g, 1.2 eq, 0.11 mol) and triethylamine (13 g, 18 mL, 1.5 eq, 0.13 mol) at 0 degrees C. The resulting mixture was stirred at 25 degrees C for 3 hours. Desired product could be detected by LCMS. The resulting mixture was diluted with water and extracted with DCM (3 x 100 mL). The

combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel and eluted with EtOAc/PE (20% gradient) to afford 4-oxocyclohexyl benzoate (7.4 g, 34 mmol, 39 %) as an oil.

1H NMR (400 MHz, Methanol-d4) δ8.14–7.97 (m, 2H), 7.59 (dt, 1H), 7.47 (q, 2H), 5.39 (p, 1H), 2.62 (dt, 1H), 2.42 (dt, 1H), 2.19 (q, 3H), 2.01–1.69 (m, 3H).



To a stirred solution of triphenyl phosphite (8 g, 1.1 eq, 0.03 mol) in DCM (50 mL) was added Br_2 (4 g, 1 mL, 1.2 eq, 0.03 mol) at -60 degrees C. The mixture was stirred for 30 minutes at 25 degrees C. 4-oxocyclohexyl benzoate (5 g, 1 eq, 0.02 mol) and triethylamine (3 g, 1.3 eq, 0.03 mol) was added into the mixture at -60 degrees C. The resulting mixture was stirred for 16 hours at 25 degrees C. The resulting mixture was diluted with H_2O (50 mL) and extracted with DCM (3 X 210 mL). The combined organic layers were washed with brine (3X100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel and eluted with EtOAc/PE (0-25% gradient) to afford 4-bromocyclohex-3-en-1-yl benzoate (5 g, 0.02 mol, 80 %) as a solid. 1H NMR (CDCl3, 400 MHz)δ2.00–2.17 (2H, m), 2.30–2.43 (1H, m), 2.50–2.59 (1H, m), 2.59–2.77 (2H, m), 5.34 (1H, dtd), 6.01 (1H, tt), 7.42–7.51 (2H, m), 7.54–7.63 (1H, m), 8.02–8.09 (2H, m).

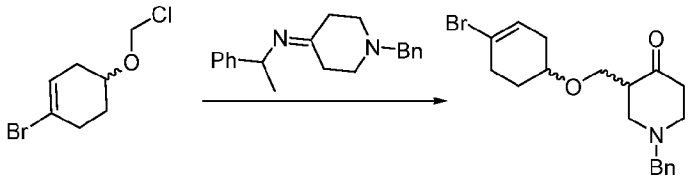


To a stirred solution of 4-bromocyclohex-3-en-1-yl benzoate (15 g, 1 eq, 53 mmol) in MeOH (150 mL) was added sodium methanolate (3.2 g, 1.1 eq, 59 mmol) in portions at 25 degrees C under N_2 atmosphere. The resulting mixture was stirred for 16 hours at 25 degrees C. Desired product could be detected by TLC. The resulting mixture was extracted with DCM (3x80 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel and eluted with EtOAc/PE (20% gradient) to afford 4-bromocyclohex-3-en-1-ol (7 g, 0.04 mol, 70 %) as an oil.

1H NMR (400 MHz, Methanol-d4) δ5.92 (ddt, 1H), 3.93 (dddd, 1H), 2.72–2.28 (m, 3H), 2.16–1.69 (m, 4H).

To a stirred solution of 4-bromocyclohex-3-en-1-ol (6.15 g, 1 eq, 34.7 mmol) and TMS-Cl (15.1 g, 17.6 mL, 4 eq, 139 mmol) in TMS-Cl (17 mL) was added paraformaldehyde (1.56 g, 1.5 eq, 52.1 mmol) in portions at 25 degrees C. The resulting mixture was stirred for 16 hours at 25 degrees C. The resulting mixture was filtered, the filter cake was washed with TMS-Cl (3 x 10 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

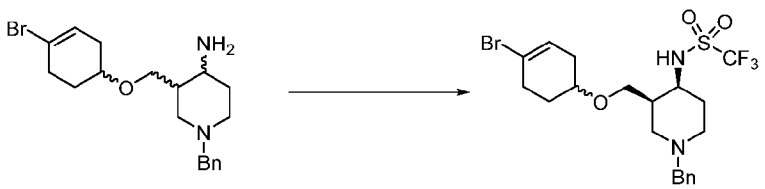
1H NMR (400 MHz, CDCl3, 22°C) δ1.8–2.05 (m, 2H), 2.13–2.44 (m, 2H), 2.45–2.66 (m, 2H), 4.12 (dddd, 1H), 5.58 (s, 1H), 5.94 (tt, 1H).



To a stirred solution of diethylamine (0.9 g, 1 mL, 1.2 eq, 0.01 mol) in tetrahydrofuran (24 mL) was added n-butyllithium (0.8 g, 1.2 eq, 0.01 mol) in portions at -78 degrees C under N_2 atmosphere. The resulting mixture was stirred for 30 minutes at -78 degrees C. To the above reaction mixture was added a solution of 1-benzyl-N-(1-phenylethyl)piperidin-4-imine (3 g, 1 eq, 0.01 mol) in tetrahydrofuran (15 mL) dropwise. The reaction mixture was stirred at -78 degrees C for an additional 1 hour. To the above reaction mixture was added a solution of 1-bromo-4-(chloromethoxy)cyclohex-1-ene (3g, 1.2eq,0.01mol) in tetrahydrofuran (15 mL) dropwise. The reaction mixture was stirred at -78 degrees C for an additional 1 hour. The reaction was quenched by the addition of saturated ammonium chloride solution and stirred for 1 hour. The resulting mixture was extracted with DCM (3 x 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, MeCN in NH_4HCO_3 water, 0% to

100% gradient in 25 min) to afford 1-benzyl-3-(((4-bromocyclohex-3-en-1-yl)oxy)methyl)piperidin-4-one (1.8 g, 4.8 mmol, 50 %) as an oil.
LCMS: m/z (ES+), [M+H]+ = 378.1.

To a stirred solution of 1-benzyl-3-(((4-bromocyclohex-3-en-1-yl)oxy)methyl)piperidin-4-one (2 g, 1 eq, 5 mmol) in MeOH (100 mL) was added added ammonium formate (5 g, 15 eq, 0.08 mol) followed by sodium cyanoborohydride (2 g, 6 eq, 0.03 mol) in portions over 15 minutes at 25 degrees C. The resulting mixture was stirred for 3 hours at 25 degrees C. The reaction was quenched by the addition of ammonium chloride saturated solution and stirred for 15 minutes. The resulting mixture was extracted with DCM (3 x 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, MeCN in NH_4HCO_3 water, 0% to 100% gradient in 20 min) to afford 1-benzyl-3-(((4-bromocyclohex-3-en-1-yl)oxy)methyl)piperidin-4-amine (1.5 g, 4.0 mmol, 70 %) as an oil.
LCMS: m/z (ES+), [M+H]+ = 379.25.



piperidine ring stereochemistry: *cis racemic*

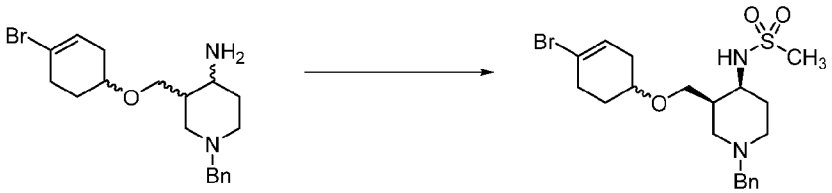
To a stirred solution of 1-benzyl-3-(((4-bromocyclohex-3-en-1-yl)oxy)methyl)piperidin-4-amine (5 g, 1 eq, 0.01 mol) and Et_3N (7 g, 9 mL, 5 eq, 0.07 mol) in DCM (250 mL) was added trifluoromethanesulfonic anhydride (4 g, 1.2 eq, 0.02 mol) in portions at -50 degrees C under N_2 atmosphere. The resulting mixture was stirred for 15 minutes at -50 degrees C. The reaction was quenched by the addition of saturated ammonium bicarbonate solution and stirred for 3 minutes. The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash

chromatography (column, C18 silica gel; mobile phase, MeCN in NH_4HCO_3 water, 0% to 100%) to afford desired product (5 g, 0.01 mol, 70 %) as an oil.

The mixture product (13.25g, combined from multiple batches) was purified by achiral SFC (column: DAICEL DCpak P4VP, 5*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: ACN: MEOH=4: 1(0.1% 2M NH_3-MEOH); Flow rate: 200 mL/min; Gradient: isocratic 30% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm) to afford the product (3.18 g, 4.8 mmol, 24 %, 97% purity) as an oil.

LCMS: m/z (ES+), [M+H]+ = 513.0.

(300 MHz, Chloroform-d) δ 7.53 – 7.02 (m, 6H), 5.89 (t, J = 4.4 Hz, 1H), 4.21 (t, J = 9.9 Hz, 1H), 3.79 – 3.22 (m, 5H), 2.80 (d, J = 11.7 Hz, 1H), 2.67 – 2.30 (m, 4H), 2.29 – 2.02(m, 4H), 2.02 – 1.72 (m, 4H).



piperidine ring stereochemistry: *cis racemic*

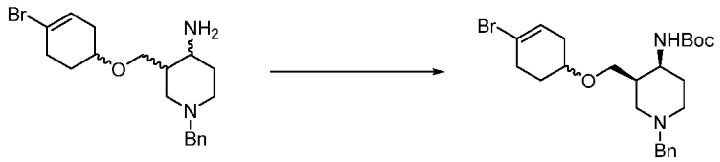
To a solution of 1-benzyl-3-(((4-bromocyclohex-3-en-1-yl)oxy)methyl)piperidin-4-amine (13.00 g, 1 eq, 34.27 mmol) in DCM (150 mL) was added TEA (10.40 g, 14.3 mL, 3 eq, 102.8 mmol). Then to the mixture was added methanesulfonic anhydride (7.163 g, 1.2 eq, 41.12 mmol) at 0 degrees C. The resulting mixture was stirred for 1.5 hours at 25 degrees C. The reaction was monitored by LCMS. The reaction was quenched by saturated $NaHCO_3$ solution. The resulting mixture was extracted with DCM (3 x 200 mL). The combined organic layers were concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 10% to 80% gradient in 40 min, hold 15 minutes at 60%) to afford the crude product (13.00 g, 28.42 mmol, 82.93 %) as an oil.

The product mixture (62g, combined from multiple batches) was purified by achiral SFC (column: DAICEL Dcpak P4VP, 4.6*50mm, 3um; Mobile Phase B: ACN: MeOH=80: 20(1% 2M NH_3-MeOH)) to afford the product (15 g, 33 mmol, 24.2 %).

(400 MHz, Chloroform-d) δ 7.38 – 7.24 (m, 5H), 5.92 (tq, J = 3.5, 1.8 Hz, 1H), 5.78 (d, J = 25.8 Hz, 1H), 3.99 (d, J = 17.4 Hz, 1H), 3.70 – 3.58 (m, 2H), 3.54 (td, J = 11.2, 10.2, 5.5Hz,

2H), 3.42 (d, J = 13.2 Hz, 1H), 2.97 (s, 3H), 2.69 (s, 1H), 2.63 – 2.43 (m, 3H), 2.43 – 2.25 (m, 3H), 2.25 – 2.03 (m, 2H), 2.03 – 1.76 (m, 4H).

Scheme 2:



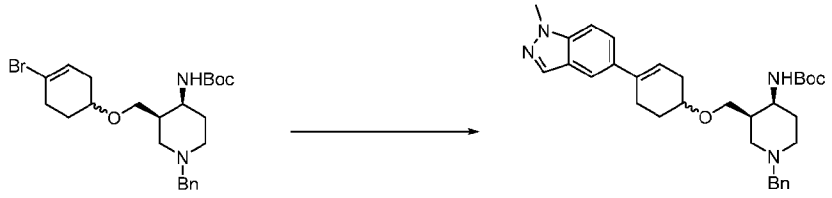
piperidine ring stereochemistry: *cis racemic*

To a solution of 1-benzyl-3-(((4-bromocyclohex-3-en-1-yl)oxy)methyl)piperidin-4-amine (8.02 g, 1 eq, 21.1 mmol) and N-ethyl-N-isopropylpropan-2-amine (8.20 g, 3 eq, 63.4 mmol) in DCM (80 mL) was added di-tert-butyl dicarbonate (4.61 g, 1 eq, 21.1 mmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The crude was purified by flash chromatography over silica gel and eluted with PE/EtOAc (0-12% gradient) to afford 4.5 g crude product as an oil.

The above mixture was purified by achiral SFC rep-achiral-SFC (column: Viridis BEH 2-EP, 100*4.6mmm, 5um; Mobile Phase B: MeOH (1% 2M NH_3-MeOH); Flow rate: 4 mL/min; Gradient: isocratic 5% B) to afford the product (1.79 g, 3.73 mmol, 17.9 %) as an oil.

LCMS: m/z (ES+), [M+H]+ = 481.1.

1H NMR (400 MHz, Chloroform-d) δ 7.33 (s, 5H), 5.91 (s, 1H), 5.68 (s, 1H), 3.83 (d, J = 47.2 Hz, 2H), 3.64 – 3.33 (m, 3H), 2.76 – 2.23 (m, 6H), 2.14 (d, J = 17.9 Hz, 2H), 2.03 (s, 1H), 1.97 – 1.73 (m, 3H), 1.46 (s, 9H).



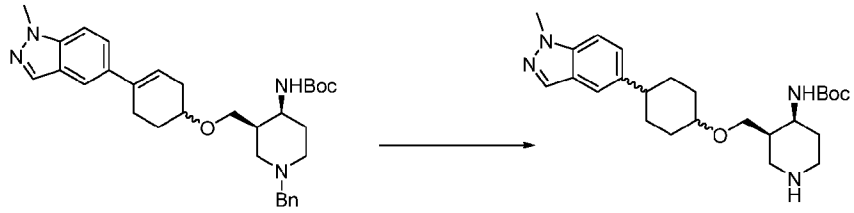
piperidine ring stereochemistry: *cis racemic*

To a solution of vinyl bromide (1.79 g, 1 eq, 3.73 mmol) and (1-methyl-1H-indazol-5-yl)boronic acid (723 mg, 1.1 eq, 4.11 mmol) in 1,4-dioxane (30 mL) and water (6.0 mL) were added Na_2CO_3 (1.19 g, 3 eq, 11.2 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (305 mg, 0.1 eq, 373 µmol). After stirring for 22 hours at 80 degrees C under a nitrogen atmosphere, the resulting mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 200 mL). The

combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with EtOAc/PE (2/1) to afford the product (1.68 g, 3.17 mmol, 84.8 %) as an oil.

LCMS: m/z (ES+), [M+H]+ = 531.5.

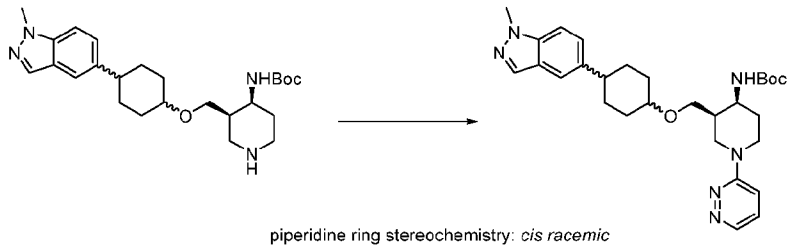
1H NMR (400 MHz, Chloroform-d) δ 7.96 (dd, J = 2.0, 1.0 Hz, 1H), 7.77 – 7.64 (m, 1H), 7.51 (dd, J = 8.8, 1.7 Hz, 1H), 7.41 – 7.25 (m, 7H), 6.01 (s, 1H), 4.09 (s, 3H), 3.94 (d, J = 25.8 Hz, 1H), 3.80 (s, 1H), 3.51 (s, 6H), 2.72 – 2.50 (m, 4H), 2.28 (d, J = 9.2 Hz, 2H), 2.07 (s, 1H), 1.86 (s, 2H), 1.65 (s, 2H), 1.51 – 1.22 (m, 9H), 1.05 (s, 1H).



piperidine ring stereochemistry: *cis racemic*

To a solution of tert-butyl olefin (1.65 g, 1 eq, 3.11 mmol) and 1,1,2-trichloroethane (498 mg, 347 µL, 1.2 eq, 3.73 mmol) in i-PrOH (40 mL) was added Pd/C (1.65 g, 10% Wt, 0.5 eq, 1.55 mmol) and palladium(2+) dihydroxide (2.18 g, 10% wt, 0.5 eq, 1.55 mmol) at nitrogen atmosphere. The resulting mixture was hydrogenated at room temperature for 4 hours under hydrogen atmosphere using a hydrogen balloon. Crude reaction mixture was filtered through a celite pad and concentrated under reduced pressure to afford the crude product. The crude product was used in the next step directly without further purification.

LCMS: m/z (ES+), [M+H]+ = 443.2.

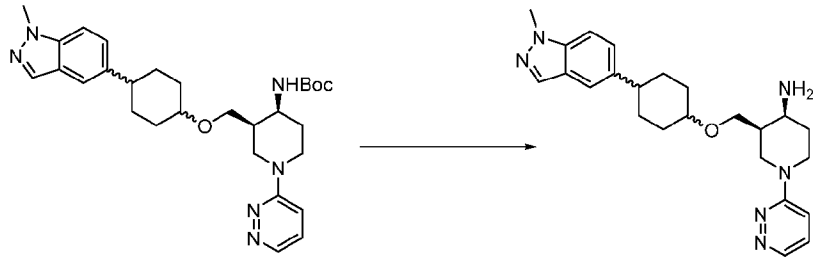


piperidine ring stereochemistry: *cis racemic*

To a solution of the amine (100.0 mg, 1 eq, 225.9 µmol) and 3-bromopyridazine (71.84 mg, 2 eq, 451.9 µmol) in DMSO (5 mL) was added Cs_2CO_3 (147.2 mg, 2 eq, 451.9 µmol) and PEPPSI-Pd (19.00 mg, 0.1 eq, 22.59 µmol). The resulting mixture was stirred for 4 hours at 120 degrees C under a nitrogen atmosphere. A total of 12 reactions were done in parallel. The

resulting mixture was extracted with ethyl acetate (3x200 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH/DCM=1/15) to afford the product (620 mg, 1.19 mmol, 47.7 %) as an oil.

LCMS: m/z (ES+), [M+H]+ =521.2.

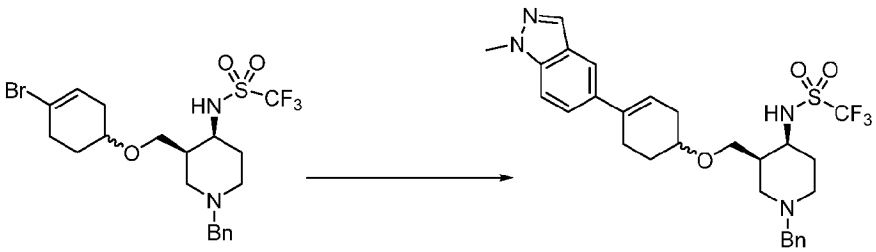


piperidine ring stereochemistry: *cis racemic*

To a stirred solution of Boc protected amine (200 mg, 1 eq, 384.1 µmol) in 1,4-dioxane (6 mL) was added HCl (70 mg, 480.1 µL, 4 molar, 5 eq, 1.921 mmol) at room temperature. The mixture solution was stirred for 1 hour at room temperature. The resulting solution was evaporated under reduced pressure to afford the product amine (150.0 mg, 356.7 µmol, 92.85 %) as a solid as HCl salt. The crude product was used in the next step directly without further purification.

LCMS: m/z (ES+), [M+H]+ = 421.30.

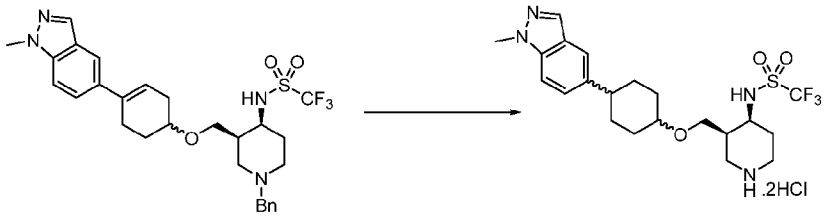
Scheme 3:



piperidine ring stereochemistry: *cis racemic*

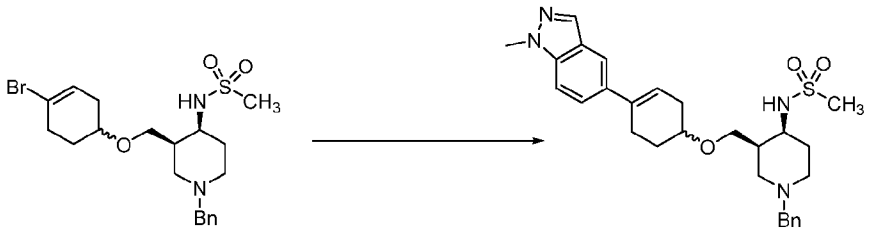
To a solution of vinyl bromide (1.50 g, 1 eq, 2.93 mmol) and $Pd(Ph_3P)_4$ (339 mg, 0.1 eq, 293 µmol) in 1,4-dioxane (20 mL) and water (4.0 mL) were added Cs_2CO_3 (2.87 g, 3 eq, 8.80 mmol) and (1-methyl-1H-indazol-6-yl)boronic acid (671 mg, 1.3 eq, 3.81 mmol). After stirring for 3 hours at 80 degrees C under a nitrogen atmosphere, the resulting mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (3x20 mL), dried over anhydrous Na_2SO_4. After filtration, the

filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with EtOAc/PE (5% TEA) to afford the product (930 mg, 1.65 mmol, 56.4 %) as a solid.
LCMS: m/z (ES+), [M+H]+ = 563.25.



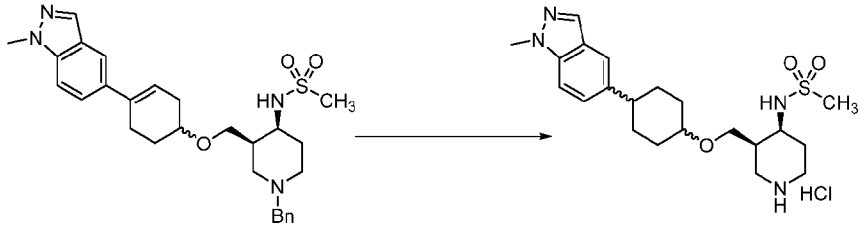
piperidine ring stereochemistry: *cis racemic*

To a solution of olefin (300 mg, 1 eq, 533 μmol) in i-PrOH (60 mL) was added $Pd(OH)_2$ (37.4 mg, 0.5 eq, 267 μmol), Pd/C (28.4 mg, 0.5 eq, 267 μmol) and 1,1,2-trichloroethane (142 mg, 2 eq, 1.07 mmol) at nitrogen atmosphere.
The resulting mixture was hydrogenated at room temperature for 3 hours under hydrogen atmosphere using a hydrogen balloon. The resulting mixture was filtered through a celite pad and concentrated under reduced pressure to afford the crude product as an HCl salt. The crude was used to the next step directly.
LCMS: m/z (ES+), [M+H]+ = 475.10.



piperidine ring stereochemistry: *cis racemic*

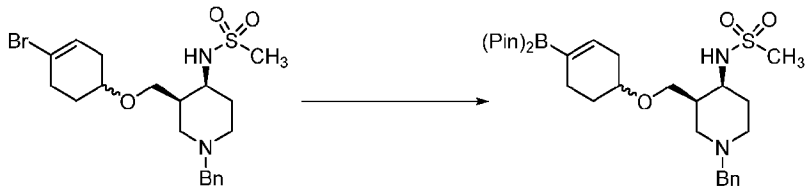
To the solution of vinyl bromide (2.00 g, 1 eq, 4.37 mmol) in 1,4-dioxane (20 mL) were added (1-methyl-1H-indazol-5-yl)boronic acid (846 mg, 1.1 eq, 4.81 mmol), K_2CO_3 (1.81 g, 3 eq, 13.1 mmol), water (4.0 mL) and $Pd(PPh_3)_4$ (505 mg, 0.1 eq, 437 μmol) at room temperature. The mixture solution was stirred for 2 hours at 80 degrees C under N_2 atmosphere. The reaction was monitored by LCMS. The mixture was diluted with water and extracted with EA. The combined organic phase was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 5 % to 65 % gradient in 30 min; detector, UV 254 nm) to afford the desired product (1.70 g, 3.34 mmol, 76.4 %) as an oil.
LCMS: m/z (ES+), [M+H]+ = 509.3.



piperidine ring stereochemistry: *cis racemic*

To the solution of olefin (1.70 g, 1 eq, 3.34 mmol) in i-PrOH (5 mL) were added 1,1,2-trichloroethane (892 mg, 621 µL, 2 eq, 6.68 mmol), $Pd(OH)_2$ (1.41 g, 10% wt, 0.3 eq, 1.00 mmol) and Pd/C (1.07 g, 10% wt, 0.3 eq, 1.00 mmol) at room temperature. The mixture was stirred for 32 hours at 20 degrees C under H_2 atmosphere. The reaction was monitored by LCMS. The solution was filtered through a celite pad and concentrated under reduced pressure to afford the product (1.40 g, 3.06 mmol, 92 %).

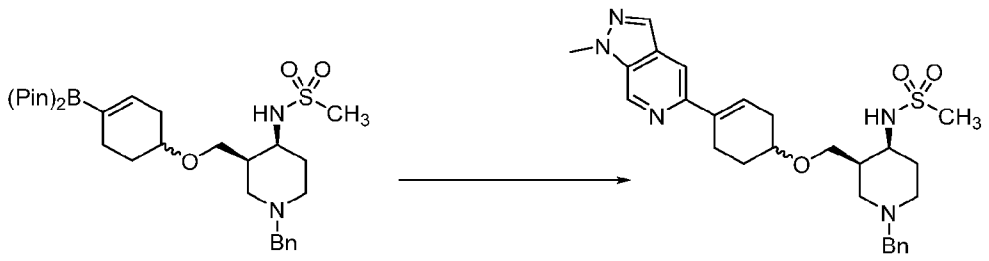
LCMS: m/z (ES+), [M+Na]+ = 421.25.



piperidine ring stereochemistry: *cis racemic*

To a solution of vinyl bromide (2.00 g, 1 eq, 4.37 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.67 g, 1.5 eq, 6.56 mmol) and KOAc (858 mg, 2 eq, 8.74 mmol) in dioxane (20 mL) was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (179 mg, 0.05 eq, 219 µmol). The resulting mixture was stirred for 4 hours at 100 degrees C under nitrogen atmosphere. The resulting mixture was filtered, the filtered cake was washed with EA (3x10 mL). The filtrate was concentrated under reduced pressure. The crude product (1.8 g) was used in the next step directly without further purification.

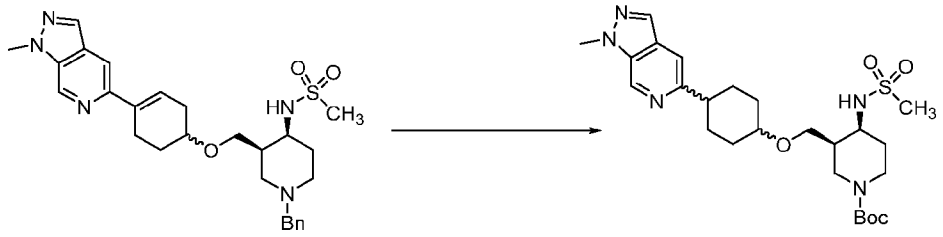
LCMS: m/z (ES+), [M+H]+ =505.



piperidine ring stereochemistry: *cis racemic*

To a solution of boronic ester (550 mg, 1 eq, 1.09 mmol) and 5-bromo-1-methyl-1H-pyrazolo[3,4-c]pyridine (231 mg, 1 eq, 1.09 mmol) in 1,4-dioxane (8 mL) and H_2O (0.2 ml) was added Na_2CO_3 (347 mg, 3 eq, 3.27 mmol) and PdCl2(dppf).CH_2Cl_2 adduct (44.5 mg, 0.05 eq, 54.5 µmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at 80 degrees C. The resulting mixture was filtered, the filtered cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water(NH_4HCO_3), mobile phase B: ACN, 55 % to 65 % gradient in 10 min; detector, UV 254 nm) to afford crude (220 mg) as a solid. The crude was purified by Prep-TLC (EA/PE=4/1,5%TEA) to afford the product (180 mg, 353 µmol, 32.4 %) as a solid.

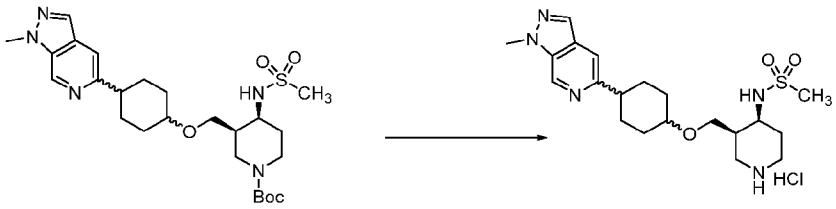
LCMS: m/z (ES+), [M+H]+ =510.0.



piperidine ring stereochemistry: *cis racemic*

To a solution of olefin (150 mg, 1 eq, 294 µmol) and Boc_2O (128 mg, 135 µL, 2 eq, 589 µmol) in i-PrOH (18 mL) was added Pd/C (150 mg, 10% wt, 0.479 eq, 141 µmol) under nitrogen atmosphere. The resulting mixture was hydrogenated at room temperature for 30 hours under hydrogen atmosphere using a hydrogen balloon. Reaction mixture was filtered through a celite pad and concentrated under reduced pressure to afford the crude product. The crude product was used in the next step directly without further purification.

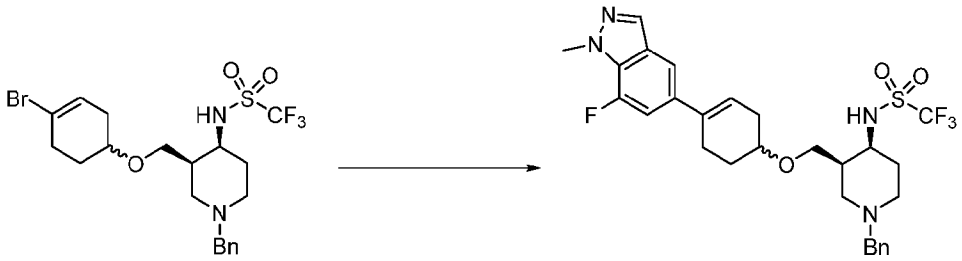
LCMS: m/z (ES+), [M+H]+ =522.



piperidine ring stereochemistry: *cis racemic*

A solution of N-Boc protected amine (150 mg, 1 eq, 288 µmol) and HCl in 1,4-dioxane (2 mL) was stirred for 1.5 hours at 25 degrees C. The resulting mixture was concentrated under reduced pressure to afford the crude product. The crude was lyophilized to afford the product amine as HCl salt (110 mg, 240 µmol, 83.5 %) as a solid.

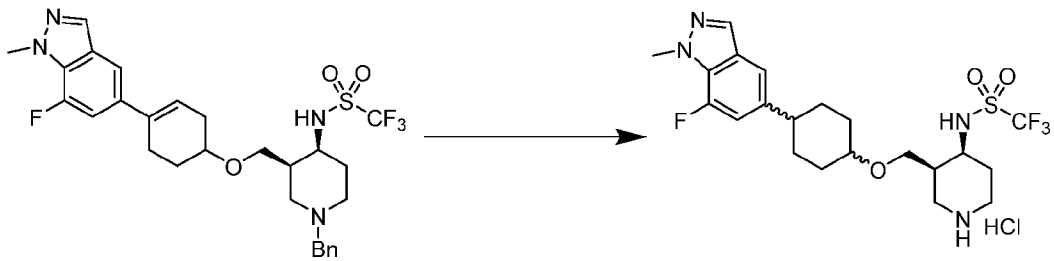
LCMS: m/z (ES+), [M+H]+ =422.



piperidine ring stereochemistry: *cis racemic*

To a solution of vinyl bromide (1.68 g, 1 eq, 3.29 mmol) and 7-fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (1 g, 1 eq, 4 mmol) and $PdCl_2(dppf).CH_2Cl_2$ adduct (240 mg, 0.1 eq, 329 µmol) and Na_2CO_3 (1.04 g, 3 eq, 9.86 mmol) in dioxane (10 mL) and water (2 mL) . The resulting mixture was stirred for 4 hours at 80 degrees C. The resulting mixture was extracted with ethyl acetate/water (3x100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel eluted with EtOAc/PE (0-100% gradient) to afford product (3.17 g, 5.46 mmol, 60 %).

LCMS: m/z (ES+), [M+H]+ = 581.45.

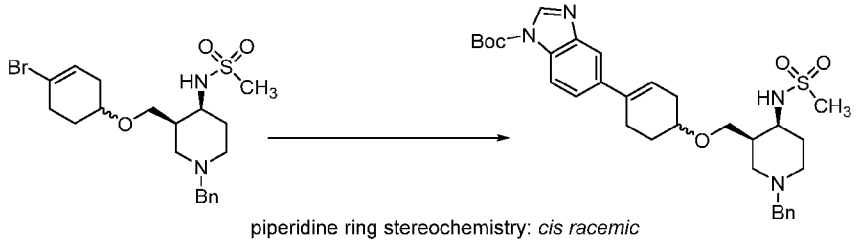


piperidine ring stereochemistry: *cis racemic*

To a solution of the olefin (2.17 g, 1 eq, 3.74 mmol) was added $Pd(OH)_2$ (2.10 g, 4 eq, 14.9 mmol) and 1,1,2-trichloroethane (499 mg, 347 µL, 1 eq, 3.74 mmol) and Pd/C (1.99 g, 5 eq, 18.7 mmol) in i-PrOH (10 mL). The resulting mixture was stirred for 3 hours at 25 degrees C. The resulting mixture was filtered, the filtered cake was washed with [isopropanol + hydrochloric acid (10%)] (3x100 ML). The filtrate was concentrated under reduced pressure to afford the product (1.92g, 2.7 mmol, 73 %, 73% purity).

LCMS: m/z (ES+), [M+H]+ = 493.10.

Scheme 4:

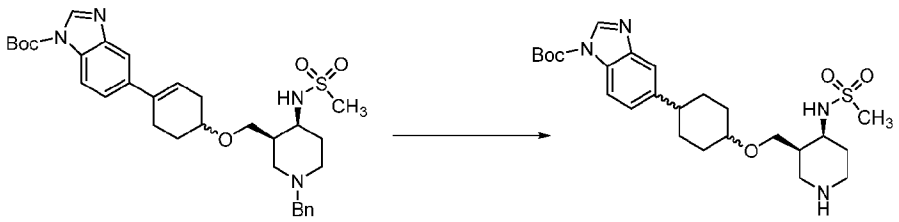


piperidine ring stereochemistry: *cis racemic*

To a test-tube fitted with an air-tight screw cap was added vinyl bromide (100 mg, 1 eq, 219 µmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole-1-carboxylate (97.8 mg, 1.3 eq, 284 µmol), Na_2CO_3 (69.5 mg, 3 eq, 656 µmol), dioxane (2 mL) and H_2O (0.7 mL) followed by $PdCl_2(dppf)$ (16.0 mg, 0.1 eq, 21.9 µmol). The resulting mixture was stirred at 80 degrees C for 1 hour. The reaction mixture was extracted with DCM (3x100mL) and water. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and purified by thin layer chromatography (PE:EA=1:3) to afford the product (70 mg, 0.10 mmol, 47 %, 87% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 595.30.

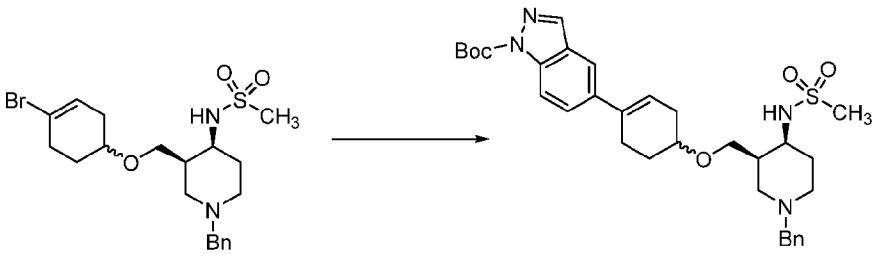
1H NMR (400 MHz, Chloroform-d) δ 1.24-1.32 (m, 2H), 1.73 (s, 9H), 1.89 (s, 3H), 2.07 (s, 1H), 2.31 (s, 5H), 2.58 (s, 3H), 2.65 (s, 3H), 2.93 (d, 3H), 3.43 (s, 1H), 3.51 (s, 1H), 3.69 (s, 3H), 4.15 (q, 1H), 6.07 (s, 1H), 7.33 (s, 6H), 7.43 (dd, 1H), 7.72 (d, 1H), 8.05 (s, 1H), 8.41 (s, 1H).



piperidine ring stereochemistry: *cis racemic*

To a test-tube fitted with an air-tight screw cap was added tert-butyl 5-(4-(((3R,4S)-1-benzyl-4-(methylsulfonamido)piperidin-3-yl)methoxy)cyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1-carboxylate (150 mg, 1 eq, 252 µmol), H_2 (5.09 mg, 10 eq, 2.52 mmol), i-PrOH (4 mL) and followed by Pd/C (8.05 mg, 0.3 eq, 75.7 µmol). The resulting mixture is stirred at 25 degrees C for 12 hours. At which point LCMS analysis indicated completion of the reaction, then the reaction mixture was filtered through a pad of celite and rinsed thoroughly with methylene chloride. The filtrate was concentrated under reduced pressure and the crude material was purified by thin layer chromatography (PE:EA=1:2) to afford product amine (60 mg, 0.12 mmol, 47 %) as a solid. LCMS: m/z (ES+), [M+H]+ = 507.25.

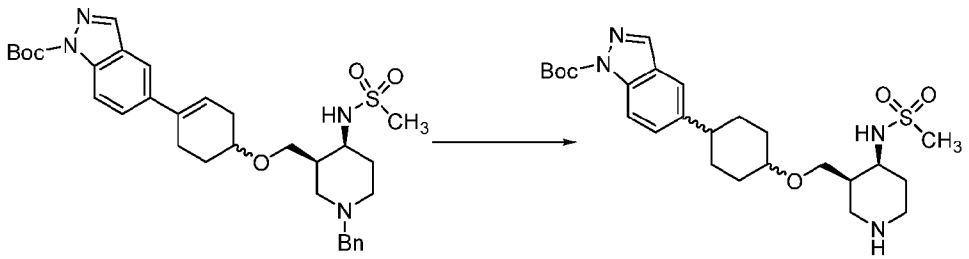
1H NMR (400 MHz, Chloroform-d) δ 0.04-0.13 (m, 1H), 0.09 (s, 12H), 1.22-1.33 (m, 5H), 1.30 (s, 1H), 1.39-1.53 (m, 1H), 1.72 (d, 11H), 1.79 (d, 1H), 1.90 (s, 1H), 1.94-2.14 (m, 2H), 2.22 (d, 2H), 2.63-2.74 (m, 1H), 2.83-3.15 (m, 2H), 3.01 (s, 2H), 3.59-3.74 (m, 2H), 3.78 (s, 1H), 3.93 (q, 1H), 6.06 (s, 1H), 6.19 (s, 0H), 7.26-7.37 (m, 1H), 7.71 (dd, 1H), 7.86-7.93 (m, 1H), 8.35-8.43 (m, 1H).



piperidine ring stereochemistry: *cis racemic*

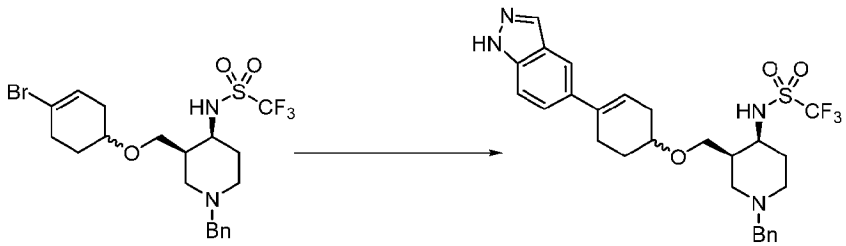
To a stirred mixture of vinyl bromide (3.60 g, 1 eq, 7.87 mmol) and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate (2.84 g, 1.05 eq, 8.26 mmol) and Na_2CO_3(139 mg, 3 eq, 1.31 mmol) in 1,4-dioxane (32 mL) and H_2O (0.4 ml) was added PdCl2(dppf) (576 mg, 0.1 eq, 787 µmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at 80 degrees C. The resulting mixture was extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure. The

crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 90 % to 100 % gradient in 20 min; detector, UV 254 nm) to afford a mixture. The mixture was concentrated under reduced pressure to afford crude (4.3 g) as a solid. This material was repurified by flash chromatography over silica gel eluted with EtOAc/PE (100% gradient) to afford the product (2.56 g, 4.30 mmol, 54.7 %) as a solid. LCMS: m/z (ES+), [M+H]+ =595.



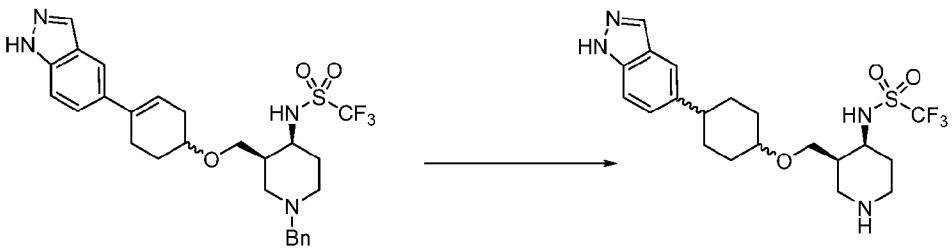
piperidine ring stereochemistry: *cis racemic*

To a solution of tert-butyl olefin (1.500 g, 1 eq, 2.522 mmol) in i-PrOH (170 mL) was added Pd/C (1.5 g, 10% wt, 0.56 eq, 1.4 mmol) at nitrogen atmosphere. The resulting mixture was stirred at room temperature for 5 days under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford the crude product (1 g). LCMS: m/z (ES+), [M+H]+ =507.



piperidine ring stereochemistry: *cis racemic*

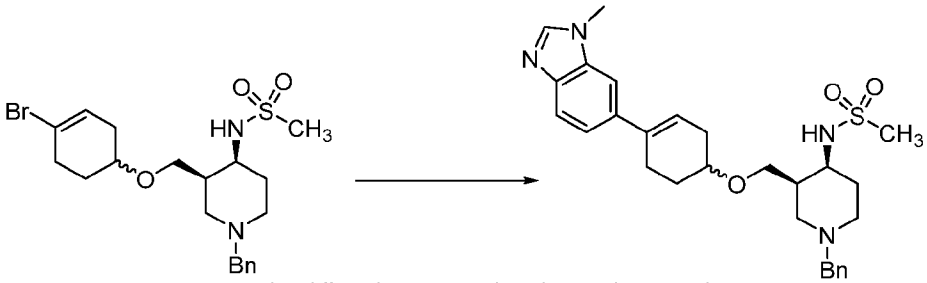
To a solution of vinyl bromide (250 mg, 1 eq, 489 µmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (143 mg, 1.2 eq, 587 µmol) in water (5 mL) 1,4-dioxane (20 mL) was added Na_2CO_3 (155 mg, 3 eq, 1.47 mmol) and $PdCl_2$(dppf) (200 mg, 0.5 eq, 244 µmol). The resulting mixture was stirred for 8 hours at 80 degrees C. The resulting mixture was extracted with dichloromethane (3x20mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EA/PE=1/1) to afford the product (100 mg, 182 µmol, 37.3 %) as a solid. LCMS: m/z (ES+), [M+H]+ = 549.20.



piperidine ring stereochemistry: *cis racemic*

To a solution of the olefin (139 mg, 1 eq, 253 µmol) in i-PrOH (20 mL) was added Pd/C (135 mg, 5 eq, 1.27 mmol). The resulting mixture was stirred for 8 hours at 25 degrees C under hydrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture filtered, the filtrate was concentrated under reduced pressure to the product amine (68 mg, 148 µmol, 58.7 %) as a solid.

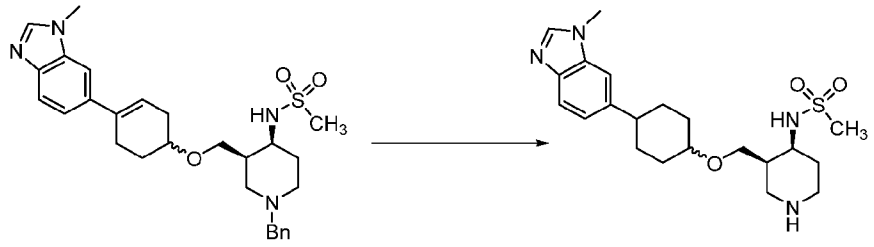
LCMS: m/z (ES+), [M+H]+ = 461.35.



piperidine ring stereochemistry: *cis racemic*

To a stirred mixture of vinyl bromide (300 mg, 1 eq, 656 µmol) and 3-hydroxy-2,3-dimethylbutan-2-yl hydrogen (1-methyl-1H-benzo[d]imidazol-6-yl)boronate (217 mg, 1.2 eq, 787 µmol) in 1,4-dioxane (15mL) and water (0.8 mL) were added Cs_2CO_3 (641 mg, 3 eq, 1.97 mmol) and Pd(Ph3P)4 (152 mg, 0.2 eq, 131 µmol) at room temperature under nitrogen atmosphere. The final reaction mixture was stirred for 3 hours at 80 degrees C. The resulting mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: 8mmol NH_4HCO_3, mobile phase B: ACN, 10 % to 90 % gradient in 45 min) to afford the product (180 mg, 354 µmol, 54.0 %) as an oil.

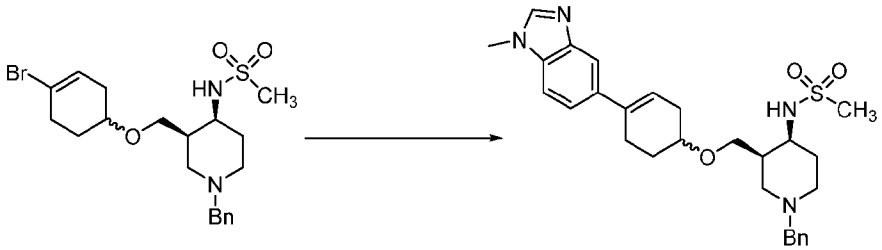
LCMS: m/z (ES+), [M+H]+ =509.



piperidine ring stereochemistry: *cis racemic*

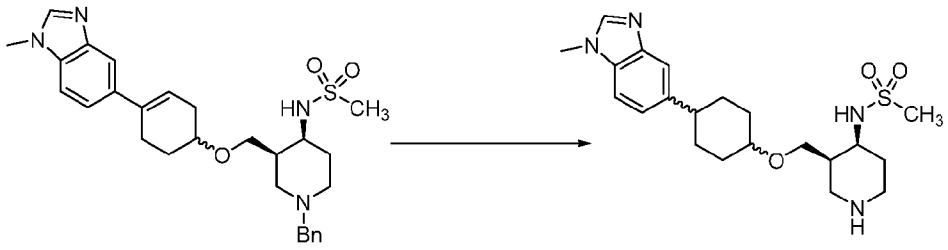
To a solution of olefin (180 mg, 1 eq, 354 µmol) in i-PrOH (10 mL) was added $Pd(OH)_2$ (24.8 mg, 0.5 eq, 177 µmol) and ammonium formate (223 mg, 176 µL, 10 eq, 3.54 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 1 hour at 60 degrees C. After filtration, the filtrate was concentrated under reduced pressure to afford crude product (130 mg, 309 µmol, 87.4 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =421.



piperidine ring stereochemistry: *cis racemic*

To a solution of vinyl bromide (1.0 g, 1 eq, 2.2 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (0.68 g, 1.2 eq, 2.6 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added $Pd(Ph_3P)_4$ (0.51 g, 0.2 eq, 0.44 mmol) and Cs_2CO_3 (2.1 g, 3 eq, 6.6 mmol). The resulting mixture was stirred for 3 hours at 80 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH/DCM=1/10) to afford the product (678 mg, 1.2 mmol, 55 %, 90% purity) as a semi-solid. LCMS: m/z (ES+), [M+H]+ = 509.30.

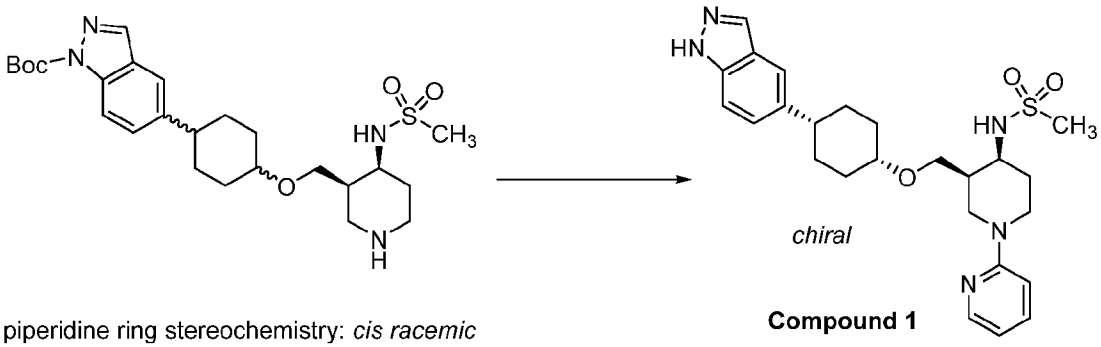


piperidine ring stereochemistry: *cis racemic*

To a solution of olefin (400 mg, 1 eq, 786 µmol) and 1,1,2-trichloroethane (210 mg, 2 eq, 1.57 mmol) in ethyl acetate (18 mL) was added Pd/C (400 mg, 10% wt, 0.478 eq, 376 µmol) and $Pd(OH)_2$ (400 mg, 3.62 eq, 2.85 mmol). The resulting mixture was hydrogenated at room temperature for 16 hours under hydrogen atmosphere using a hydrogen balloon. The reaction was monitored by LCMS. The mixture was filtered through a celite pad and concentrated under reduced pressure to afford the crude product (330 mg).

LCMS: m/z (ES+), [M+H]+ =421.20.

Compound 1:



piperidine ring stereochemistry: *cis racemic*

Compound 1

To a solution of amine (700 mg, 1 eq, 1.38 mmol) and pyridin-2-yl trifluoromethanesulfonate (471 mg, 1.5 eq, 2.07 mmol) in DMSO (13 mL) was added TEA (280 mg, 385 µL, 2 eq, 2.76 mmol). The resulting mixture was stirred for 5 hours at 120 degrees C. The resulting mixture was extracted with dichloromethane (3x15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water (NH_4HCO_3), mobile phase B: ACN, 45 % to 55 % gradient in 10 min) to afford isomeric mixture of product (330 mg, 565 µmol, 40.9 %) as a solid.

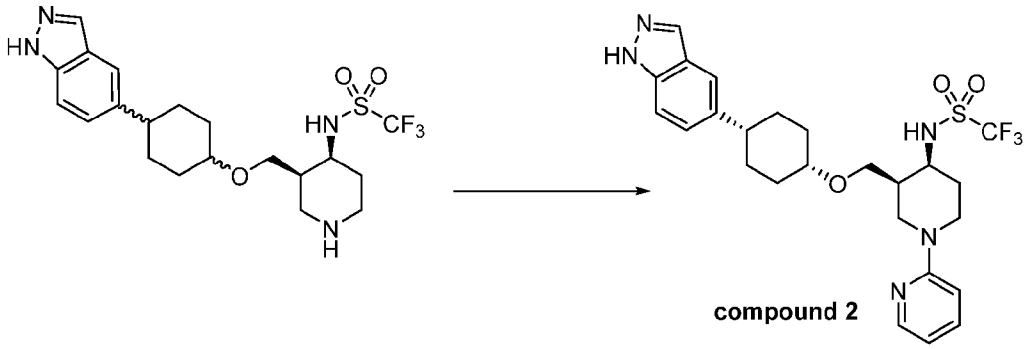
The isomeric mixture was separated by chiral prep-HPLC (Column: CHIRALPAK IG, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 19 min) to afford N-

((3R,4S)-3-((((1s,4S)-4-(1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl)methanesulfonamide (101 mg, 209 µmol, 34%) as a solid.

LCMS: m/z (ES+), [M+H]+ = 484.

1H NMR (400 MHz, Methanol-d4) δ 8.07 (ddd, J = 5.1, 2.0, 0.9 Hz, 1H), 7.97 (d, J = 1.0 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.55 – 7.43 (m, 2H), 7.33 (dd, J = 8.7, 1.6 Hz, 1H), 6.88 (dt, J = 8.7, 0.9 Hz, 1H), 6.63 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 3.88 (dq, J = 12.0, 6.7, 6.1 Hz, 2H), 3.78 (dd, J = 13.3, 6.8 Hz, 1H), 3.69 (dd, J = 9.4, 5.9 Hz, 1H), 3.64 (d, J = 4.0 Hz, 1H), 3.61 – 3.54 (m, 2H), 3.50 – 3.42 (m, 1H), 3.37 (s, 1H), 3.06 (s, 3H), 2.72 – 2.64 (m, 1H), 2.30 (dq, J = 10.7, 7.3, 5.5 Hz, 1H), 2.09 (d, J = 12.9 Hz, 2H), 1.97 – 1.82 (m, 4H), 1.72 – 1.56 (m, 4H).

Compound 2:



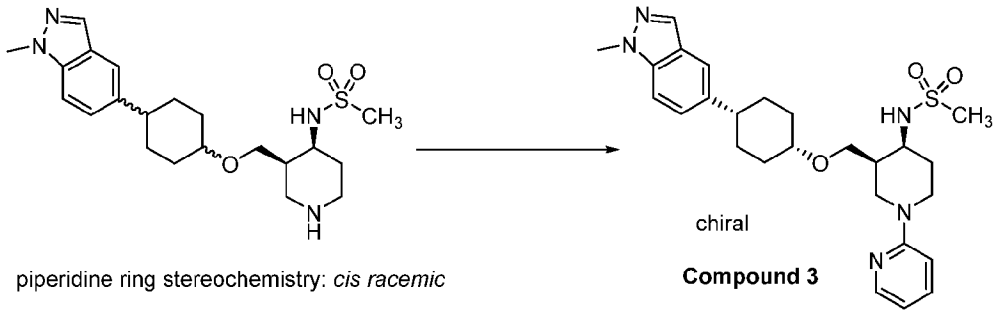
piperidine ring stereochemistry: *cis racemic* piperidine ring stereochemistry: *cis racemic*

To a solution of amine (80 mg, 1 eq, 0.17 mmol) in DMSO (4 mL) was added TEA (35 mg, 48 µL, 2 eq, 0.35 mmol) and 1,1,1-trifluoro-N-(pyridin-2-yl)methanesulfonamide (59 mg, 1.5 eq, 0.26 mmol). The resulting mixture was stirred for 8 hours at 120 degrees C. The reaction was monitored by LCMS, The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 0 % to 55% gradient in 20 minutes and keep the gradient for 30 minutes; detector, UV 254 nm) to afford isomeric mixture of product (17 mg, 32 µmol, 18 %) as a solid. Above 17 mg material was re-purified by reverse flash chromatography (column: XBridge Prep OBD C18 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: 40% B to 68% B in 8 min, 68% B) to afford racemic mixture of N-((3R,4S)-3-((((1s,4S)-4-(1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl) -1,1,1-trifluoromethanesulfonamide and N-((3R,4S)-3-((((1s,4S)-4-(1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl) -1,1,1-trifluoromethanesulfonamide (4.1 mg, 7.6 µmol, 24 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 538.1.

1H NMR (400 MHz, Chloroform-d) δ 8.19 (d, J = 5.1 Hz, 1H), 8.04 (s, 1H), 7.87 (d, J = 6.4 Hz, 1H), 7.60 (s, 1H), 7.54 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 6.69 (s, 2H), 4.31 (d, J = 13.7 Hz, 1H), 4.06 (dq, J = 22.6, 13.0 Hz, 3H), 3.78 (s, 1H), 3.68 (s, 1H), 3.18 (d, J = 52.7 Hz, 2H), 2.66 (s, 1H), 2.53 (d, J = 8.3 Hz, 1H), 2.09 (s, 4H), 1.76 (d, J = 9.1 Hz, 6H).

Compound 3:

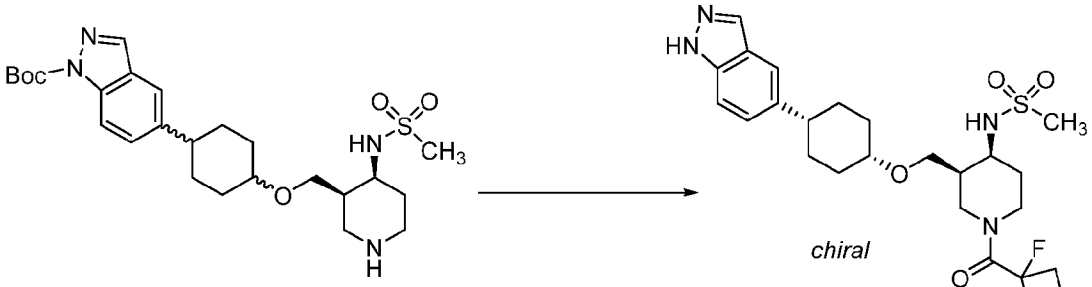


To a solution of amine (300 mg, 1 eq, 713 µmol) and Et_3N (144 mg, 199 µL, 2 eq, 1.43 mmol) in DMSO (5 mL) was added pyridin-2-yl trifluoromethanesulfonate (243 mg, 1.5 eq, 1.07 mmol). The resulting mixture was stirred for 12 hours at 120 degrees C. The resulting mixture was extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EA) to afford isomeric mixture of the product (135 mg, 271 µmol, 38.0 %) as a solid. The product (135 mg) was purified by Prep-HPLC (Column: XBridge Prep OBD C18 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: 39% B to 63% B in 8 min, 63% B) to afford two peaks. The more polar product (50 mg) was purified by Chiral-Prep-HPLC (Column: DZ-CHIRALPAK IG-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=60: 40) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl)methanesulfonamide (11.9 mg, 23.9 µmol, 24 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 498.

1H NMR (400 MHz, Methanol-d4) δ 8.15 – 8.05 (m, 1H), 7.92 (d, J = 0.9 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.50 – 7.44 (m, 1H), 7.35 (dd, J = 8.7, 1.6 Hz, 1H), 6.92 – 6.85 (m, 1H), 6.71 – 6.9 (m, 1H), 4.05 (s, 3H), 3.87 – 3.78 (m, 2H), 3.77 – 3.48 (m, 6H), 3.05 (s, 3H), 2.70 – 2.61 (m, 1H), 2.27 – 2.16 (m, 3H), 2.00 – 1.82 (m, 4H), 1.66 – 1.35 (m, 5H).

Compound 4:



To a solution of amine (50 mg, 1 eq, 99 µmol) and 1-fluorocyclobutane-1-carboxylic acid (17 mg, 1.5 eq, 0.15 mmol) in DCM (2 mL) was added N-ethyl-N-isopropylpropan-2-amine (38 mg, 3 eq, 0.30 mmol) N,N-dimethylpyridin-4-amine (1.2 mg, 0.1 eq, 9.9 µmol) 1H-benzo[d][1,2,3]triazol-1-ol hydrate (23 mg, 1.5 eq, 0.15 mmol) and 3-(((ethylimino)methylene)amino) -N,N-dimethylpropan-1-amine (23 mg, 1.5 eq, 0.15 mmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The reaction was monitored by LCMS. The resulting mixture was extracted with dichloromethane (3x5 mL). The combined organic layers were washed with brine, dried over anhydrous Na2SO4, after filtration, the filtrate was concentrated under reduced pressure to afford isomeric mixture of product (58 mg, 96 umol, 97 %) as an oil.

LCMS: m/z (ES+), [M+H]+ = 607.55.

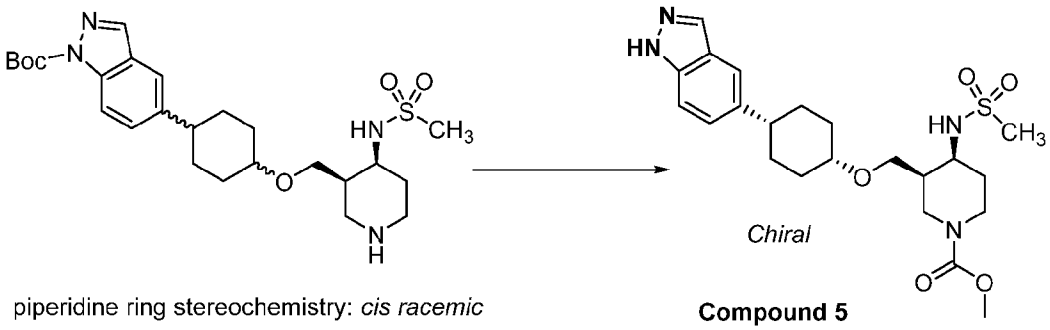
To a stirred mixture of above tert-butyl 5-(4-(((3R,4S)-1-(1-fluorocyclobutane-1-carbonyl)-4-(methylsulfonamido)piperidin-3-yl)methoxy)cyclohexyl)-1H-indazole-1-carboxylate (78 mg, 1 eq, 0.13 mmol) in DCM (5 mL) was added a solution of TFA (1 ml) dropwise at 25 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 hours at 25 degrees C. The resulting mixture was extracted with dichloromethane (3x10mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC (Column: X Bridge Shield RP18 OBD Column, 30*150 mm, 5µm; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 48% B in 8 min, 48% B) followed by chiral prep-HPLC (Column: CHIRALPAK IC, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 14 min) to afford desired isomer N-((3R, 4S)-3-((((1s,4R)-4-(1H-indazol-5-

yl)cyclohexyl)oxy)methyl)-1-(1-fluorocyclobutane-1-carbonyl)piperidin-4-yl)methanesulfonamide (6 mg, 0.01 mmol, 30 %, 99.5% Purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 507.45.

1H NMR (400 MHz, Chloroform-d) δ 8.09 (s, 1H), 7.66 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 5.2 Hz, 1H), 4.06 – 3.83 (m, 2H), 3.82 – 3.59 (m, 5H), 3.46 (dd, J = 56.8, 13.4 Hz, 2H), 3.01 (s, 3H), 2.72 (d, J = 30.5 Hz, 3H), 2.37 (d, J = 58.6 Hz, 3H), 2.17 – 1.86 (m, 6H), 1.72 (d, J = 46.7 Hz, 6H).

Compound 5:



To a solution of amine (70 mg, 1 eq, 0.14 mmol) in DCM (2 mL) was added pyridine (87 mg, 89 µL, 8 eq, 1.1 mmol) and triphosgene (20 mg, 0.5 eq, 69 µmol). The resulting mixture was stirred for 2 hours at 25 degrees C. Solvent was removed and MeOH (2 ml) was added to the mixture. The resulting mixture was stirred for 0.5 hours at 80 degrees C, the reaction mixture was monitored by LCMS. The crude was purified by reverse phase chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 5 % to 95 % gradient in 30 min; detector, UV 254 nm) to afford isomeric mixture of product (78 mg, 0.14 mmol, 100 %) as a solid.

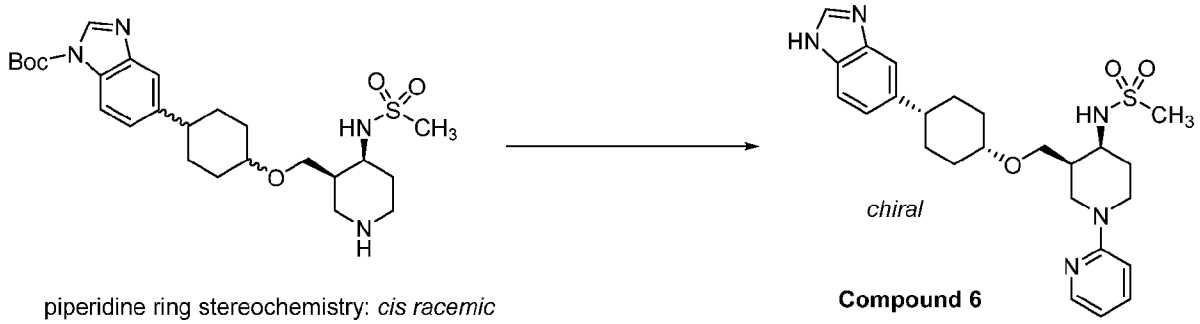
LCMS: m/z (ES+), [M+H]+ = 565.20.

The above mixture was purified by prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5µm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 37% B to 48% B in 7 min, 48% B) followed by prep-Chiral-HPLC (Column: DZ-CHIRALPAK IF-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (MeOH: DCM=1: 1)=80: 20) to afford methyl (3R,4S)-3-((((1s,4R)-4-(1H-indazol-5-yl)cyclohexyl)oxy)methyl)-4-(methylsulfonamido)piperidine-1-carboxylate (13.6 mg, 29.1 µmol, 39 %, 99.5% Purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 465.35.

1H NMR (400 MHz, Chloroform-d) δ 8.08 (s, 1H), 7.66 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.41 – 7.35 (m, 1H), 6.48 (s, 1H), 3.80 (dd, J = 11.2, 7.0 Hz, 4H), 3.72 (s, 3H), 3.67 (s, 2H), 3.45 – 3.24 (m, 2H), 3.00 (s, 3H), 2.66 (d, J = 15.1 Hz, 1H), 2.26 (s, 1H), 2.09 (d, J = 13.9 Hz, 2H), 1.96 (dd, J = 9.0, 4.4 Hz, 1H), 1.89 – 1.72 (m, 5H), 1.63 (s, 2H).

Compound 6:

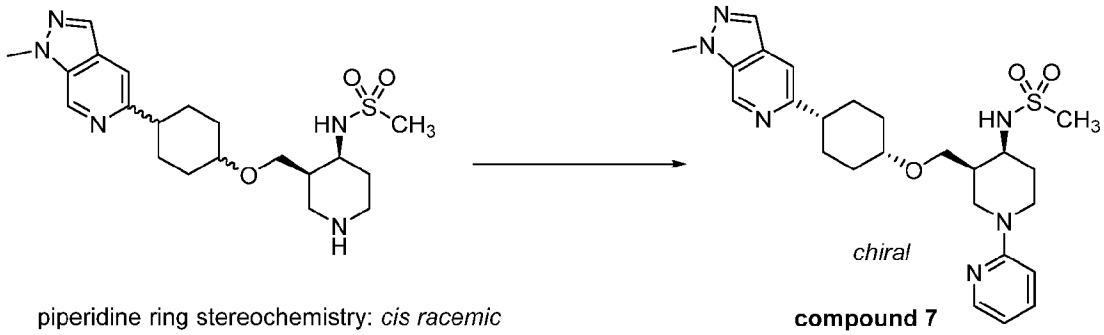


To a test-tube fitted with an air-tight screw cap was added amine, TEA (24 mg, 33 µL, 2 eq, 0.24 mmol), and DMSO (2 mL) followed by pyridin-2-yl trifluoromethanesulfonate (40 mg, 1.5 eq, 0.18 mmol). The resulting mixture was stirred at 120 degrees C for 12 hours. The reaction mixture was extracted with DCM (3x100mL) and water. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, after filtration, the filtrate was concentrated under reduced pressure and purified by thin layer chromatography (PE:EA=1:1) to afford isomeric mixture of product (35 mg, 72 µmol, 61 %) as a solid. This compound was re-purified by prep-HPLC (column: XBridge Prep C18 OBD Column, 30*50 mm, 5µm 13nm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN) to afford N-((3R,4S)-3-((((1s,4S)-4-(1H-benzo[d]imidazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4 yl)methanesulfonamide (3.6 mg, 7.1 µmol, 17 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 484.20.

1H NMR (400 MHz, Chloroform-d) δ 1.28 (s, 1H), 1.55-1.67 (m, 3H), 1.78 (s, 4H), 1.83 (d, 1H), 2.05 (s, 4H), 2.09 (s, 1H), 2.40 (s, 2H), 2.69 (s, 2H), 3.04 (s, 3H), 3.44 (dd, 1H), 3.64 (s, 1H), 3.68 (dd, 1H), 3.83-3.88 (m, 1H), 3.95 (q, 2H), 4.06 (dd, 1H), 6.52 (d, 1H), 6.60-6.67 (m, 1H), 6.69 (d, 1H), 7.19 (d, 1H), 7.45-7.54 (m, 1H), 7.58-7.67 (m, 2H), 8.05 (s, 1H), 8.19 (d, 1H).

Compound 7:



piperidine ring stereochemistry: *cis racemic* **compound 7**

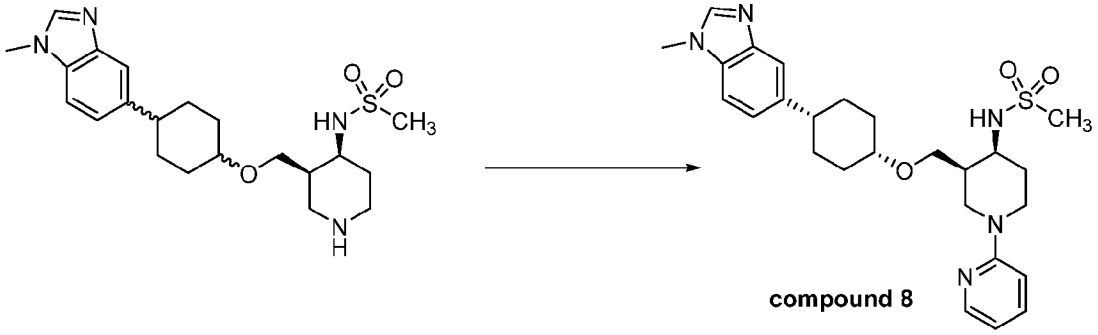
To a solution of amine (110 mg, 1 eq, 261 µmol) and pyridin-2-yl trifluoromethanesulfonate (88.9 mg, 1.5 eq, 391 µmol) in DMSO (3 mL) was added TEA (79.2 mg, 109 µL, 3 eq, 783 µmol). The resulting mixture was stirred for 6 hours at 120 degrees C. The crude was purified by reverse phase chromatography (C18 column; mobile phase A: water (NH_4HCO_3), mobile phase B: ACN, 40 % to 55 % gradient in 30 min; detector, UV 254 nm) to afford isomeric mixture of product (50 mg, 0.10 mmol, 39 %) as a solid.

The crude product was purified by prep-chiral-HPLC (Column: DZ-CHIRALPAK IG-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=50: 50) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl)methanesulfonamide (18 mg, 36 µmol, 36 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =499.

1H NMR (400 MHz, DMSO-d6) δ 9.07 (d, J = 1.1 Hz, 1H), 8.09 – 8.04 (m, 2H), 7.51 – 7.43 (m, 2H), 7.22 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.56 (dd, J = 7.1, 4.9 Hz, 1H), 4.15 (s, 3H), 3.73 (dt, J = 14.1, 8.5 Hz, 2H), 3.61 – 3.47 (m, 6H), 2.99 (s, 3H), 2.81 (ddd, J = 11.5, 8.1, 3.7 Hz, 1H), 2.12 (d, J = 29.1 Hz, 2H), 1.99 – 1.82 (m, 5H), 1.78 – 1.50 (m, 7H), 1.36 – 1.22 (m, 1H).

Compound 8:



compound 8

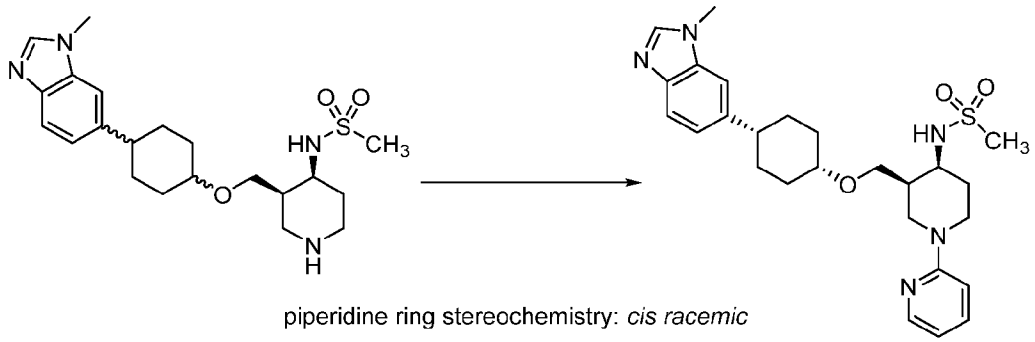
piperidine ring stereochemistry: *cis racemic*

To a solution of amine (100 mg, 1 eq, 238 µmol) and triethylamine (48.1 mg, 66.3 µL, 2 eq, 476 µmol) in DMSO (2 mL) was added pyridin-2-yl trifluoromethanesulfonate (81.0 mg, 1.5 eq, 357 µmol). The resulting mixture was stirred for 3 hours at 120 degrees C. The reaction solution was concentrated under reduced pressure to afford the crude product. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 35 % to 65 % gradient) to afford racemic mixture of product (4.9 mg, 9.8 µmol, 16 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 498.25.

1H NMR (400 MHz, Methanol-d4) δ 8.10 – 8.04 (m, 1H), 8.07 (s, 1H), 7.57 – 7.43 (m, 3H), 7.27 (dd, 1H), 6.92 – 6.85 (m, 1H), 6.62 (ddd, 1H), 3.90 (s, 3H), 3.86 (d, 1H), 3.77 (dd, 1H), 3.69 (dd, 1H), 3.64 (s, 1H), 3.62 – 3.54 (m, 2H), 3.54 – 3.43 (m, 1H), 3.06 (s, 3H), 2.71 (t, 1H), 2.31 (s, 1H), 2.09 (d, 2H), 2.01 – 1.81 (m, 4H), 1.66 (q, 4H).

Compound 9:



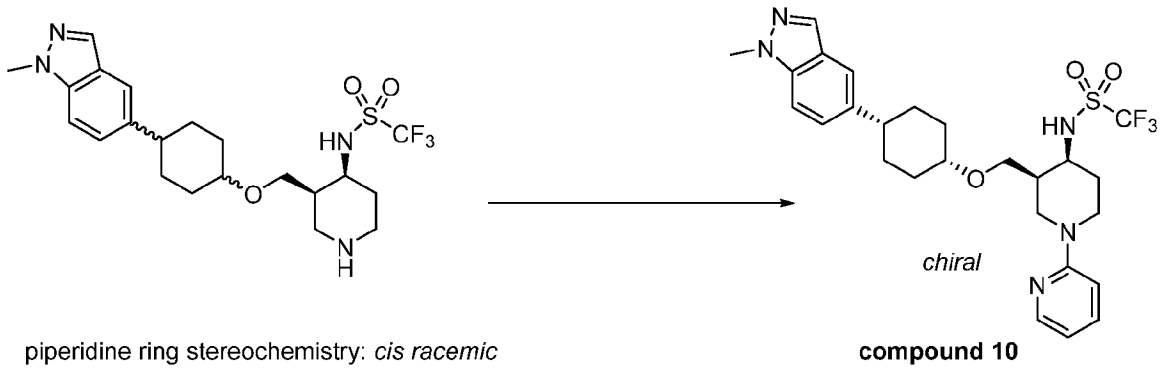
piperidine ring stereochemistry: *cis racemic*

compound 9

To a solution of amine (130 mg, 1 eq, 309 µmol) and pyridin-2-yl trifluoromethanesulfonate (84.3 mg, 1.2 eq, 371 µmol) in DMSO (5 mL) was added TEA (93.8 mg, 129 µL, 3 eq, 927 µmol). After stirring for 3 hours at 120 degrees C under a nitrogen atmosphere, the resulting

mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3x20mL). The combined organic layers were washed with brine (1x50mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: 8mmol NH_4HCO_3, mobile phase B: ACN, 20 % to 70 % gradient in 30 min; detector, UV 254 nm) to afford isomeric mixture of product (minor peak 5mg, major peak 18mg). This isomeric mixture (18mg) was purified by PREP-HPLC with the following conditions (Column: XBridge Prep OBD C18 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: 28% B to 58% B in 8 min, 58% B) to afford enantiomeric mixture of N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-benzo[d]imidazol-6-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl)methanesulfonamide and N-((3S,4R)-3-((((1s,4S)-4-(1-methyl-1H-benzo[d]imidazol-6-yl)cyclohexyl)oxy)methyl)-1-(pyridin-2-yl)piperidin-4-yl)methanesulfonamide (7.2 mg, 14 μmol, 40 %) as a solid.
LCMS: m/z (ES+), [M+H]+ =498.
1H NMR (400 MHz, Methanol-d4) δ 8.10 – 8.02 (m, 2H), 7.61 – 7.48 (m, 2H), 7.46 (d, 1H), 7.19 (dd, , 1H), 6.91 - 6.84 (m, 1H), 6.70 - 6.59 (m, 1H), 3.89 (s, 5H), 3.82 – 3.43 (m, 6H), 3.06 (s, 3H), 2.81 – 2.68 (m, 1H), 2.38 - 2.29 (m, 1H), 2.10 (d, 2H), 2.01 - 1.85 (m, 4H), 1.76 - 1.58 (m, 4H), 1.41 – 1.23 (m, 2H), 0.96 – 0.86 (m, 1H).

Compound 10:



piperidine ring stereochemistry: *cis racemic* **compound 10**

To a solution of amine (700 mg, 1 eq, 1.48 mmol) and 2-bromopyridine (466 mg, 2 eq, 2.95 mmol) in 1,4-dioxane (36 mL) were added Cs_2CO_3 (1.44 g, 3 eq, 4.43 mmol) and Pd-PEPPSI-Ipent (124 mg, 0.1 eq, 148 μmol). After stirring overnight at 100 degrees C under a nitrogen atmosphere, the resulting mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3x150 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.

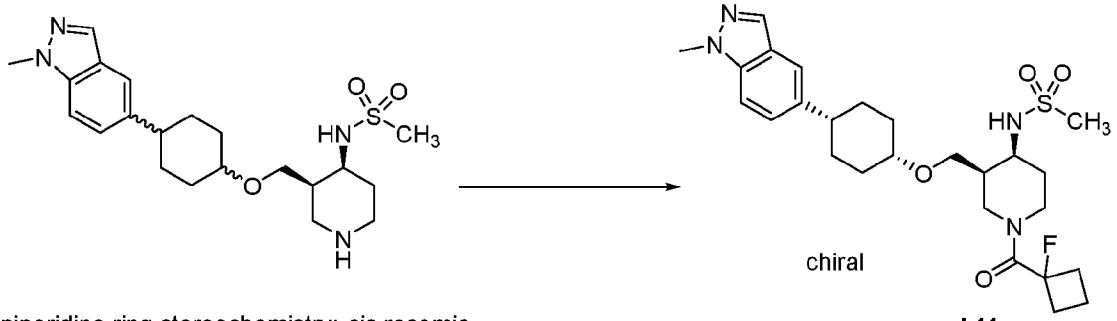
The crude was purified by reverse flash chromatography (C18 column; mobile phase A: 0.9g/L NH_4HCO_3 to water, mobile phase B: ACN, 5 % to 95 % gradient in 30 min) to afford isomeric mixture of product (550 mg, 997 µmol, 67.6 %) as a solid.

Above isomeric mixture was purified by chiral prep-HPLC (column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B) to afford 1,1,1-trifluoro-N-((3R, 4S)-3-((((1s,4R)-4-(1-methyl-1H-indazol-5-yl) cyclohexyl) oxy) methyl)-1-(pyridin-2-yl) piperidin-4-yl) methanesulfonamide (98.5 mg, 174 µmol, 29.1 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =552.25.

1H NMR (400 MHz, Methanol-d4) δ 8.09 – 8.03 (m, 1H), 7.92 (d, 1H), 7.59 – 7.49 (m, 2H), 7.47 (d, 1H), 7.36 (d, 1H), 6.91 (d, 1H), 6.65 (dd, 1H), 4.05 (d, 3H), 4.01 (d, 1H), 3.88 (ddd, 2H), 3.66 – 3.60 (m, 2H), 3.59 – 3.51 (m, 2H), 3.44 (dd, 1H), 2.69 (t, 1H), 2.32 (s, 1H), 2.14 – 2.03 (m, 2H), 1.99 – 1.79 (m, 4H), 1.65 (q, 4H), 1.34 – 1.28 (m, 1H).

Compound 11:



piperidine ring stereochemistry: *cis racemic* **compound 11**

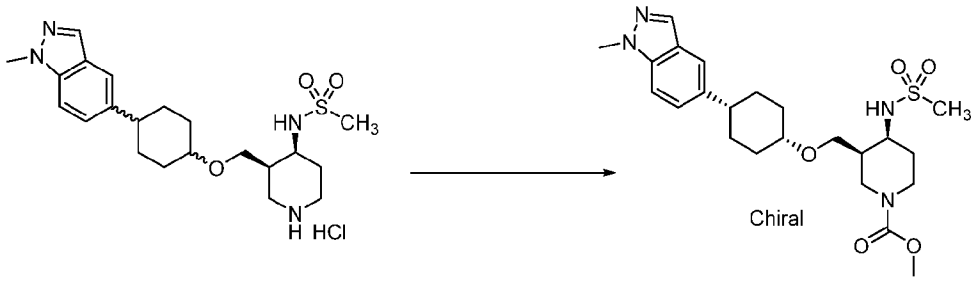
To a solution of amine (220.00 mg, 1 eq, 523.10 µmol) and N-ethyl-N-isopropylpropan-2-amine (202.83 mg, 3 eq, 1.5693 mmol) in DCM (15 mL) were added 1H-benzo[d][1,2,3]triazol-1-ol (106.03 mg, 1.5 eq, 784.65 µmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (150.4 mg, 1.5 eq, 784.65 µmol) and 1-fluorocyclobutane-1-carboxylic acid (61.783 mg, 1 eq, 523.10 µmol), the resulting mixture was stirred for 2 hours at 25 degrees C. The resulting mixture was extracted with DCM (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 60 % to 80 % gradient in 10 min; detector, UV 254 nm) to afford isomeric mixture of product (200.00 mg, 384.13 µmol, 73 %) as an oil.

This isomeric mixture was purified by Prep Chiral-HPLC (column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 μm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=60: 40; Flow rate: 1 mL/min; Gradient: 0% B to 0% B) to afford N-((3R,4S)-1-(1-fluorocyclobutane-1-carbonyl)-3-((((1s,4R)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (65.00 mg, 124.8 μmol, 32.50 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 521.20.

1H NMR (400 MHz, Methanol-d4) δ 7.92 (s, 1H), 7.62 (d, J = 16.1 Hz, 1H), 7.49 – 7.35 (m, 2H), 4.05 (d, J = 2.0 Hz, 4H), 3.97 – 3.77 (m, 2H), 3.74 – 3.58 (m, 3H), 3.49 (q, J = 9.0 Hz, 2H),3.37 (s, 1H), 3.04 (d, J = 4.0 Hz, 3H), 2.73 (s, 3H), 2.07 (d, J = 14.9 Hz, 3H), 1.90 (dd, J = 19.0, 9.3 Hz, 5H), 1.65 (d, J = 9.5 Hz, 5H).

Compound 12:



piperidine ring stereochemistry: *cis racemic*

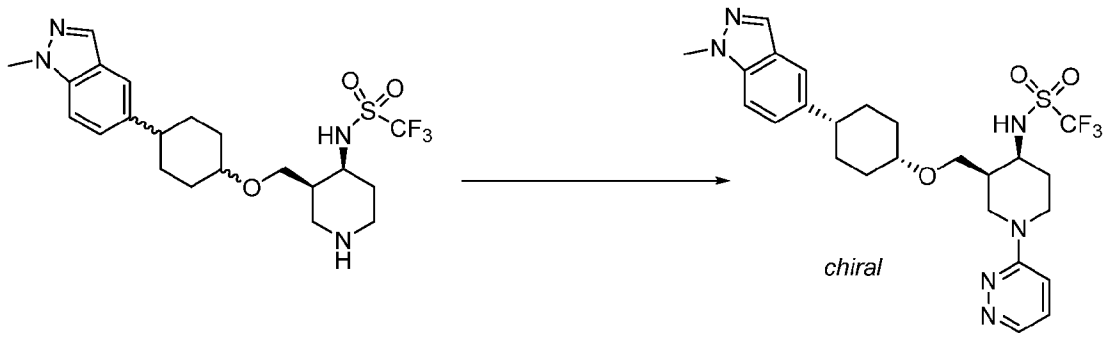
Compound 12

To the solution of amine (HCl salt) (400 mg, 1 eq, 875 μmol) in DCM (5 mL) were added pyridine (208 mg, 212 μL, 3 eq, 2.63 mmol) and triphosgene (130 mg, 0.5 eq, 438 μmol) at room temperature. The solution was stirred for 2 hours at 25 degrees C. The mixture was concentrated under reduced pressure. The residue was re-dissolved in the MeOH (28.0 g, 35.4 mL, 1000 eq, 875 mmol) and the resulting solution was heated to 80 degrees C and stirred for 30 minutes. The mixture was monitored by LCMS. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 0 % to 70 % gradient) to afford crude as a mixture of 4 isomers (350 mg, 731 μmol, 83.6 %) as a solid. The mixture was purified by prep-Chiral HPLC (column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1:1) to afford methyl (3R,4S)-3-((((1s,4R)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-4-(methylsulfonamido)piperidine-1-carboxylate (60 mg, 0.13 mmol, 17 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 479.25.

1H NMR (SNB06-439): (400 MHz, Methanol-d4) δ 7.93 (d, J = 1.0 Hz, 1H), 7.61 (s, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 4.05 (s, 3H), 3.81 (s, 1H), 3.65 (d, J = 22.4 Hz, 10H), 3.03 (s, 3H), 2.69 (d, J = 12.1 Hz, 1H), 2.19 (s, 1H), 2.10 (s, 2H), 1.90 (s, 2H), 1.80 (s, 2H), 1.74 – 1.57 (m, 4H).

Compound 13:



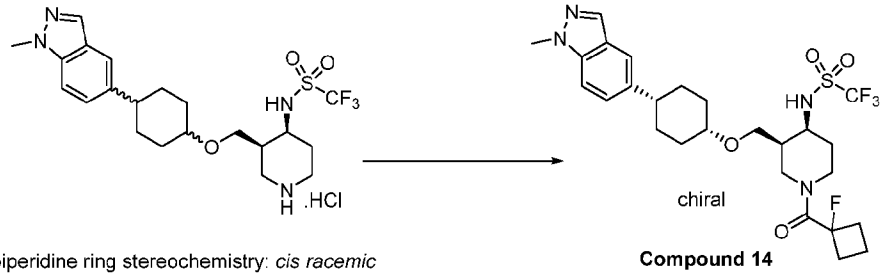
piperidine ring stereochemistry: *cis racemic* **compound 13**

To a solution of amine (150 mg, 1 eq, 316 µmol) and 3-bromopyridazine (101 mg, 2 eq, 632 µmol) in 1,4-dioxane (2 mL) was added PEPPSI-Pd (26.6 mg, 0.1 eq, 31.6 µmol) and Cs_2CO_3 (309 mg, 3 eq, 948 µmol). The resulting mixture was stirred for 3 hours at 100 degrees C. The reaction was monitored by LCMS. The resulting mixture was extracted with ethyl acetate (3x30mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EA/PE=2/1) to afford isomeric mixture of product (140 mg, 155 µmol, 49.0 %) as a solid. The crude product was purified by prep-HPLC (column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=60: 40) to afford 1,1,1-trifluoro-N-((3R,4S)-3-((((1s,4R)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridazin-3-yl)piperidin-4-yl)methanesulfonamide (115 mg, 207 µmol, 76.7 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 553.25.

1H NMR (400 MHz, Methanol-d4) δ 8.07 (s, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.25 (dd, J = 8.4, 1.6 Hz, 1H), 3.89 (s, 3H), 3.87 – 3.82 (m, 1H), 3.78 – 3.65 (m, 2H), 3.65 – 3.54 (m, 1H),3.51 (d, J = 9.4 Hz, 1H), 3.46 – 3.35 (m, 2H), 3.03 (s, 3H), 2.83 – 2.60 (m, 3H), 2.46 (dq, J = 22.5, 10.2 Hz, 2H), 2.28 – 2.04 (m, 3H), 2.02 – 1.89 (m, 3H), 1.84 (d, J = 13.4 Hz, 2H), 1.62 (q, J = 13.5, 12.6 Hz, 3H), 1.55 – 1.33 (m, 3H).

Compound 14:



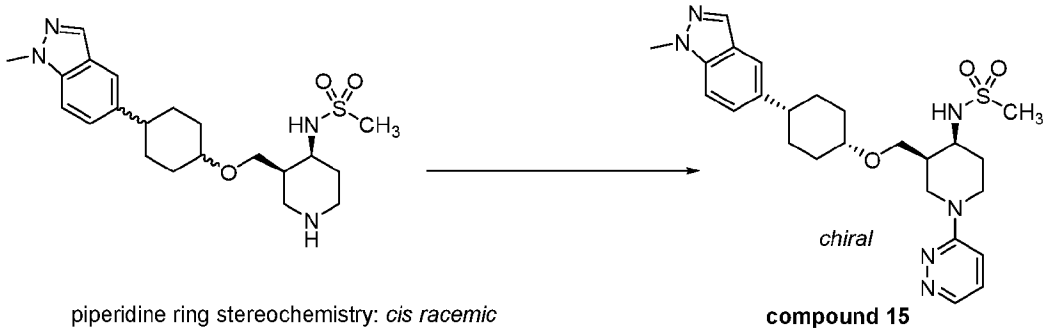
piperidine ring stereochemistry: *cis racemic* **Compound 14**

To a solution of amine (HCl salt) (260 mg, 1 eq, 548 µmol) and 1-fluorocyclobutane-1-carboxylic acid (77.7 mg, 1.2 eq, 657 µmol) in DCM (6 mL) was added DIPEA (212 mg, 286 µL, 3 eq, 1.64 mmol) and HOBt (126 mg, 1.5 eq, 822 µmol) and 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (158 mg, 1.5 eq, 822 µmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The mixture was concentrated under reduced pressure to afford the crude product. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 5 % to 95 % gradient in 30 min) to afford crude product as a mixture of 4 isomers (260 mg, 452 µmol, 82.6 %) as a solid. The isomer mixtures was purified by chiral prep-HPLC (Column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=70: 30) to afford desired isomer 1,1,1-trifluoro-N-((3R,4S)-1-(1-fluorocyclobutane-1-carbonyl)-3-((((1s,4R)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (48.4 mg, 83.6 µmol, 17.8 %) as a solid.

LCMS: m/z (ES+), [M+Na]+ = 597.15.

1H NMR (400 MHz, Chloroform-d) δ 7.96 (s, 1H), 7.85 (dd, J = 15.6, 6.4 Hz, 1H), 7.57 (d, J = 1.3 Hz, 1H), 7.42 – 7.31 (m, 2H), 4.38 (dd, J = 26.6, 13.9 Hz, 1H), 4.09 (s, 3H), 3.99 – 3.65 (m, 5H), 3.33 – 3.02 (m, 2H), 2.97 – 2.74 (m, 1H), 2.70 – 2.58 (m, 2H), 2.46 (dq, J = 22.9, 12.5 Hz, 4H), 2.12 – 1.89 (m, 5H), 1.76 (s, 1H), 1.68 (dd, J = 24.1, 13.9 Hz, 4H).

Compound 15:



piperidine ring stereochemistry: *cis racemic* **compound 15**

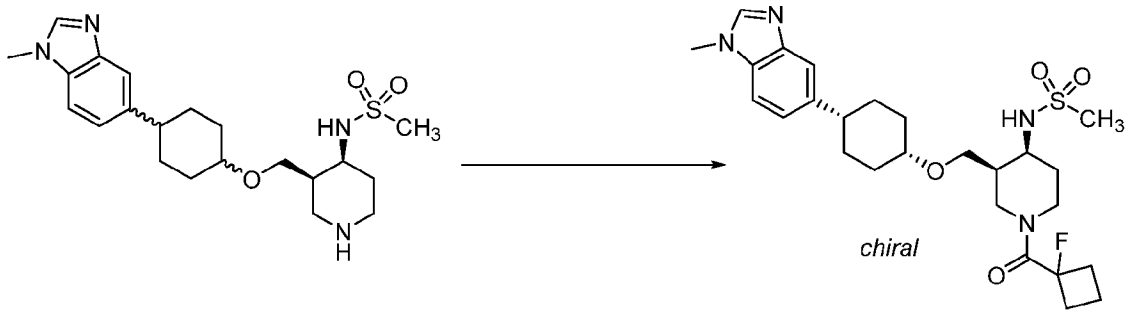
To a solution of amine (450 mg, 1 eq, 1.07 mmol) and 3-bromo-pyridazine (255 mg, 148 µL, 1.5 eq, 1.60 mmol) in 1,4-dioxane (18 mL) were added Cs_2CO_3 (1.05 g, 3 eq, 3.21 mmol) and Pd-PEPPSI (89.9 mg, 0.1 eq, 107 µmol). After stirring for 3 hours at 100 degrees C under a nitrogen atmosphere. The resulting mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: 0.9g/L NH_4HCO_3 to water, mobile phase B: ACN, 5 % to 95 % gradient in 30 min) to afford isomeric mixture of product (330 mg, 662 µmol, 62 %) as a solid.

The above isomeric mixture was purified by chiral HPLC (Column: DZ-CHIRALPAK IF-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: MtBE (0.2% DEA): (MeOH: DCM=1: 1) =85: 15; Flow rate: 1 mL/min; Gradient: 0% B to 0% B) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl) cyclohexyl) oxy) methyl)-1-(pyridazin-3-yl) piperidin-4-yl) methanesulfonamide (69.5 mg, 139 µmol, 38.5 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 499.25.

1H NMR (400 MHz, DMSO-d6) δ 8.52 (dd, 1H), 7.96 (d, 1H), 7.56 – 7.49 (m, 2H), 7.35 – 7.21 (m, 4H), 4.01 (s, 3H), 3.88 (dt, 1H), 3.74 (dd, 2H), 3.70 – 3.48 (m, 4H), 3.38 (d, 1H), 3.00 (s, 3H), 2.69 – 2.58 (m, 1H), 2.14 (s, 1H), 1.95 (t, 2H), 1.85 – 1.66 (m, 4H), 1.62 – 1.44 (m, 4H).

Compound 16:



piperidine ring stereochemistry: *cis racemic* **compound 16**

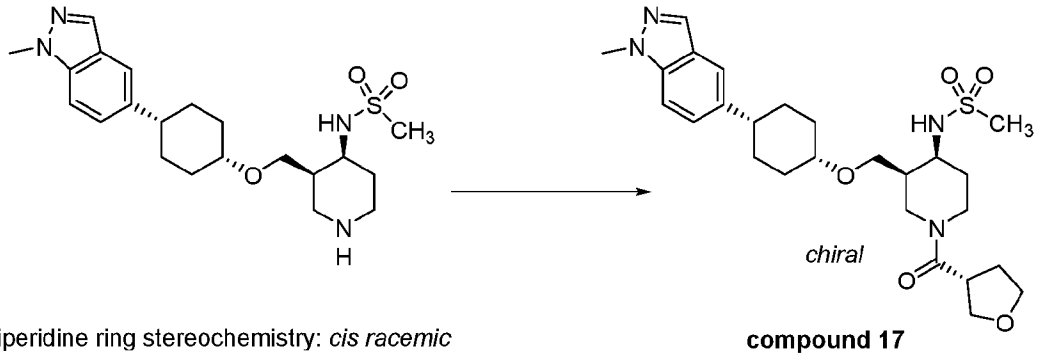
To a solution of amine (300.0 mg, 1 eq, 713.3 µmol) and 1-fluorocyclobutane-1-carboxylic acid (101.1 mg, 1.2 eq, 856.0 µmol) in DCM (8 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol hydrate (163.9 mg, 1.5 eq, 1.070 mmol), EDC (205.1 mg, 1.5 eq, 1.070 mmol) and DIEA (276.6 mg, 373 µL, 3 eq, 2.140 mmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The reaction was monitored by LCMS. The resulting mixture was extracted with dichloromethane (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH/DCM=1/12) to afford isomeric mixture of product (190 mg, 324 µmol, 45.4 %) as a solid.

The crude product was purified by prep-CHIRAL-HPLC (Column: CHIRALPAK IC, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 11 min) to afford N-((3R,4S)-1-(1-fluorocyclobutane-1-carbonyl)-3-((((1s,4S)-4-(1-methyl-1H-benzo[d]imidazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (49.6 mg, 94.4 µmol, 25%) as a solid.

LCMS: m/z (ES+), [M+H]+ = 521.30.

1H NMR (400 MHz, Methanol-d4) δ 8.06 (d, J = 3.2 Hz, 1H), 7.54 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.36 – 7.25 (m, 1H), 3.89 (d, J = 1.3 Hz, 4H), 3.74 (s, 1H), 3.72 – 3.58 (m, 3H), 3.49 (q, J = 9.1, 8.4 Hz, 2H), 3.04 (d, J = 5.6 Hz, 3H), 2.82 – 2.64 (m, 3H), 2.48 (d, J = 20.9 Hz, 2H), 2.31 – 1.99 (m, 3H), 2.00 – 1.75 (m, 6H), 1.75 – 1.53 (m, 5H).

Compound 17:



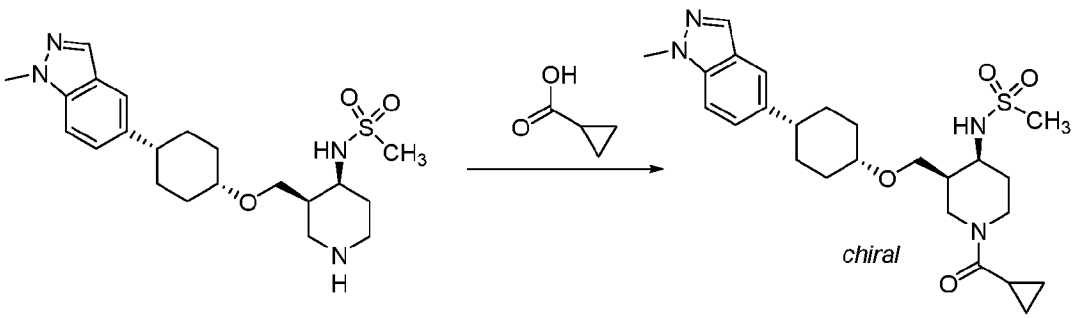
piperidine ring stereochemistry: *cis racemic* **compound 17**

To a stirred solution of amine (80 mg, 1 eq, 0.19 mmol) and (R)-tetrahydrofuran-3-carboxylic acid (33 mg, 1.5 eq, 0.29 mmol) in DCM (2 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol hydrate (44 mg, 1.5 eq, 0.29 mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (55 mg, 1.5 eq, 0.29 mmol) and DIPEA (74 mg, 99 µL, 3 eq, 0.57 mmol) in portions at 25 degrees C under nitrogen atmosphere. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 0 % to 100 % gradient in 30 min; detector, UV 220 nm) to afford isomeric mixture of product (90 mg, 0.17 mmol, 91 %) as an oil. The crude product (100 mg) was purified by Prep-Chiral-HPLC (Column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=30: 70) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-((R)-tetrahydrofuran-3-carbonyl)piperidin-4-yl)methanesulfonamide (30 mg, 58 µmol, 30%) as a solid.

LCMS: m/z (ES+), [M+H]+ = 519.3.

1H NMR (400 MHz, Methanol-d4) δ 7.93 (d, 1H), 7.61 (d, 1H), 7.47 (dd, 1H), 7.38 (ddd, 1H), 4.05 (d, 3H), 4.01 – 3.72 (m, 7H), 3.71 – 3.45 (m, 6H), 3.04 (d, 3H), 2.70 (q, 1H), 2.31 – 1.97 (m, 5H), 1.95 – 1.55 (m, 8H).

Compound 18:



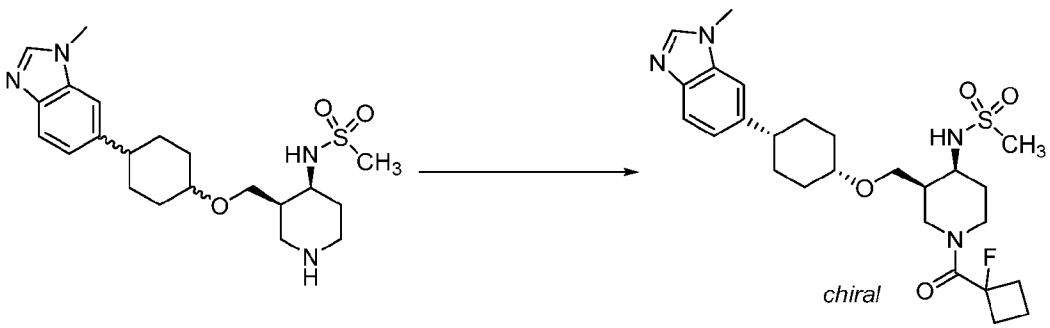
piperidine ring stereochemistry: *cis racemic* **compound 18**

To a solution of amine (80.0 mg, 1 eq, 190 µmol), HOBt (43.7 mg, 1.5 eq, 285 µmol) and EDC (54.7 mg, 1.5 eq, 285 µmol) in DCM (2 mL) was added DIEA (49.2 mg, 66.3 µL, 2 eq, 380 µmol) and cyclopropanecarboxylic acid (24.6 mg, 1.5 eq, 285 µmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The reaction was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 30 % to 60 % gradient in 20 min; detector, UV 254 nm) to afford isomeric mixture of produt (90.0 mg, 184 µmol, 96.8 %) as an oil. The crude product (95 mg) was purified by prep-chiral-HPLC (Column: DZ-CHIRALPAK IG-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (IPA: DCM=1: 1)=55: 45) to afford N-((3R,4S)-1-(cyclopropanecarbonyl)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (37.0 mg, 75.7 µmol, 39%) as a solid.

LCMS: m/z (ES+), [M+H]+ = 489.20.

1H NMR (400 MHz, Methanol-d4) δ 7.93 (d, 1H), 7.59 (d, 1H), 7.46 (d, 1H), 7.38 (dd, 1H), 4.05 (s, 4H), 3.94 – 3.77 (m, 2H), 3.68 (d, 3H), 3.50 (dd, 1H), 3.05 (d, 3H), 2.70 (d, 1H), 2.33 – 2.02 (m, 4H), 1.97 – 1.83 (m, 3H), 1.78 – 1.59 (m, 5H), 0.96 – 0.77 (m, 4H).

Compound 19:



piperidine ring stereochemistry: *cis racemic* **compound 19**

To a solution of amine (330 mg, 1 eq, 785 µmol) in DCM (14 mL) was added 3 (((ethylimino) methylene) amino)-N, N-dimethylpropan-1-amine hydrochloride (226 mg, 1.5 eq, 1.18 mmol) and DIEA (304 mg, 410 µL, 3 eq, 2.35 mmol) and HOBt (180 mg, 1.5 eq, 1.18 mmol) and 1- fluorocyclobutanecarboxylic acid (111 mg, 1.2 eq, 942 µmol). The resulting mixture was stirred for 2 hours at room temperature. The filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 5 % to 95 % gradient in 30 min;

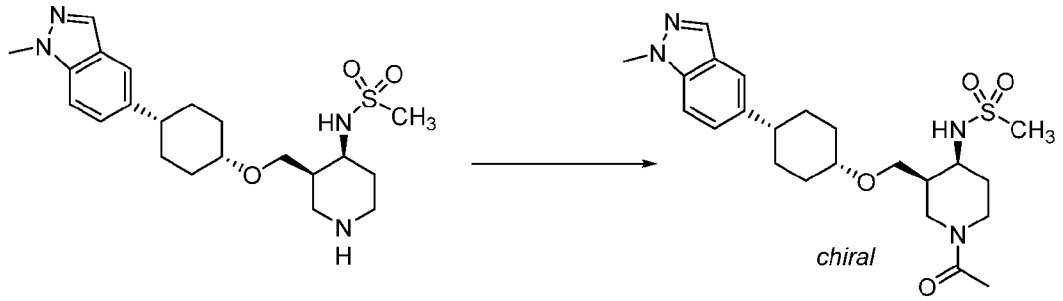
detector, UV 254 nm) to afford isomeric mixture of product (68 mg, 0.13 mmol, 17 %) as a solid.

The isomeric mixture was purified by CHIRAL-HPLC (Column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 μm; Mobile Phase A: MtBE (0.2% DEA): (MeOH: DCM=1: 1) =75: 25; Flow rate: 1 mL/min; Gradient: 0% B to 0% B) to afford N-((3R,4S)-1-(1-fluorocyclobutane-1-carbonyl)-3-((((1s,4S)-4-(1-methyl-1H-benzo[d]imidazol-6-yl) cyclohexyl) oxy) methyl) piperidin-4-yl) methanesulfonamide (7.6 mg, 14 μmol, 27 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =521.25.

1H NMR (400 MHz, Methanol-d4) δ 8.07 (d, 1H), 7.57 (dd, 1H), 7.49 (d, 1H), 7.26 – 7.19 (m, 1H), 3.91 (d, 5H), 3.77 – 3.59 (m, 3H), 3.52 (dd, 2H), 3.39 (d, 2H), 3.05 (d, 3H), 2.85 – 2.65 (m, 3H), 2.45 (tp,2H), 2.32 – 2.04 (m, 3H), 2.02 – 1.78 (m, 5H), 1.75 – 1.53 (m, 5H).

Compound 20:



piperidine ring stereochemistry: *cis racemic* **compound 20**

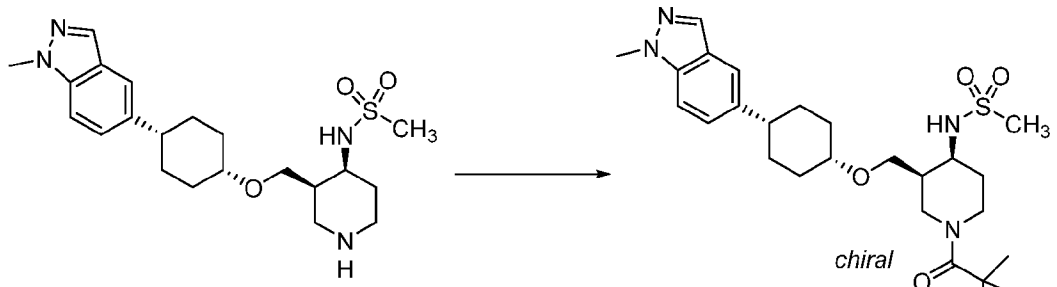
To a stirred solution of amine (70 mg, 1 eq, 0.17 mmol) in DCM (2 mL) was added triethylamine (51 mg, 3 eq, 0.50 mmol) and acetic anhydride (34 mg, 2 eq, 0.33 mmol) dropwise at 25 degrees C under nitrogen atmosphere. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 10:1) to afford isomeric mixture of product (70 mg, 0.11 mmol, 64 %) as a solid. The crude product (78 mg) was purified by Prep-Chiral-HPLC (Column: DZ-CHIRALPAK IH-3, 4.6*50 mm, 3.0 μm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=60: 40) to afford N-((3R,4S)-1-acetyl-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (23.2 mg, 48.1 μmol, 29 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =463.2.

1H NMR (400 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.60 (d, 1H), 7.47 (d, 1H), 7.42 – 7.34 (m, 1H), 4.09 – 3.94 (m, 4H), 3.82 (dd, 2H), 3.73 – 3.61 (m, 3H), 3.52 (dd, 2H), 3.38 (d, 1H),

3.04 (d, 3H), 2.69 (t, 1H), 2.31 – 2.04 (m, 6H), 1.90 (d, 3H), 1.71 (ddd, 16.6, 9.0 Hz, 5H), 0.11 (d, 1H).

Compound 21:



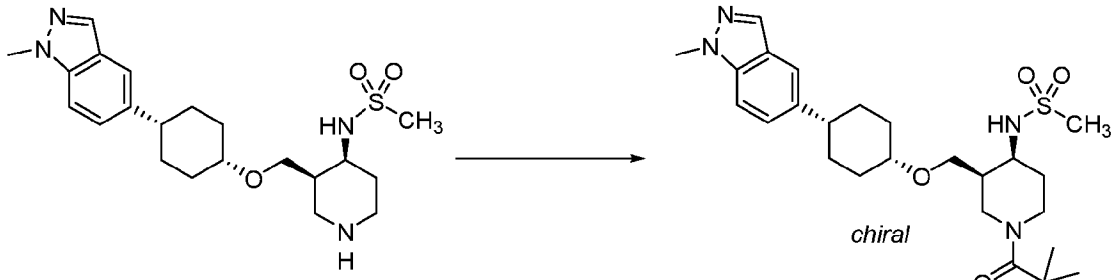
piperidine ring stereochemistry: *cis racemic* **compound 21**

To a stirred solution of amine (65 mg, 1 eq, 0.15 mmol) and 2-hydroxy-2-methylpropanoic acid (48 mg, 3 eq, 0.46 mmol) in DCM (2 mL) was added 1H-benzo[d][1,2,3]triazol-1-ol hydrate (71 mg, 3 eq, 0.46 mmol) EDC (89 mg, 3 eq, 0.46 mmol) DIEA (0.12 g, 0.16 mL, 6 eq, 0.93 mmol) in portions at 25 degrees C under nitrogen atmosphere. The residue was purified by Preparative-TLC (CH_2Cl_2/MeOH 10:1) to afford isomeric mixture of product (70 mg, 0.14 mmol, 89 %) as a solid. The crude product (70 mg) was purified by Prep-Chiral-HPLC (Column: DZ-CHIRALPAK IG-3, 4.6*50 mm, 3.0 μm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=60: 40) to afford N-((3R,4S)-1-(2-hydroxy-2-methylpropanoyl)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (25.1 mg, 48 μmol, 35 %,) as a solid.

LCMS: m/z (ES+), [M+H]+ =507.3.

1H NMR (400 MHz, Methanol-d4) δ 7.92 (s, 1H), 7.63 (s, 1H), 7.46 (d, 1H), 7.43 – 7.38 (m, 1H), 4.05 (s, 4H), 3.88 (d, 1H), 3.70 – 3.59 (m, 3H), 3.51 (dd, 1H), 3.04 (s, 3H), 2.69 (t, 1H), 2.22 (s, 1H), 2.16 – 2.03 (m, 2H), 1.91 (d, 4H), 1.67 (d, 4H), 1.47 (s, 6H), 1.31 (s, 2H), 0.12 (s, 1H).

Compound 22:



piperidine ring stereochemistry: *cis racemic* **compound 22**

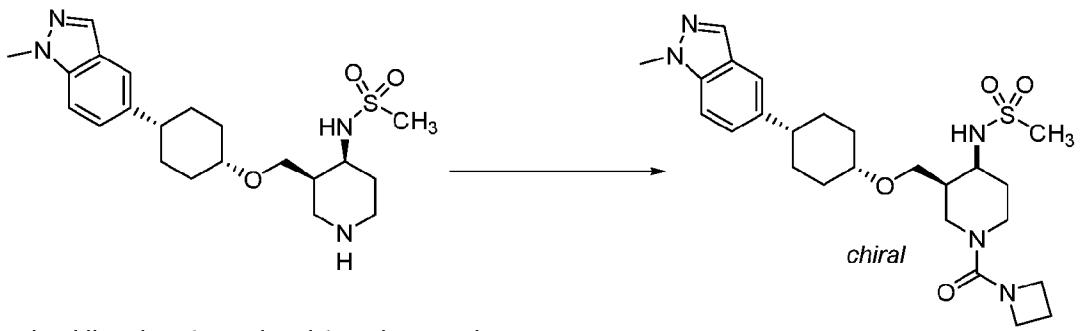
To a solution of amine (100 mg, 1 eq, 238 µmol) and TEA (72.2 mg, 99.4 µL, 3 eq, 713 µmol) in DCM (1.5 mL) was added trimethylacetyl chloride (34.4 mg, 35.0 µL, 1.2 eq, 285 µmol). The resulting mixture was stirred for 30 minutes at room temperature. The residue was purified by Prep-TLC (EA/PE=1/3) to afford crude as a solid. The filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: 0.9g/L NH_4HCO_3 aqueous solution, mobile phase B: ACN, 5 % to 95 %) to afford isomeric mixture of product (80 mg, 0.16 mmol, 67 %) as a solid.

The crude product was purified by prep-CHIRAL-HPLC (Column: DZ-CHIRALPAK IF-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex (0.2% DEA): (EtOH: DCM=1: 1) =80: 20) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl) cyclohexyl) oxy) methyl)-1-pivaloylpiperidin-4-yl) methanesulfonamide (30.7 mg, 60.5 µmol, 38 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =505.25.

1H NMR (400 MHz, DMSO-d6) δ 7.93 (s, 1H), 7.55 – 7.52 (m, 2H), 7.29 (dd, 2H), 4.01 (s, 3H), 3.93 (s, 2H), 3.75 – 3.68 (m, 1H), 3.59 (s, 1H), 3.43 (dd, 1H), 3.38 (s, 2H), 3.30 (s, 1H), 2.96 (s, 3H), 2.64 (d, 1H), 1.96 (dd, 3H), 1.75 – 1.50 (m, 8H).

Compound 23:



piperidine ring stereochemistry: *cis racemic* **compound 23**

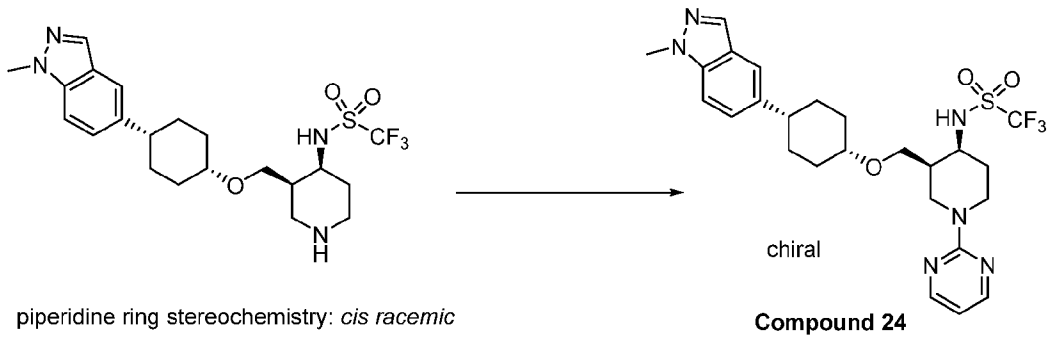
To a solution of amine (100 mg, 1 eq, 238 µmol) and TEA (120 mg, 166 µL, 5 eq, 1.19 mmol) in DCM (1.5 mL) was added triphosgene (42.3 mg, 26 µL, 0.6 eq, 143 µmol). The resulting mixture was stirred for 30 minutes at 0 degrees C. To the above mixture was added a solution of azetidine hydrochloride (26.7 mg, 1.2 eq, 285 µmol) in DCM (0.2mL) dropwise over 1 minute at 25 degrees C under nitrogen atmosphere. The resulting mixture was stirred for an additional 1 hour at room temperature. The crude product was purified by prep-HPLC (XBridge Prep OBD C18 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: 28% B to 48% B in 8 min, 48% B; Wavelength: 254 nm). Solvents were evaporated to afford isomeric mixture of product (60 mg, 0.12 mmol, 50 %) as a solid.

The above isomeric mixture was purified by prep-CHIRAL-HPLC (CHIRALPAK IE-3, 4.6*50mm; Mobile Phase A: MtBE (0.2% DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B) to afford N-((3R,4S)-1-(azetidine-1-carbonyl)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl) cyclohexyl) oxy) methyl) piperidin-4-yl) methanesulfonamide (22.4 mg, 43.3 µmol, 36 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =504.30.

1H NMR (400 MHz, Chloroform-d) δ 7.96 (s, 1H), 7.60 (s, 1H), 7.37 (d, 2H), 6.44 (d, 1H), 4.09 (s, 3H), 4.05 – 3.97 (m, 4H), 3.80 (td, 2H), 3.70 – 3.59 (m, 4H), 3.31 (dd, 1H), 3.17 (td, 1H), 3.00 (s, 3H), 2.67 (dq, 1H), 2.25 (p, 3H), 2.12 – 2.02 (m, 2H), 1.95 (dtd, 1H), 1.89 – 1.73 (m, 5H), 1.68 – 1.53 (m, 2H).

Compound 24:



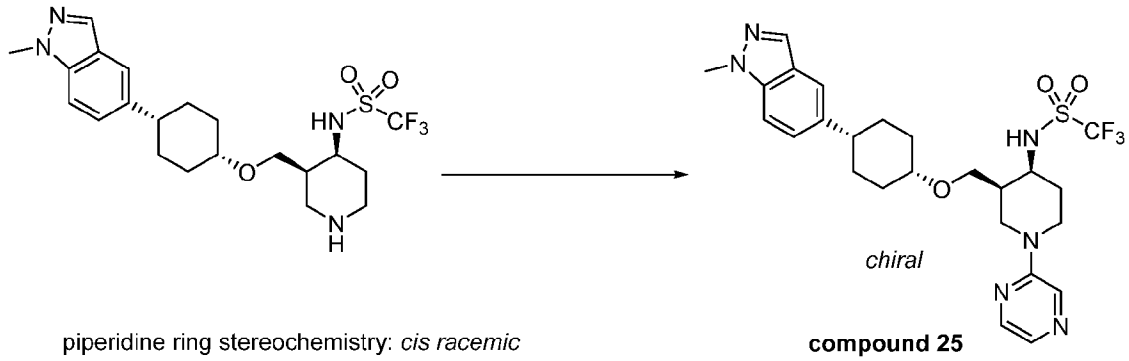
To a solution of amine (120.0 mg, 1 eq, 252.9 µmol) and 2-fluoropyrimidine (29.76 mg, 1.2 eq, 303.5 µmol) in DMSO (1.2 mL) was added K_2CO_3 (87.37 mg, 2.5 eq, 632.2 µmol). The resulting mixture was stirred for 2 hours at 100 degrees C. The reaction was monitored by LCMS. The crude was purified by reverse flash chromatography (C18 column; mobile phase

A: NH_4HCO_3, mobile phase B: ACN, 5 % to 100 % gradient in 30 minutes and keep 61.5% gradient in 8 minutes) to afford 1,1,1-trifluoro-N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyrimidin-2-yl)piperidin-4-yl)methanesulfonamide (117.1 mg, 210 µmol, 83.2 %, 99.3% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 553.25.

1H NMR (400 MHz, Chloroform-d) δ 8.34 (d, J = 4.8 Hz, 2H), 7.96 (s, 1H), 7.86 (d, J = 6.4 Hz, 1H), 7.56 (s, 1H), 7.42 – 7.30 (m, 2H), 6.55 (t, J = 4.7 Hz, 1H), 4.68 (t, J = 13.1 Hz, 2H), 4.07 (s, 3H), 4.01 (s,1H), 3.91 (t, J = 9.9 Hz, 1H), 3.78 (dd, J = 9.8, 3.8 Hz, 1H), 3.71 – 3.62 (m, 1H), 3.36 (d, J = 13.9 Hz, 1H), 3.29 – 3.13 (m, 1H), 2.75 – 2.58 (m, 1H), 2.52 (t, J = 5.8 Hz, 1H), 2.19 – 1.95 (m, 4H), 1.88 – 1.66 (m, 4H), 1.66 – 1.52 (m, 2H).

Compound 25:



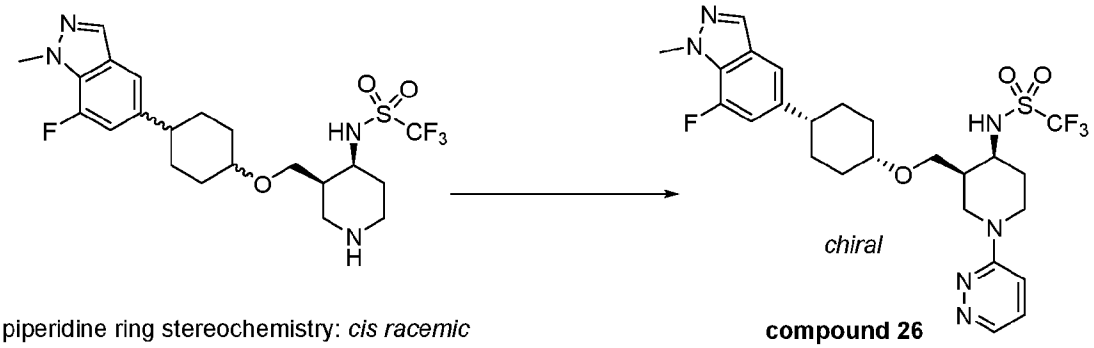
piperidine ring stereochemistry: *cis racemic* **compound 25**

To a solution of amine (120.0 mg, 1 eq, 252.9 µmol) and 2-fluoropyrazine (49.60 mg, 2 eq, 505.8 µmol) in DMSO (1 mL) was added K_2CO_3 (104.8 mg, 3 eq, 758.6 µmol). The resulting mixture was stirred for 16 hours at 25 degrees C. The reaction was monitored by LCMS. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water (5 mmol NH_4HCO_3), mobile phase B: ACN, 5 % to 95 % gradient in 30 min; detector, UV 254 nm) to afford isomeric mixture of product (119.4 mg, 213 µmol, 87 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 553.3.

1H NMR (400 MHz, Chloroform-d) δ 8.18 (s, 1H), 8.11 (d, J = 2.3 Hz, 1H), 7.93 (d, J = 0.9 Hz, 1H), 7.89 (s, 1H), 7.82 (d, J = 6.3 Hz, 1H), 7.56 (s, 1H), 7.38 – 7.29 (m, 2H), 4.33 – 4.25 (m, 1H), 4.19 (d, J = 13.8 Hz, 1H), 4.07 (s, 3H), 4.04 – 3.91 (m, 2H), 3.76 (dd, J = 9.8, 3.9 Hz, 1H), 3.68 (t, J = 2.9 Hz, 1H), 3.33 (dd, J = 13.8, 3.4 Hz, 1H), 3.21 (ddd, J = 13.7, 9.1, 4.8 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.54 (t, J = 5.0 Hz, 1H), 2.17 – 2.00 (m, 4H), 1.82 – 1.69 (m, 4H), 1.59 (s, 2H).

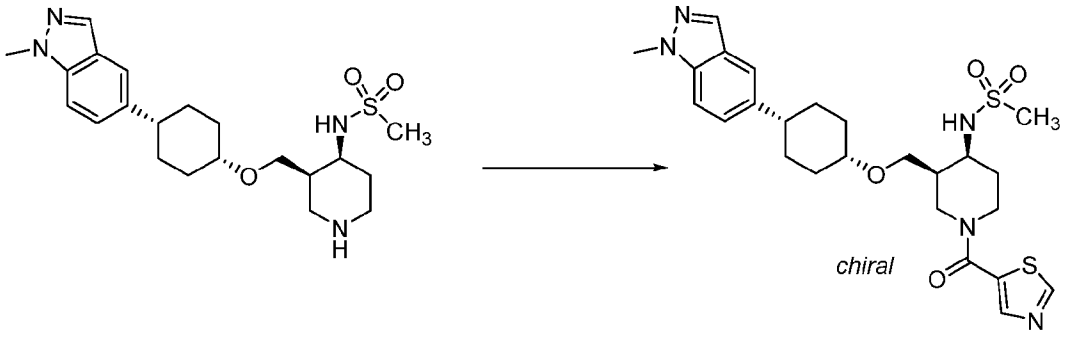
Compound 26:



piperidine ring stereochemistry: *cis racemic* **compound 26**

To a solution of amine (800 mg, 80% wt, 1 eq, 1.30 mmol) and 3-bromopyridazine (620 mg, 3 eq, 3.90 mmol) and PEPPSI-pd (111 mg, 0.1 eq, 130 µmol) and Cs_2CO_3 (1.27 g, 3 eq, 3.90 mmol) in DMSO (5 mL). The resulting mixture was stirred for 8 hours at 120 degrees C. The resulting mixture was extracted with ethyl acetate/water (3x100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EA) to afford crude product (220 mg, 386 µmol, 30 %) as a solid. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water(NH_4HCO_3), mobile phase B: ACN, 5 % to 95 % gradient in 30 min; detector, UV 220 nm) to afford isomeric mixture of product (150 mg, 263 µmol, 58%) as a solid. This isomeric mixture was further purified by reverse flash chromatography (Column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: MtBE (0.2% DEA): (EtOH: DCM=1: 1)=70: 30) to afford 1,1,1-trifluoro-N-((3R,4S)-3-((((1s,4S)-4-(7-fluoro-1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridazin-3-yl)piperidin-4-yl)methanesulfonamide (21.9 mg, 38.4 µmol, 23 %) as a solid.
LCMS: m/z (ES+), [M+H]+ = 571.20.
1H NMR (400 MHz, Methanol-d4) δ 8.45 (dd, J = 4.2, 1.4 Hz, 1H), 7.96 (d, J = 2.3 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.05 (dd, J = 13.5, 1.3 Hz, 1H), 4.20 (d, J = 0.9 Hz, 3H), 4.07 (dq, J = 11.7, 5.9 Hz, 2H), 3.90 (dt, J = 12.7, 6.3 Hz, 1H), 3.76 – 3.46 (m, 5H), 3.06 (q, J = 7.3 Hz, 3H), 2.67 (t, J = 12.0 Hz, 1H), 2.33 (s, 1H), 2.09 (d, J = 12.8 Hz, 2H), 1.99 – 1.76 (m, 4H), 1.74 – 1.55 (m, 4H), 1.31 (t, J = 7.3 Hz, 5H).

Compound 27:



piperidine ring stereochemistry: *cis racemic* **compound 27**

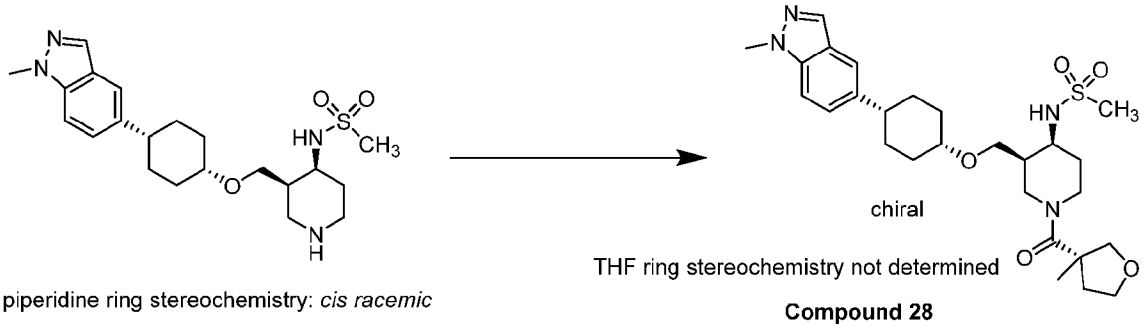
To a solution of amine (80 mg, 1 eq, 0.19 mmol) and thiazole-5-carboxylic acid (37 mg, 1.5 eq, 0.29 mmol) in DCM (3 mL) was added HOBt (44 mg, 1.5 eq, 0.29 mmol), EDC (55 mg, 1.5 eq, 0.29 mmol) and DIEA (74 mg, 99 µL, 3 eq, 0.57 mmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The reaction was monitored by LCMS. The resulting mixture was extracted with dichloromethane (3x15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water, mobile phase B: ACN, 25 % to 60 % gradient in 30 min; detector, UV 254 nm) to afford isomeric mixture of product (50 mg, 94 µmol, 49 %) as a solid.

Above isomeric mixture (50mg) was purified by CHIRAL-HPLC (Column: DZ-CHIRALPAK IC-3, 4.6*50 mm, 3.0 µm; Mobile Phase A: Hex(0.2% DEA): (EtOH: DCM=1: 1)=35: 65) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(thiazole-5-carbonyl)piperidin-4-yl)methanesulfonamide (21.6 mg, 40.6 µmol, 43 %) as a solid.

LCMS: m/z (ES+), [M+H]+ = 532.20.

1H NMR (400 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.25 (s, 1H), 7.93 (s, 1H), 7.54 (s, 1H), 7.45 (d, 1H), 7.32 (s, 1H), 4.04 (s, 3H), 3.95 - 3.84 (m, 4H), 3.72 – 3.44 (m, 3H), 3.04 (s, 3H), 2.62 (d, 1H), 2.17 (d, 3H), 1.97 – 1.53 (m, 9H).

Compound 28:

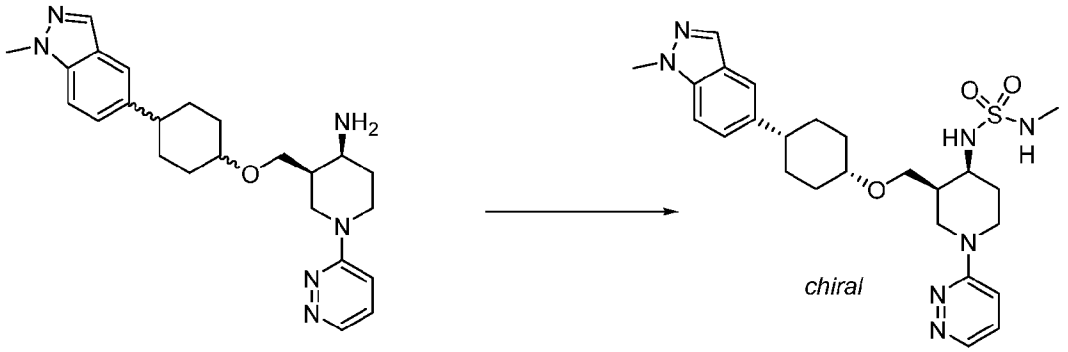


piperidine ring stereochemistry: *cis racemic*

Compound 28

To a solution of amine (50 mg, 1 eq, 0.12 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (34 mg, 1.5 eq, 0.18 mmol), 3-methyltetrahydrofuran-3-carboxylic acid (31 mg, 2 eq, 0.24 mmol) and 1-hydroxy-1H-benzotriazole (24 mg, 25 µL, 1.5 eq, 0.18 mmol) and diisopropylethylamine (46 mg, 61 µL, 3 eq, 0.36 mmol) in DCM (1 mL). The resulting mixture was stirred for 2 hours at 25 degrees C. The crude was purified by reverse flash chromatography (C18 column; mobile phase A: water(NH_4HCO_3), mobile phase B: ACN, 5 % to 95 % gradient in 30 min) to afford crude product as a mixture of isomers (60 mg, 0.11 mmol, 95 %) as a solid. The isomeric mixture was purified by prep-HPLC
(column: CHIRALPAK IC, 2*25 cm, 5 µm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH) to afford desired isomer N-((3R,4S)-3-((((1s,4R)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-((S)3-methyltetrahydrofuran-3-carbonyl)piperidin-4-yl)methanesulfonamide (10.8 mg, 12 %) as a solid.
LCMS: m/z (ES+), [M+H]+ = 533.20.
1H NMR (400 MHz, Methanol-d4) δ 7.91 (d, J = 0.9 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.08 (d, J = 8.9 Hz, 1H), 4.03 (s, 3H), 3.83 (ddt, J = 22.4, 8.5, 4.6 Hz, 4H), 3.68 – 3.62 (m, 2H), 3.59 (dd, J = 9.5, 5.3 Hz, 1H), 3.47 (t, J = 8.9 Hz, 1H), 3.01 (s, 3H), 2.68 (t, J = 12.3 Hz, 1H), 2.42 (q, J = 10.4, 9.2 Hz, 1H), 2.25 – 2.13 (m, 1H), 2.07 (t, J = 14.3 Hz, 2H), 2.01 – 1.75 (m, 5H), 1.64 (dd, J = 21.1, 9.0 Hz, 4H), 1.41 (s, 3H), 0.10 (s, 1H).

Compound 29:



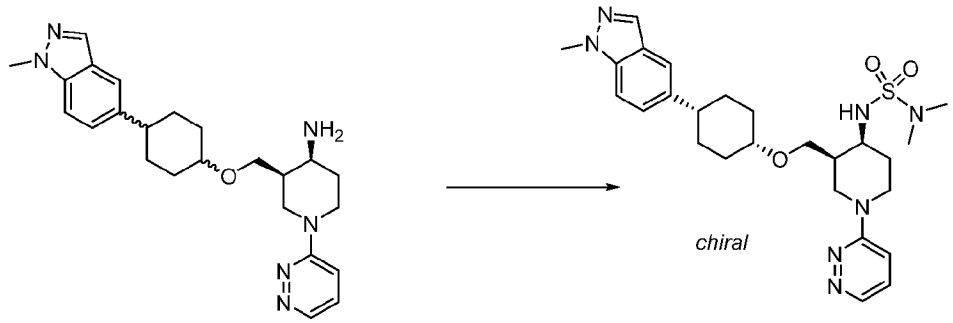
piperidine ring stereochemistry: *cis racemic* **Compound 29**

To a solution of amine (150.0 mg, 1 eq, 288.1 µmol) and TEA (87.45 mg, 120 µL, 3 eq, 864.3 µmol) in DCM (8 mL) was added methylsulfamoyl chloride (74.65 mg, 2 eq, 576.2 µmol). The resulting mixture was stirred for 16 hours at 25 degrees C. The residue was purified by Prep-TLC (MeOH/DCM=1/12) to afford mixture of 4 isomers (120.0 mg, 233.6 µmol, 81.09 %) as an oil. The isomers were separated by prep-Chiral-HPLC (conditions: Column: CHIRALPAK IH, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: IPA: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 16.5 min) to afford desired isomer N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridazin-3-yl)piperidin-4-yl)methylsulfamide (24.4 mg, 47.3 µmol, 20.3 %, 99.6% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 514.20.

1H NMR (400 MHz, Chloroform-d) δ 8.58 (d, J = 4.4 Hz, 1H), 7.94 (s, 1H), 7.60 (s, 1H), 7.36 (d, J = 1.2 Hz, 3H), 7.19 (d, J = 9.4 Hz, 1H), 6.44 (d, J = 4.7 Hz, 1H), 4.30 (d, J = 5.6 Hz, 1H), 4.07 (s, 5H), 3.96 – 3.80 (m, 3H), 3.74 (dd, J = 9.9, 3.8 Hz, 1H), 3.67 (s, 1H), 3.55 (s, 1H), 2.79 (d, J = 5.3 Hz, 3H), 2.74 – 2.63 (m, 1H), 2.39 (s, 1H), 2.19 (s, 1H), 2.06 (t, J = 13.1 Hz, 2H), 1.94 (s, 1H), 1.84 (d, J = 11.9 Hz, 4H), 1.61 (m, J = 13.7 Hz, 2H).

Compound 30:



piperidine ring stereochemistry: *cis racemic*

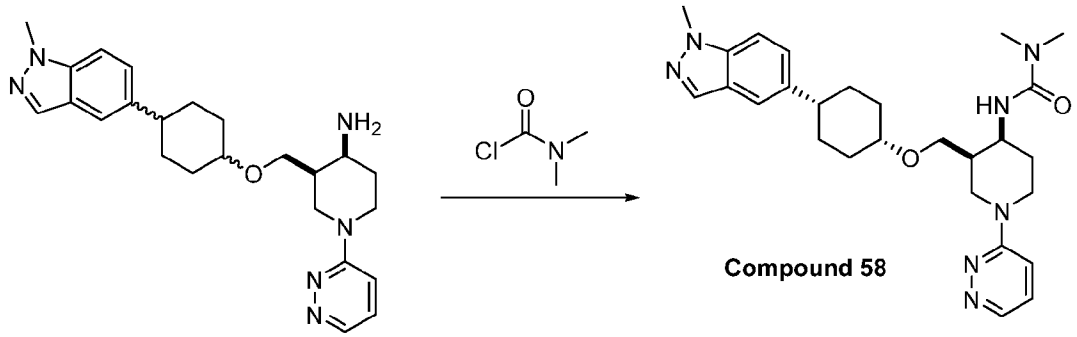
Compound 30

To a solution of amine (200.0 mg, 1 eq, 475.6 µmol) and triethylamine (288.7 mg, 6 eq, 2.853 mmol) in DCM (2 mL) was added dimethylsulfamoyl chloride (136.6 mg, 2 eq, 951.1 µmol). The resulting mixture was stirred for 16 hours at 25 degrees C. The residue was purified by Prep-TLC (MeOH/DCM=1/12) to afford a mixture of 4 isomers (81.0 mg, 153 µmol, 32.4 %) as a solid. The isomers were separated by prep-Chiral-HPLC (column: CHIRALPAK IG, 2*25 cm, 5 µm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 23 min) to afford N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridazin-3-yl)piperidin-4-yl)dimethylsulfamide (15.3 mg, 28.9 µmol, 18.9 %, 99.8% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 528.30.

1H NMR (400 MHz, Chloroform-d) δ 8.56 (d, J = 4.4 Hz, 1H), 7.91 (s, 1H), 7.56 (d, J = 1.3 Hz, 1H), 7.33 (d, J = 1.2 Hz, 2H), 7.20 (dd, J = 9.3, 4.4 Hz, 1H), 6.94 (dd, J = 9.3, 1.2 Hz, 1H), 6.38 (d, J = 5.5 Hz, 1H), 4.23 – 4.11 (m, 1H), 4.04 (s, 4H), 3.86 (dd, J = 9.8, 7.7 Hz, 1H), 3.78 (m, J = 9.1, 4.2 Hz, 1H), 3.74 – 3.59 (m, 3H), 3.48 (s, 1H), 3.35 (m, J = 12.9, 8.6, 3.6 Hz, 1H), 2.83 (s, 6H), 2.64 (m, J = 11.6, 3.7 Hz, 1H), 2.45 – 2.32 (m, 1H), 2.17 – 2.00 (m, 4H), 1.95 (m, J = 9.9, 6.3, 3.5 Hz, 1H), 1.81 (m, J = 24.7, 13.9, 10.7 Hz, 4H), 1.66 – 1.49 (m, 2H).

Compound 58:

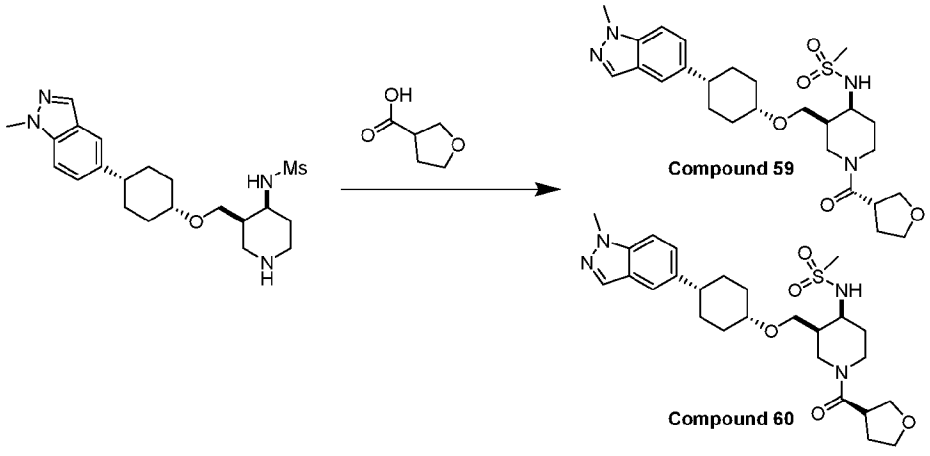


To a solution of (3R,4S)-3-(((4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)-1-(pyridazin-3-yl)piperidin-4-amine (90.0 mg, 1 eq, 214 µmol) and TEA (130 mg, 179 µL, 6 Eq, 1.28 mmol) in DCM (6 mL) was added dimethylcarbamic chloride (34.5 mg, 1.5 Eq, 321 µmol). The resulting mixture was stirred for 16 hours at 25 degrees C. The residue was purified by Prep-TLC (MeOH/DCM=1/12) to afford crude product (85.0 mg, 161 µmol, 75 %, 93.0% purity) as an oil. The crude product was purified by prep-chiral-HPLC to afford desired compound (20.2 mg, 40.9 µmol, 16.7 %, 99.5% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ = 492.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 4.2 Hz, 1H), 7.95 (s, 1H), 7.60 – 7.45 (m, 2H), 7.34 – 7.17 (m, 3H), 5.97 (d, J = 7.3 Hz, 1H), 4.04 (d, J = 20.1 Hz, 6H), 3.45 (d, J = 5.7 Hz, 3H), 2.80 (s, 6H), 2.60 (d, J = 12.5 Hz, 1H), 2.18 (s, 1H), 1.93 (d, J = 13.1 Hz, 2H), 1.73 (dd, J = 27.7, 13.2 Hz, 4H), 1.51 (s, 4H).

Compound 59 and 60:



To a solution of N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (50 mg, 1 eq, 0.12 mmol) and tetrahydrofuran-2-carboxylic acid (28 mg, 2 eq, 0.24 mmol) in DCM (1 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (34 mg, 1.5 Eq, 0.18 mmol) and 1-hydroxy-1H-benzotriazole (24 mg, 25 µL, 1.5 Eq, 0.18 mmol) and diisopropylethylamine (46 mg, 61 µL, 3 eq, 0.36 mmol). The resulting mixture was stirred for 2 hours at 25 degrees C. The resulting mixture was concentrated under reduced pressure. The crude was purified by reverse flash chromatography followed by prep-chiral-HPLC to afford:

Isomer 1 (12.9 mg, 24.9 µmol, 14%) as a solid.

LCMS: m/z (ES+), [M+H]+ = 519.20

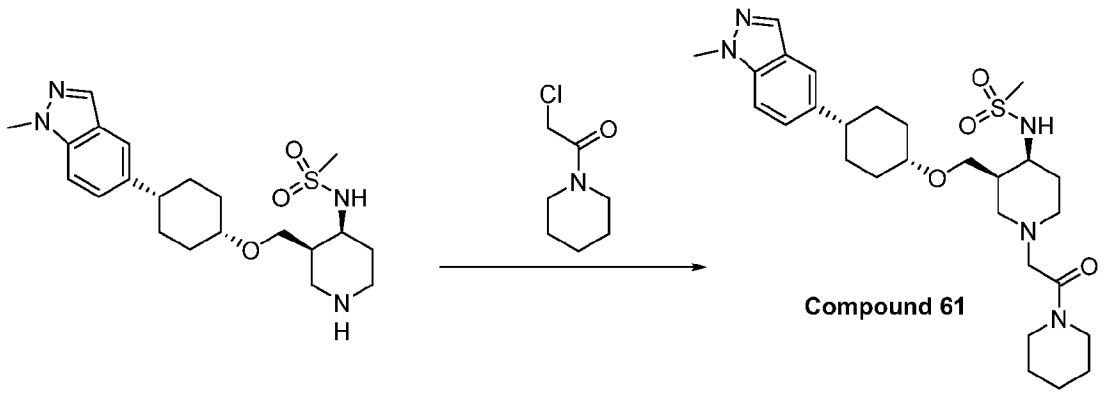
1H NMR (400 MHz, Methanol-d4) δ 7.93 – 7.89 (m, 1H), 7.62 – 7.56 (m, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.37 (td, J = 9.2, 8.7, 1.5 Hz, 1H), 4.90 (dd, J = 8.2, 5.4 Hz, 1H), 4.03 (d, J = 0.9 Hz,3H), 4.00 – 3.53 (m, 8H), 3.52 – 3.37 (m, 2H), 3.34 (s, 7H), 3.01 (d, J = 8.7 Hz, 3H), 2.66 (dd, J = 12.2, 8.9 Hz, 1H), 2.34 – 2.14 (m, 2H), 2.14 – 1.51 (m, 13H), 1.29 (s, 1H).

Isomer 2 (12.7 mg, 24.5 µmol, 13 %) as a solid

LCMS: m/z (ES+), [M+H]+ = 519.2

^{1}H NMR (400 MHz, Methanol-*d*4) δ 7.93 – 7.88 (m, 1H), 7.58 (d, *J* = 11.1 Hz, 1H), 7.47 – 7.32 (m, 2H), 4.94 – 4.87 (m, 1H), 4.02 (d, *J* = 1.1 Hz, 3H), 3.99 – 3.88 (m, 2H), 3.88 – 3.77 (m,2H), 3.76 – 3.54 (m, 5H), 3.51 – 3.38 (m, 2H), 3.01 (d, *J* = 8.5 Hz, 3H), 2.74 – 2.60 (m, 1H), 2.33 – 2.14 (m, 2H), 2.05 (td, *J* = 13.4, 12.7, 4.8 Hz, 3H), 1.97 – 1.55 (m, 11H).

Compound 61:

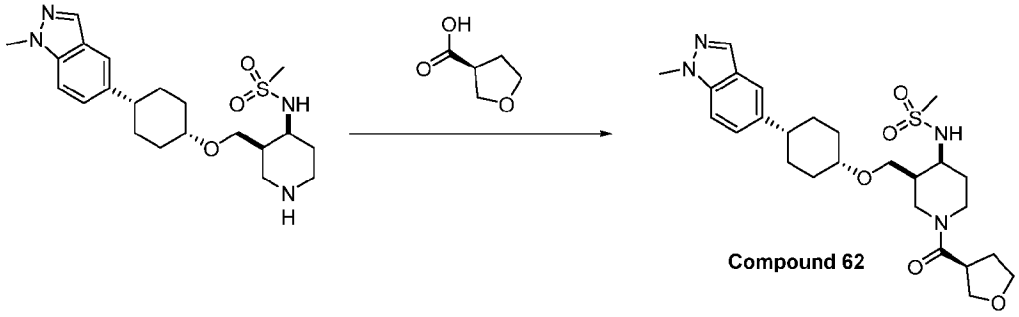


To a stirred solution of N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (100 mg, 1 eq, 238 µmol) in acetonitrile (2 mL) was added 2-chloro-1-(piperidin-1-yl)ethan-1-one (38.4 mg, 1 eq, 238 µmol) N-ethyl-N-isopropylpropan-2-amine (36.9 mg, 1.2 eq, 285 µmol) dropwise and potassium iodide (39.5 mg, 1 eq, 238 µmol) in portions at 25 degrees C under hydrogen/nitrogen atmosphere. The residue was purified by Prep-TLC followed by Prep-Chiral-HPLC to afford the product (23.5 mg, 42.2 µmol, 21%, 97.9% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ =546.4

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (d, 1H), 7.60 (d, 1H), 7.47 (d, 1H), 7.38 (dd, 1H), 4.05 (s, 3H), 3.71 – 3.56 (m, 6H), 3.51 – 3.44 (m, 1H), 3.42 – 3.36 (m, 1H), 3.28 (s, 1H), 3.16 (d, 1H), 3.01 (s, 3H), 2.75 – 2.51 (m, 5H), 2.26 (d, 1H), 2.09 (d, 2H), 1.93 – 1.81 (m, 4H), 1.69 – 1.48 (m, 11H).

Compound 62:

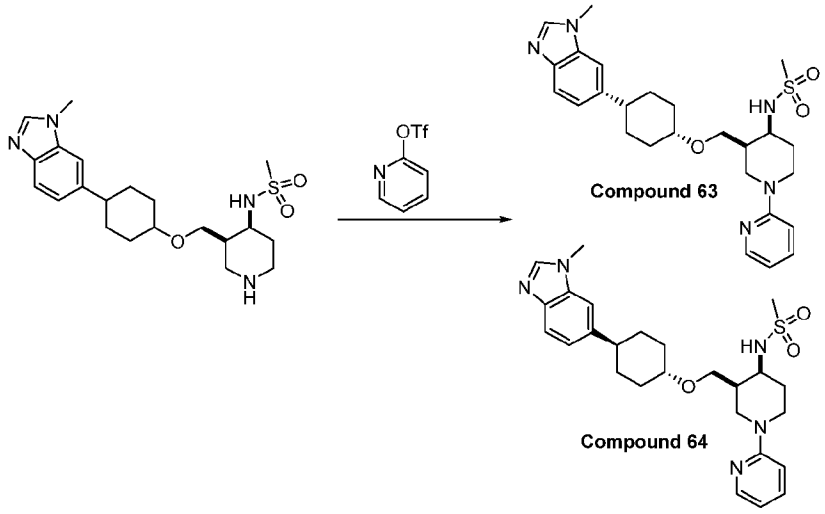


To a solution of N-((3R,4S)-3-((((1s,4S)-4-(1-methyl-1H-indazol-5-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (80 mg, 1 eq, 0.19 mmol) and HOBt (44 mg, 1.5 Eq, 0.29 mmol) in DCM (2 mL) were added EDC (55 mg, 1.5 Eq, 0.29 mmol) and DIEA (74 mg, 99 µL, 3 eq, 0.57 mmol) and (S)-tetrahydrofuran-3-carboxylic acid (33 mg, 1.5 eq, 0.29 mmol). After stirring for 8 h at 25 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The crude was purified by reverse flash chromatography followed by prep-Chiral-HPLC to afford desired product (16 mg, 31 µmol, 16 %, 99% purity) as a solid.

LCMS: m/z (ES+), [M+H]+ =519.3

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (s, 1H), 7.60 (d, 1H), 7.47 (d, 1H), 7.38 (dd, 1H), 4.09 – 4.02 (m, 3H), 4.00 – 3.73 (m, 7H), 3.70 – 3.44 (m, 6H), 3.04 (d, 3H), 2.70 (d, 1H), 2.32 – 1.99 (m, 5H), 1.97 – 1.57 (m, 8H).

Compound 63 and 64:



To a solution of N-((3R,4S)-3-(((4-(1-methyl-1H-benzo[d]imidazol-6-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (130 mg, 1 Eq, 309 µmol) and pyridin-2-yl trifluoromethanesulfonate (84.3 mg, 1.2 eq, 371 µmol) in DMSO (5 mL) was added TEA (93.8 mg, 129 µL, 3 eq, 927 µmol). After stirring for 3 h at 120 degrees C under a nitrogen atmosphere, the resulting mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3x20mL). The combined organic layers were washed with brine (1x50mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.

The crude was purified by reverse flash chromatography to afford:

Isomer 1 (7.2 mg, 14 µmol, 40 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =498

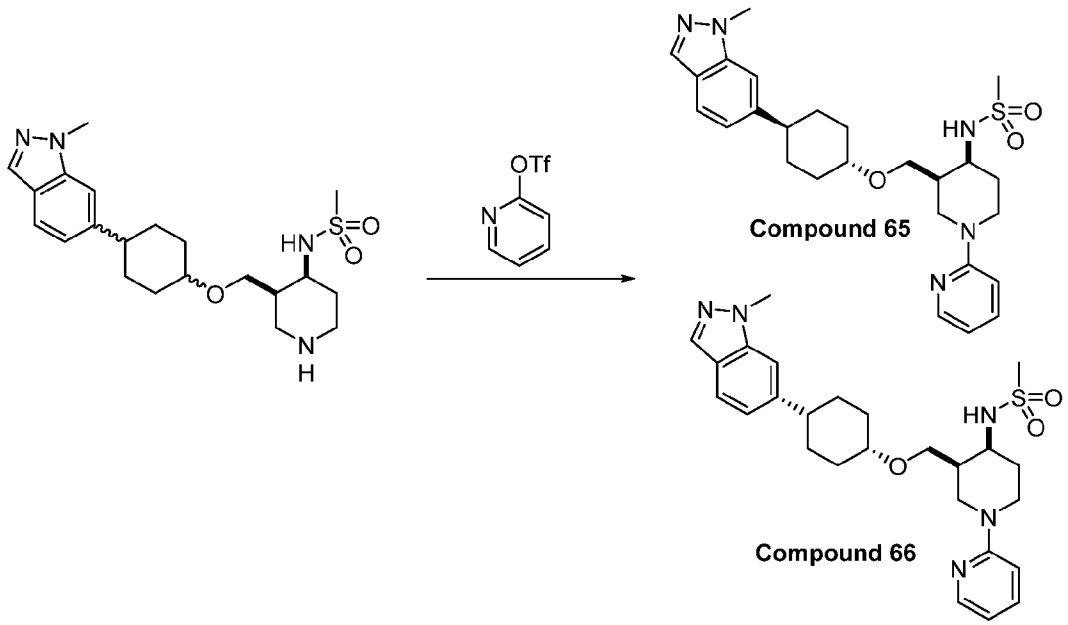
^{1}H NMR (400 MHz, Methanol-d4) δ 8.10 – 8.02 (m, 2H), 7.61 – 7.48 (m, 2H), 7.46 (d, 1H), 7.19 (dd, , 1H), 6.91 - 6.84 (m, 1H), 6.70 - 6.59 (m, 1H), 3.89 (s, 5H), 3.82 – 3.43 (m, 6H), 3.06 (s, 3H), 2.81 – 2.68 (m, 1H), 2.38 - 2.29 (m, 1H), 2.10 (d, 2H), 2.01 - 1.85 (m, 4H), 1.76 - 1.58 (m, 4H), 1.41 – 1.23 (m, 2H), 0.96 – 0.86 (m, 1H).

Isomer 2 (1 mg, 2 μmol, 20 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =498

^{1}H NMR (400 MHz, Methanol-d4) δ 8.08 (d, 1H), 7.57 (t, 1H), 7.41 (s, 1H), 7.19 (d, 1H), 6.89 (d, 1H), 6.72 – 6.63 (m, 1H), 4.64 (s, 2H), 3.89 (s, 3H), 3.75 (dd, 2H), 3.65 – 3.54 (m, 3H), 3.05 (s, 2H), 2.71 (s, 1H), 2.21 (s, 3H), 1.98 (d, 1H), 1.87 (d, 1H), 1.64 (d, 2H), 1.43 (s, 2H), 1.31 (s, 3H), 0.92 (s, 1H).

Compound 65 and 66:



To a solution of N-((3R,4S)-3-(((4-(1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)methyl)piperidin-4-yl)methanesulfonamide (100 mg, 1 eq, 238 μmol) and pyridin-2-yl trifluoromethanesulfonate (59.4 mg, 1.1 eq, 262 μmol) in DMSO (5 mL) was added TEA (72.2 mg, 99.4 μL, 3 eq, 713 μmol). After stirring for 3 h at 120 degrees C under a nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude was purified by reverse flash chromatography followed by CHIRAL-HPLC to afford:

Isomer 1:

LCMS: m/z (ES+), [M+H]+ =498

^{1}H NMR (400 MHz, Chloroform-d) δ 8.19 (dd, 1H), 7.92 (s, 1H), 7.63 (d, 1H), 7.53 (s, 1H), 7.40 (s, 1H), 7.04 (d, 1H), 6.78 – 6.64 (m, 2H), 6.57 (d, 1H), 4.10 (s, 3H), 4.05 (dd, 1H), 3.96 (t, 2H), 3.87 (s, 1H), 3.73 (d, 1H), 3.67 (s, 1H), 3.55 (s, 1H), 3.33 (s, 1H), 3.03 (s, 3H), 2.69 (d, 1H), 2.41 (s, 1H), 2.10 (d, 3H), 2.03 (s, 1H), 1.83 (d, 4H), 1.28 (s, 1H), 0.09 (s, 7H).

Isomer 2 (5.7 mg, 11 µmol, 38 %) as a solid.

LCMS: m/z (ES+), [M+H]+ =498

^{1}H NMR (400 MHz, Methanol-d4) δ 8.08 (dd, 1H), 7.92 (d, 1H), 7.65 (d, 1H), 7.62 - 7.55 (m, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 7.08 (dd, 1H), 6.90 (d, 1H), 6.67 (dd, 1H), 4.04 (s, 3H), 3.89 – 3.79 (m, 2H), 3.75 (dd, 1H), 3.69 – 3.47 (m, 4H), 3.40 (dd, , 1H), 3.05 (s, 3H), 2.70 (t, 1H), 2.22 (d, 3H), 1.99 (d, 2H), 1.87 (q, 2H), 1.74 – 1.53 (m, 2H), 1.44 (q, 2H), 1.31 (s, 1H).

Example 2: Human OX_2R IP1 assay

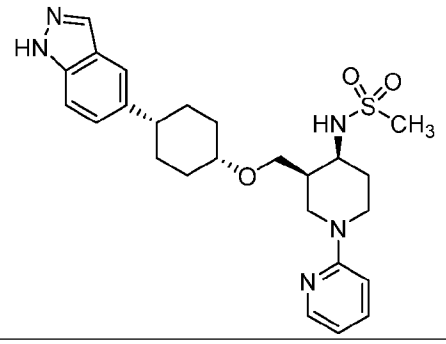
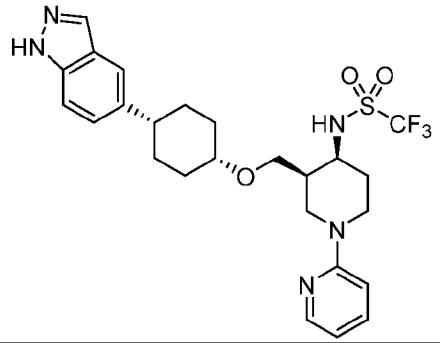
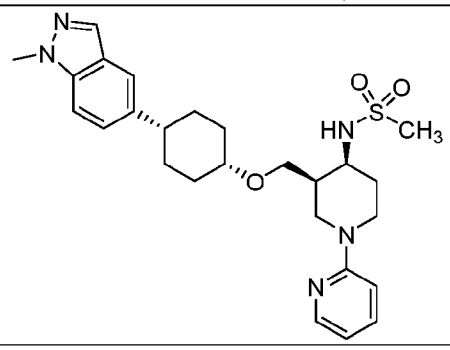
T-Rex CHO cells stably overexpressing the human orexin-2 receptor (OX_2R) were induced overnight with 1 µg/mL of doxycycline in a T225 flask. 24 hours post induction, cells were lifted with accutase and plated into a 384-well proxy plate at 30,000 cells/well. Cells were then treated with different test compounds in 1X stimulation buffer containing 10 mM Hepes, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 4.2 mM KCl, 146 mM NaCl, 5.5 mM glucose, and 50 mM LiCl, pH 7.4, for 1 hr at 37 degrees C. Following incubation, the reaction was terminated by the addition of detection mix, which is composed of IP1-d2 and anti-IP1-cryptate diluted in lysis buffer as well as 1X stimulation buffer. The plates were allowed to incubate for 1 hour at room temperature and were then read in the EnVision® multimode plate reader, measuring inositol phosphate levels.

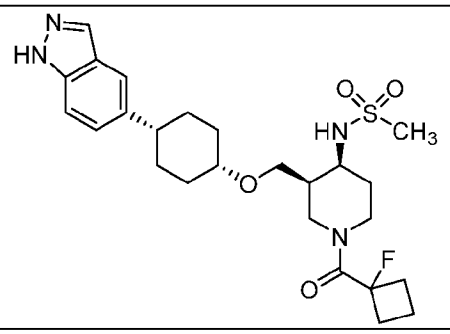
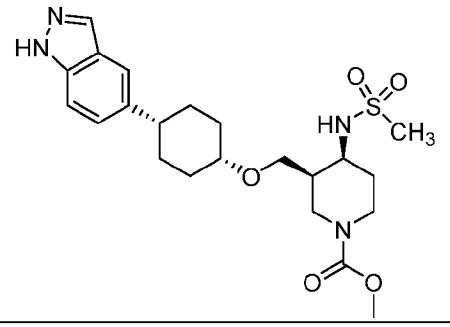
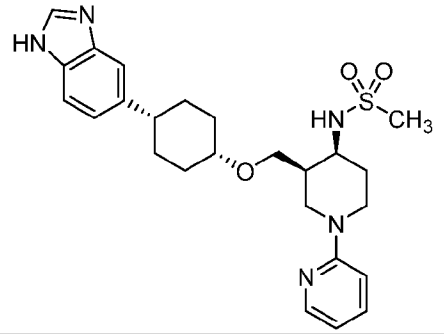
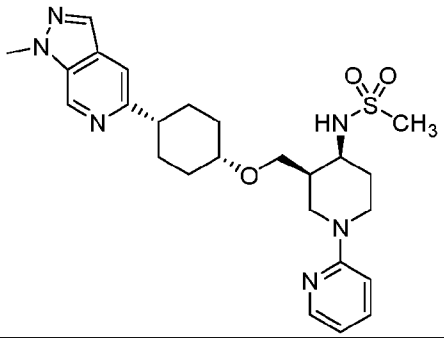
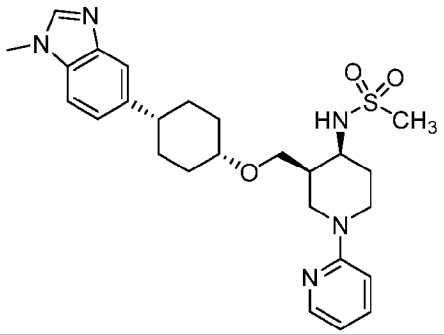
Cisbio IP1 is a cell-based functional assay quantifying the accumulation of inositol monophosphate (IP), a metabolite released as a result of orexin 2 receptor activation through the phospholipase C-Gq signaling pathway. This is a competitive immunoassay in which the IP1 produced by the cells upon receptor activation competes with the IP1 analog coupled to the d2 fluorophore (acceptor) for binding to an anti-IP1 monoclonal antibody labeled with Eu

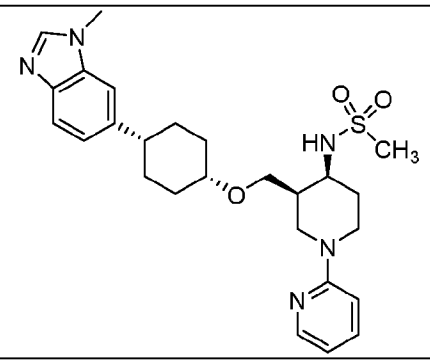
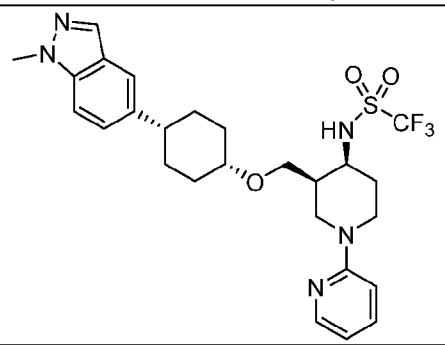
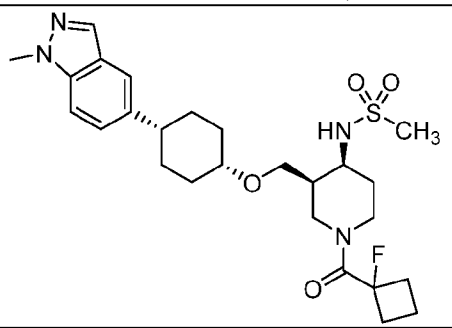
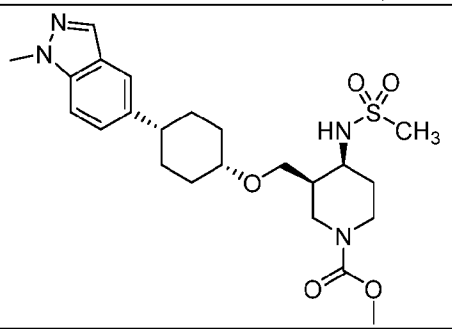
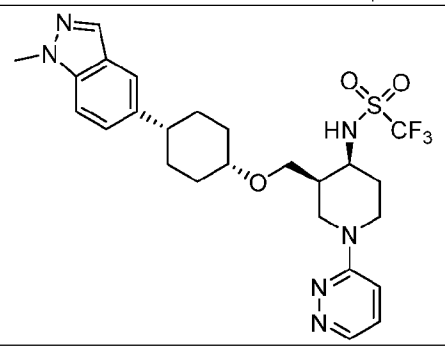
cryptate (donor). The measured HTRF-FRET based signal is inversely proportional to the IP1 concentration produced.

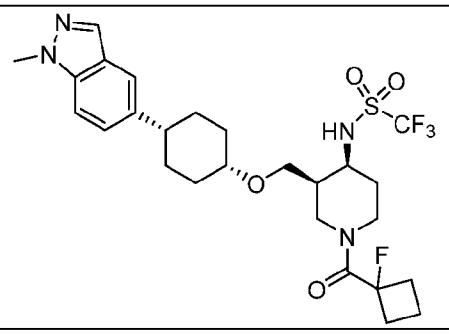
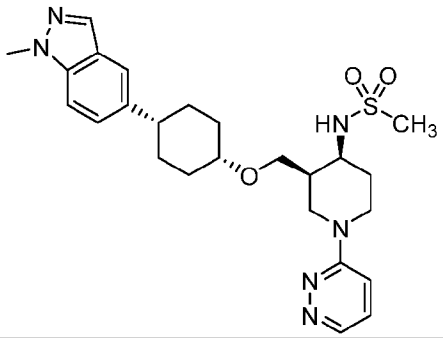
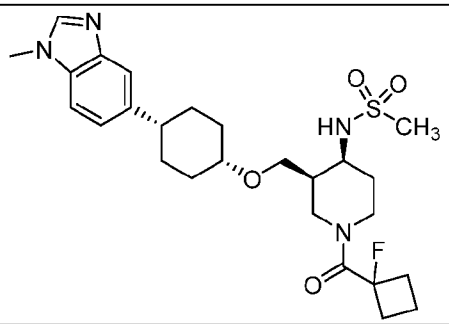
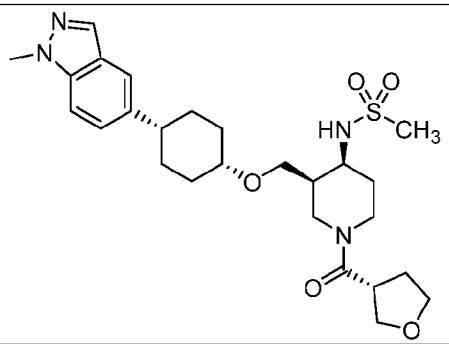
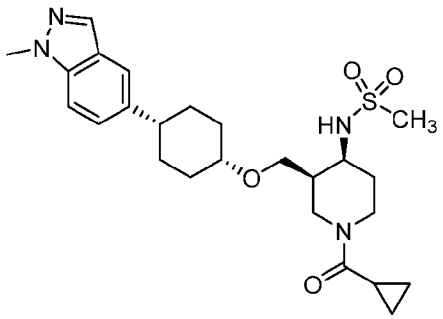
The EC_{50} values reported in Table 2 were obtained according to the human OX_2R IP1 assay described above. Data are the mean EC_{50} values ± S.E.M.

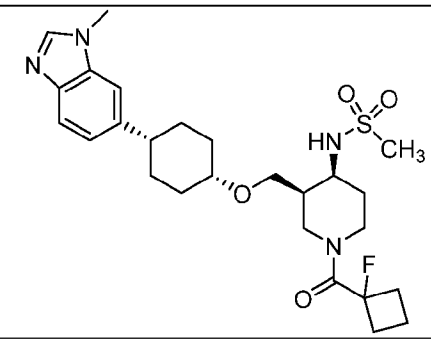
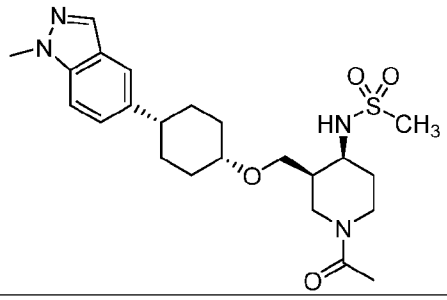
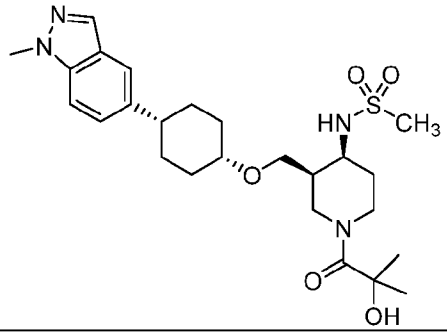
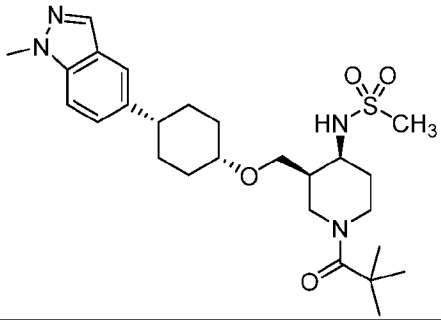
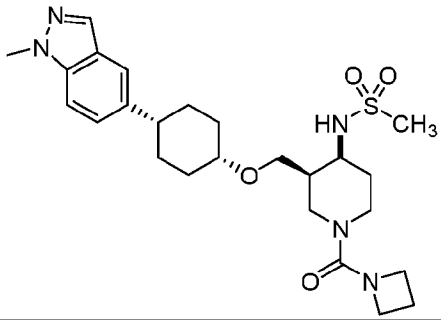
Table 2.

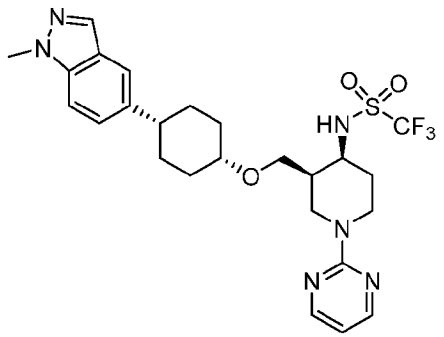
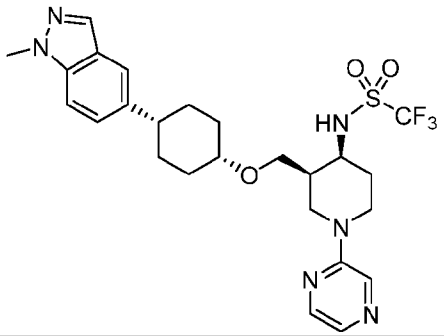
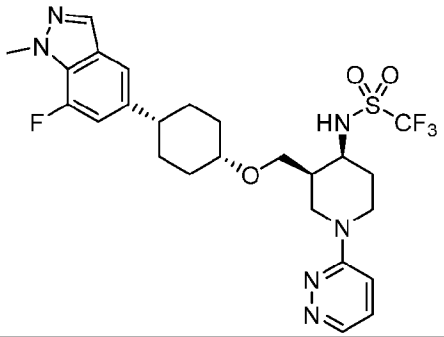
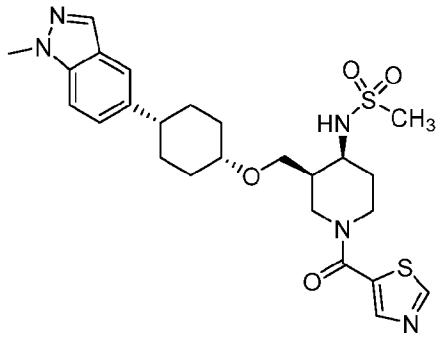
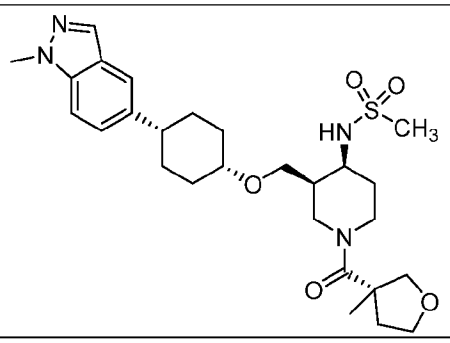
Structure	Compound No.	EC_{50} (nM)
	1	***
	2	**
	3	***

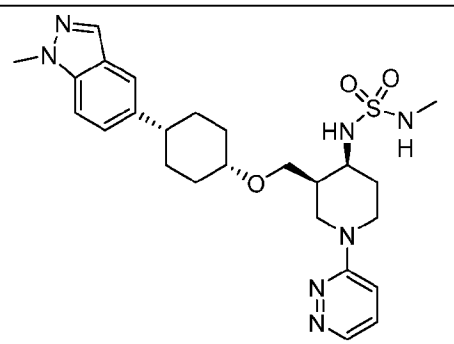
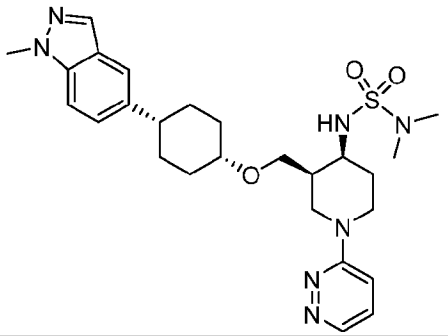
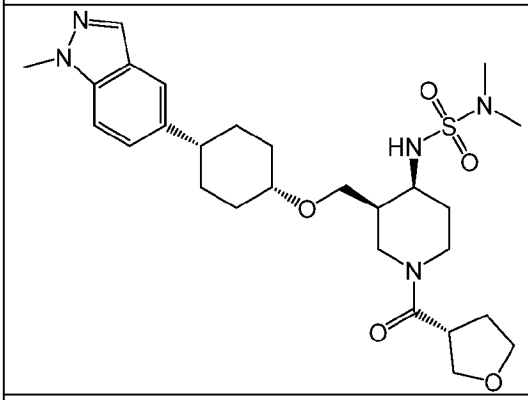
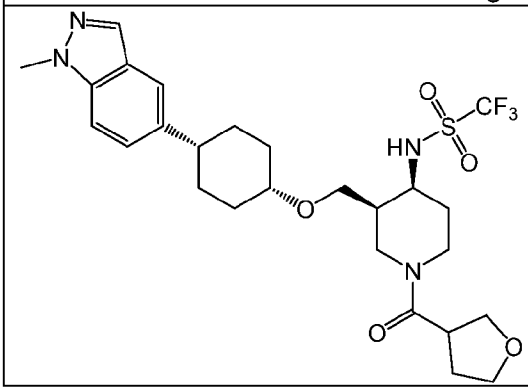
	4	**
	5	**
	6	*
	7	*
	8	**

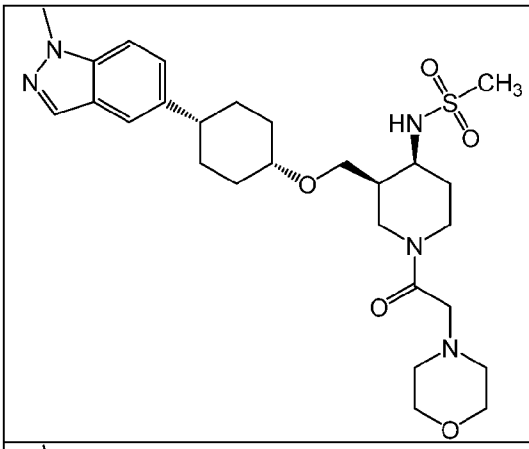
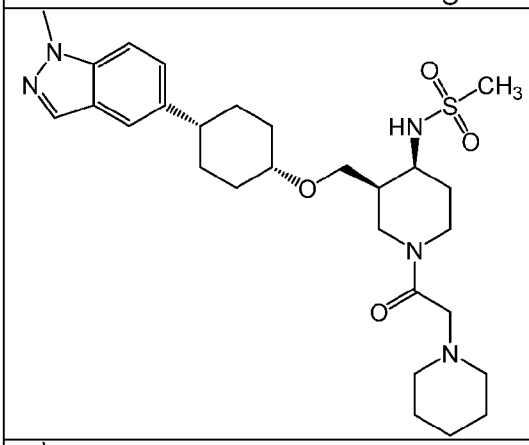
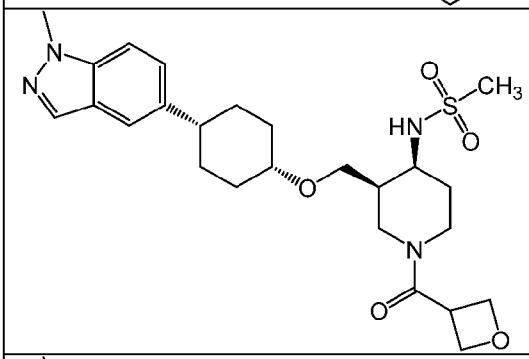
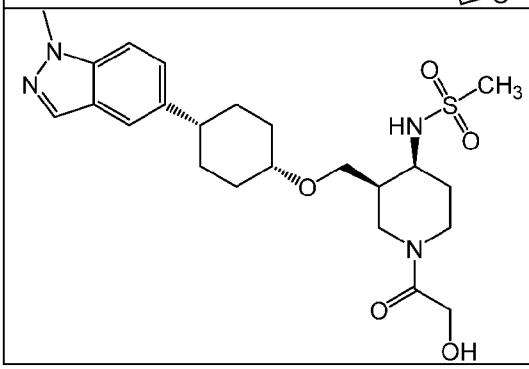
	9	**
	10	***
	11	***
	12	**
	13	***

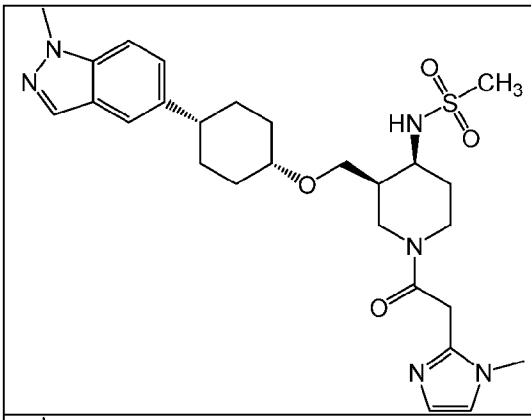
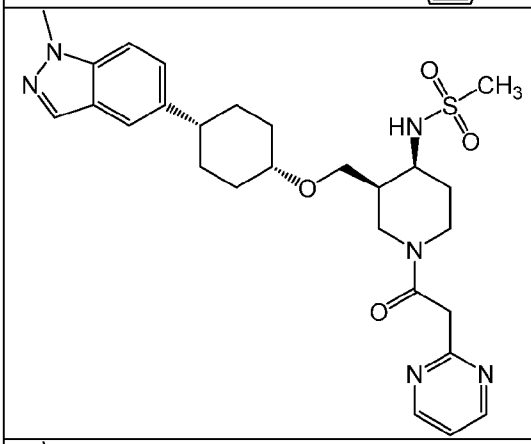
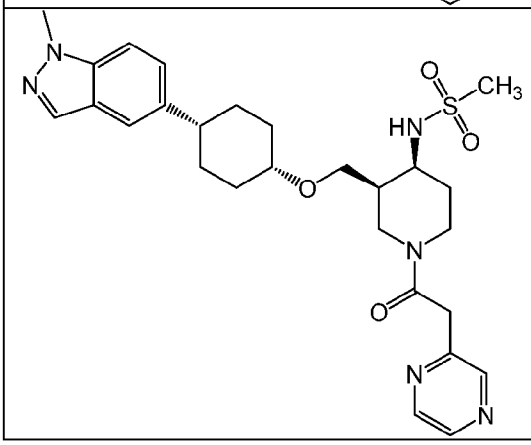
	14	**
	15	**
	16	***
	17	**
	18	**

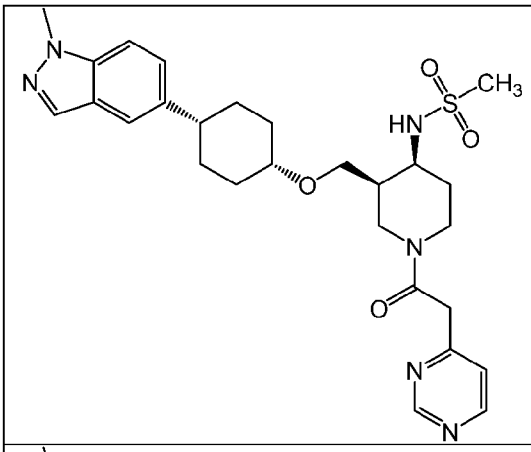
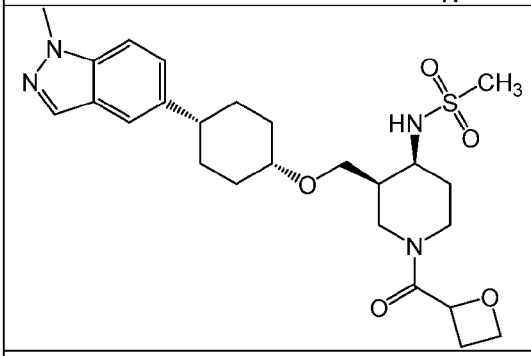
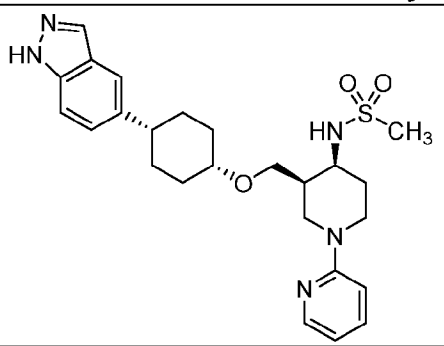
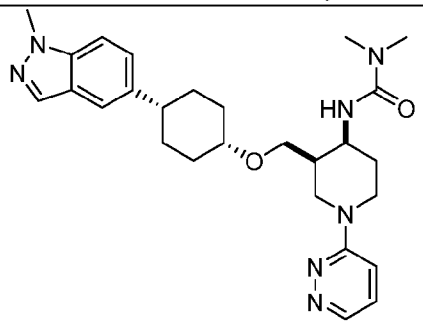
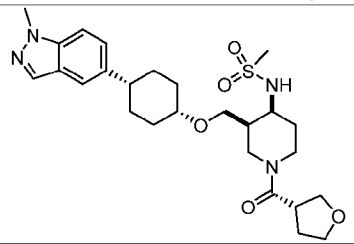
	19	**
	20	*
	21	**
	22	**
	23	**

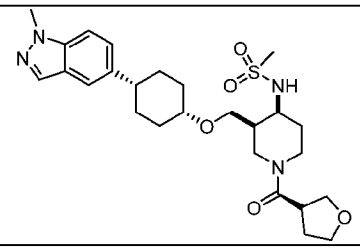
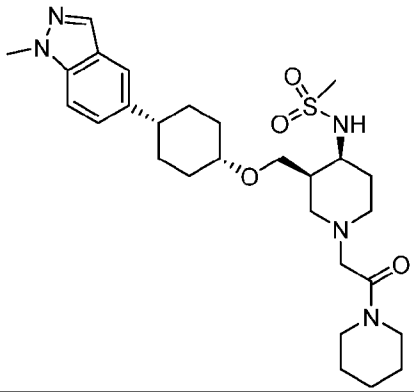
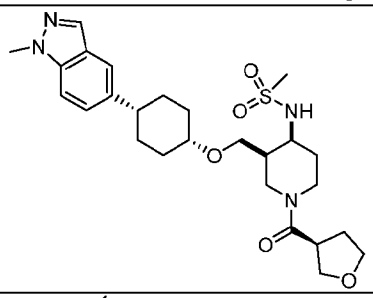
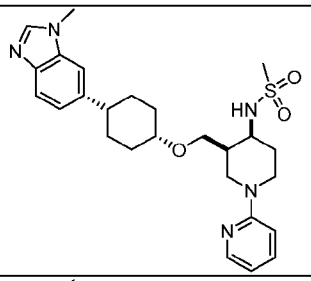
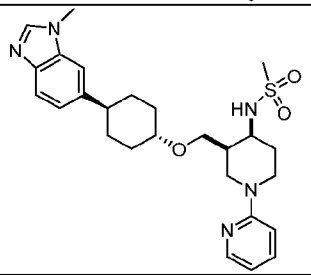
	24	**
	25	**
	26	**
	27	**
	28	**

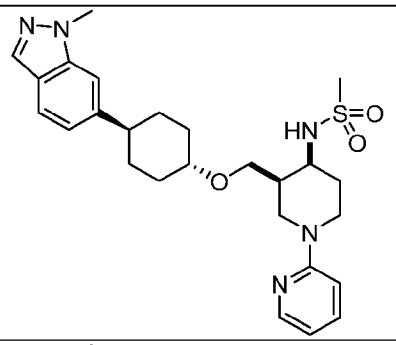
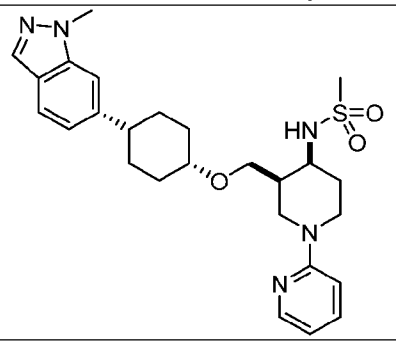
	29	***
	30	***
	31	**
	33	**

	45	*
	46	*
	47	*
	48	*

	49	*
	50	*
	51	*

	52	*
	53	*
	55	***
	58	*
	59	**

	60	*
	61	*
	62	*
	63	*
	64	**

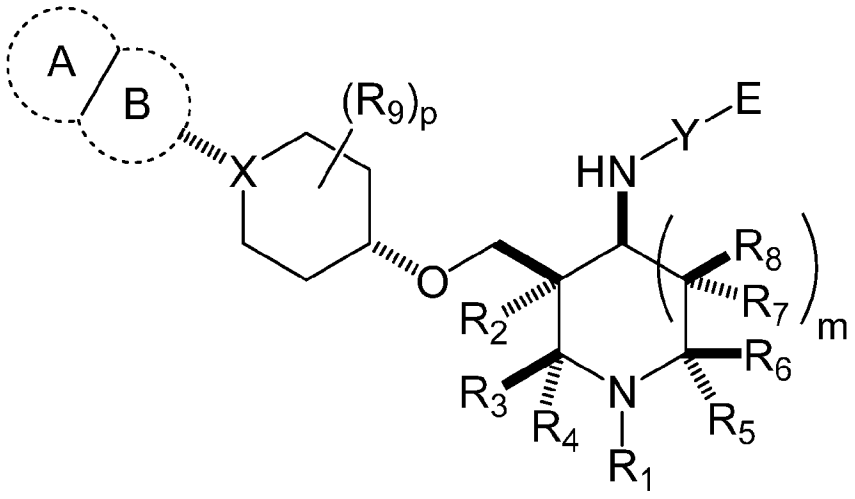
	65	*
	66	*

***EC_{50} < 1 nM
**EC_{50} 1-10 nM
*EC_{50} > 10 nM

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

What is claimed is:

1. A compound of Formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

ring A is fused to ring B;

ring A is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

ring B is selected from the group consisting of C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

X is N or CH;

Y is $S(=O)_2$, C(=O), or $S(=O)(=NR_e)$;

R_e is selected from the group consisting of H, C_1-C_3 alkyl, or C_3-C_5 cycloalkyl;

E is selected from the group consisting of NR_aR_b, C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl and C_1-C_3 alkylene-(5- to 7-membered

heteroaryl), wherein the C_1-C_3 alkylene-NR_aR_b, C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

R_a and R_b are each, independently, selected from the group consisting of H, C_1-C_3 alkyl, C_3-C_5 cycloalkyl, and 4- to 7-membered heterocyclyl, wherein the C_1-C_3 alkyl, C_3-C_5 cycloalkyl, or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl;

or, alternatively, R_a and R_b, together with the N atom to which they are attached, form a 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, C_1-C_3 alkyl, C_1-C_3 alkoxyl, or C_1-C_3 alkyl substituted with 1-3 halogen;

R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), $(CR_cR_d)_n$-(C_6-C_{10} aryl) and $(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

R_c and R_d are each, independently, H, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

n is 0, 1, or 2;

each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium;

or, alternatively, R_3 and R_6, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

or, alternatively, R_4 and R_5, together form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen;

m is 0 or 1;

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

each R_9 is, independently, selected from the group consisting of deuterium, halogen, hydroxyl, and cyano.

2. The compound according to claim 1, wherein ring A is selected from the group consisting of: C_3-C_8 cycloalkyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

3. The compound according to claim 1, wherein ring A is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

4. The compound according to claim 1, wherein ring A is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

5. The compound according to claim 1, wherein ring A is selected from the group consisting of: C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

6. The compound according to claim 1, wherein ring A is selected from the group consisting of: C_3-C_8 cycloalkyl and 4- to 7-membered heterocyclyl, wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

7. The compound according to claim 1, wherein ring A is selected from the group consisting of: C_3-C_8 cycloalkyl and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl or C_6-C_{10} aryl

is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

8. The compound according to claim 1, wherein ring A is selected from the group consisting of: 4- to 7-membered heterocyclyl and C_6-C_{10} aryl, wherein the 4- to 7-membered heterocyclyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

9. The compound according to claim 1, wherein ring A is selected from the group consisting of: 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

10. The compound according to claim 1, wherein ring A is C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

11. The compound according to claim 1, wherein ring A is 4- to 7-membered heterocyclyl, wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

12. The compound according to claim 1, wherein ring A is C_6-C_{10} aryl, wherein the C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

13. The compound according to claim 1, wherein ring A is 5- to 7-membered heteroaryl wherein the 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

14. The compound according to claim 1, wherein ring B is selected from the group consisting of: 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

15. The compound according to claim 1, wherein ring B is selected from the group consisting of: C_3-C_8 cycloalkyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

16. The compound according to claim 1, wherein ring B is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

17. The compound according to claim 1, wherein ring B is selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

18. The compound according to claim 1, wherein ring B is selected from the group consisting of: C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

19. The compound according to claim 1, wherein ring B is selected from the group consisting of: C_3-C_8 cycloalkyl and 4- to 7-membered heterocyclyl, wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

20. The compound according to claim 1, wherein ring B is selected from the group consisting of: C_3-C_8 cycloalkyl and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

21. The compound according to claim 1, wherein ring B is selected from the group consisting of: 4- to 7-membered heterocyclyl and C_6-C_{10} aryl, wherein the 4- to 7-membered

heterocyclyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

22. The compound according to claim 1, wherein ring B is selected from the group consisting of: 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

23. The compound according to claim 1, wherein ring B is C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

24. The compound according to claim 1, wherein ring B is 4- to 7-membered heterocyclyl, wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

25. The compound according to claim 1, wherein ring B is C_6-C_{10} aryl, wherein the C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

26. The compound according to claim 1, wherein ring B is 5- to 7-membered heteroaryl wherein the 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

27. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: 4- to 7-membered heterocyclyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl, C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

28. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl, C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{10} aryl or 5- to 7-membered

heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

29. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

30. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

31. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: C_6-C_{10} aryl and 5- to 7-membered heteroaryl, wherein the C_6-C_{10} aryl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

32. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl and 4- to 7-membered heterocyclyl, wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

33. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: C_3-C_8 cycloalkyl and C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl or C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

34. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: 4- to 7-membered heterocyclyl and C_6-C_{10} aryl, wherein the 4- to 7-membered heterocyclyl or C_6-C_{10} aryl is unsubstituted or

substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

35. The compound according to claim 1, wherein ring A and ring B are each, independently, selected from the group consisting of: 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl or 5- to 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

36. The compound according to claim 1, wherein ring A is 5- to 7-membered heteroaryl and ring B is C_6-C_{10} aryl, wherein the 5- to 7-membered heteroaryl and C_6-C_{10} aryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

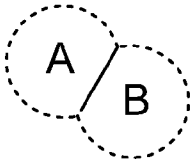
37. The compound according to claim 1, wherein ring A is 5- to 7-membered heteroaryl and ring B is 5- to 7-membered heteroaryl, wherein each 5- to 7-membered heteroaryl, independently, is unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

38. The compound according to claim 1, wherein ring A is 4- to 7-membered heterocyclyl and ring B is C_6-C_{10} aryl, wherein the 4- to 7-membered heterocyclyl and C_6-C_{10} aryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

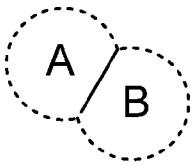
39. The compound according to claim 1, wherein ring A is 4- to 7-membered heterocyclyl and ring B is 5- to 7-membered heteroaryl, wherein the 4- to 7-membered heterocyclyl and 5- to 7-membered heteroaryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

40. The compound according to claim 1, wherein ring A is C_3-C_8 cycloalkyl and ring B is C_6-C_{10} aryl, wherein the C_3-C_8 cycloalkyl and C_6-C_{10} aryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

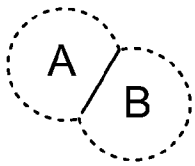
41. The compound according to claim 1, wherein ring A is C_3-C_8 cycloalkyl and ring B is 5- to 7-membered heteroaryl, wherein the C_3-C_8 cycloalkyl and 5- to 7-membered heteroaryl are each, independently, unsubstituted or substituted with one or more halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.



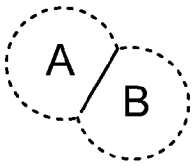
42. The compound according to claim 1, wherein is selected from the group consisting of benzoimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, imidazo[1,5-*a*]pyridinyl, indolyl, isoindolyl, indolinyl, indazolyl, isoindazolyl, benzothiazolyl, purinyl, benzofuranyl, benzoisoxazolyl, benzoisothiazolyl, isobenzofuranyl, benzothiofuranyl, indoleninyl, pyrano[3,4-*b*]-pyrrolyl, indoxazinyl, benzoxazolyl, anthranilyl, and indolizinyl, wherein the benzoimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, imidazo[1,5-*a*]pyridinyl, indolyl, isoindolyl, indolinyl, indazolyl, isoindazolyl, benzothiazolyl, purinyl, benzofuranyl, benzoisoxazolyl, benzoisothiazolyl, isobenzofuranyl, benzothiofuranyl, indoleninyl, pyrano[3,4-*b*]-pyrrolyl, indoxazinyl, benzoxazolyl, anthranilyl, and indolizinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



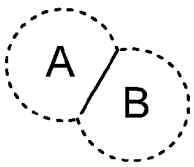
43. The compound according to claim 1, wherein is benzoimidazolyl, wherein the benzoimidazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.



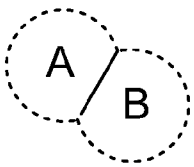
44. The compound according to claim 1, wherein is 1*H*-pyrazolo[3,4-*c*]pyridinyl, wherein the 1*H*-pyrazolo[3,4-*c*]pyridinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

45. The compound according to claim 1, wherein 

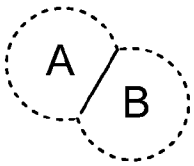
is imidazo[1,5-*a*]pyridinyl, wherein the imidazo[1,5-*a*]pyridinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

46. The compound according to claim 1, wherein 

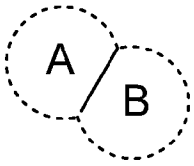
is indolyl, wherein the indolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

47. The compound according to claim 1, wherein 

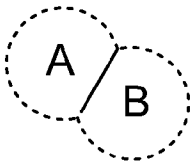
is isoindolyl, wherein the isoindolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

48. The compound according to claim 1, wherein 

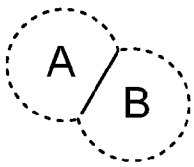
is indolinyl, wherein the indolinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

49. The compound according to claim 1, wherein 

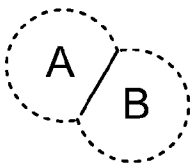
is indazolyl, wherein the indazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

50. The compound according to claim 1, wherein 

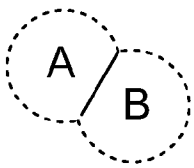
is isoindazolyl, wherein the isoindazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

51. The compound according to claim 1, wherein 

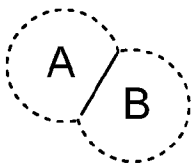
is benzothiazolyl, wherein the benzothiazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

52. The compound according to claim 1, wherein 

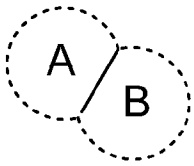
is purinyl, wherein the purinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

53. The compound according to claim 1, wherein 

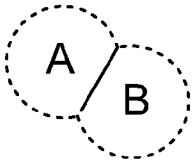
is benzofuranyl, wherein the benzofuranyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

54. The compound according to claim 1, wherein 

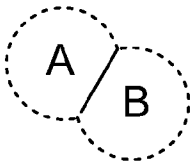
is benzoisoxazolyl, wherein the benzoisoxazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

55. The compound according to claim 1, wherein 

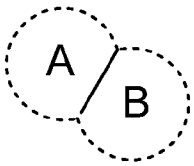
is benzoisothiazolyl, wherein the benzoisothiazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

56. The compound according to claim 1, wherein 

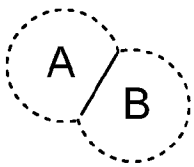
is isobenzofuranyl, wherein the isobenzofuranyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

57. The compound according to claim 1, wherein 

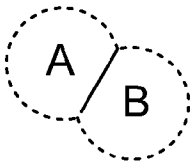
is benzothiofuranyl, wherein the benzothiofuranyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

58. The compound according to claim 1, wherein 

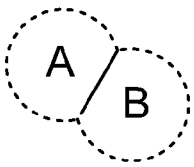
is indoleninyl, wherein the indoleninyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

59. The compound according to claim 1, wherein 

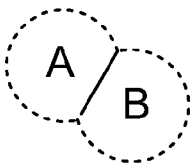
is pyrano[3,4-*b*]-pyrrolyl, wherein the pyrano[3,4-*b*]-pyrrolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

60. The compound according to claim 1, wherein 

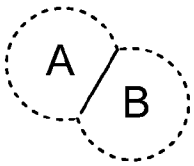
is indoxazinyl, wherein the indoxazinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

61. The compound according to claim 1, wherein 

is benzoxazolyl, wherein the benzoxazolyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

62. The compound according to claim 1, wherein 

is anthranilyl, wherein the anthranilyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

63. The compound according to claim 1, wherein 

is indolizinyl, wherein the indolizinyl is unsubstituted or substituted with 1-3 substituents selected from halogen, hydroxyl, C_1-C_3 alkoxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with 1-3 halogen or deuterium atoms.

64. The compound according to any one of claims 1-63, wherein p is 0.

65. The compound according to any one of claims 1-63, wherein p is 1.

66. The compound according to any one of claims 1-63, wherein p is 2.

67. The compound according to any one of claims 1-63, wherein p is 3.

68. The compound according to any one of claims 1-63, wherein p is 4.

69. The compound according to any one of claims 1-63, wherein p is 0, 1, or 2.

70. The compound according to any one of claims 1-63, wherein p is 0 or 1.

71. The compound according to any one of claims 1-70, wherein E is NR_aR_b.

72. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkylene-NR_aR_b.

73. The compound according to any one of claims 1-70, wherein E is unsubstituted C_1-C_3 alkyl, unsubstituted C_2-C_4 alkenyl or unsubstituted C_2-C_4 alkynyl.

74. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl substituted with one or more halogen, hydroxyl, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

75. The compound according to any one of claims 1-70, wherein E is unsubstituted C_1-C_3 alkyl.

76. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

77. The compound according to any one of claims 1-70, wherein E is unsubstituted C_3-C_8 cycloalkyl.

78. The compound according to any one of claims 1-70, wherein E is C_3-C_8 cycloalkyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

79. The compound according to any one of claims 1-70, wherein E is unsubstituted C_1-C_3 alkylene-(C_3-C_8 cycloalkyl).

80. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkylene-(C_3-C_8 cycloalkyl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

81. The compound according to any one of claims 1-70, wherein E is unsubstituted 4- to 10-membered heterocyclyl.

82. The compound according to any one of claims 1-70, wherein E is 4- to 10-membered heterocyclyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

83. The compound according to any one of claims 1-70, wherein E is unsubstituted C_1-C_3 alkylene-(4- to 10-membered heterocyclyl).

84. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkylene-(4- to 10-membered heterocyclyl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

85. The compound according to any one of claims 1-70, wherein E is unsubstituted C_6-C_{10} aryl.

86. The compound according to any one of claims 1-70, wherein E is C_6-C_{10} aryl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

87. The compound according to any one of claims 1-70, wherein E is unsubstituted C_1-C_3 alkylene-(C_6-C_{10} aryl).

88. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkylene-(C_6-C_{10} aryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

89. The compound according to any one of claims 1-70, wherein E is unsubstituted 5- to 7-membered heteroaryl.

90. The compound according to any one of claims 1-70, wherein E is 5- to 7-membered heteroaryl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

91. The compound according to any one of claims 1-70, wherein E is unsubstituted C_1-C_3 alkylene-(5- to 7-membered heteroaryl).

92. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkylene-(5- to 7-membered heteroaryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

93. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), wherein the C_1-C_3alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl) is

unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

94. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl), wherein the C_1-C_3alkyl, C_3-C_8 cycloalkyl, C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), 4- to 10-membered heterocyclyl, or C_1-C_3 alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

95. The compound according to any one of claims 1-70, wherein E is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, or C_1-C_3 alkylene-(C_3-C_8 cycloalkyl), wherein the C_1-C_3alkyl, C_3-C_8 cycloalkyl, or C_1-C_3 alkylene-(C_3-C_8 cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

96. The compound according to any one of claims 1-70, wherein E is methyl.

97. The compound according to any one of claims 1-70, wherein E is methyl substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

98. The compound according to any one of claims 1-70, wherein E is CF_3.

99. The compound according to any one of claims 1-70, wherein E is CHF_2.

100. The compound according to any one of claims 1-70, wherein E is CH_2F.

101. The compound according to any one of claims 1-70, wherein E is $NH(CH_3)$.

102. The compound according to any one of claims 1-70, wherein E is $N(CH_3)_2$.

103. The compound according to any one of claims 1-70, wherein E is C_6-C_{10} aryl, C_1-C_3 alkylene-(C_6-C_{10} aryl), 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl).

104. The compound according to any one of claims 1-70, wherein E is unsubstituted C_6-C_{10} aryl or C_1-C_3 alkylene-(C_6-C_{10} aryl).

105. The compound according to any one of claims 1-70, wherein E is C_6-C_{10} aryl or C_1-C_3 alkylene-(C_6-C_{10} aryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

106. The compound according to any one of claims 1-70, wherein E is 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl).

107. The compound according to any one of claims 1-70, wherein E is unsubstituted 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl).

108. The compound according to any one of claims 1-70, wherein E is 5- to 7-membered heteroaryl or C_1-C_3 alkylene-(5- to 7-membered heteroaryl) substituted with one or more halogen, hydroxyl, NR_cR_d, CF_3, CHF_2, CH_2F, C_1-C_3 alkyl, or C_1-C_3 alkoxyl.

109. The compound according to any one of claims 1-108, wherein Y is $S(=O)_2$.

110. The compound according to any one of claims 1-108, wherein Y is C(=O).

111. The compound according to any one of claims 1-108, wherein Y is $S(=O)(=NR_e)$.

112. The compound according to any one of claims 1-111, wherein X is N.

113. The compound according to any one of claims 1-111, wherein X is CH.

114. The compound according to any one of claims 1-113, wherein R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), and C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, C_3-C_8 cycloalkyl, 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

115. The compound according to any one of claims 1-113, wherein R_1 is selected from the group consisting of C(=O)-C_1-C_4 alkyl, C(=O)-C_1-C_4 alkoxyl, and C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, wherein the C_1-C_4 alkyl, C_1-C_4 alkoxyl, or C_3-C_8 cycloalkyl, is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

116. The compound according to any one of claims 1-113, wherein R_1 is selected from the group consisting of C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), and C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the 4- to 7-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

117. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is unsubstituted or substituted with one or more halogen,

hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

118. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-C_1-C_4 alkoxyl, wherein the C_1-C_4 alkoxyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

119. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

120. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

121. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(C_6-C_{10} aryl), wherein the C_6-C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

122. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 10-membered heteroaryl), wherein the 5- to 10-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

123. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heterocyclyl), wherein the 5- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

124. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 6-membered heterocyclyl), wherein the 5- to 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

125. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(5-membered heterocyclyl), wherein the 5-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

126. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(6-membered heterocyclyl), wherein the 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

127. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6 aryl), wherein the C_6 aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

128. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_8 aryl), wherein the C_8 aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

129. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_{10} aryl), wherein the C_{10} aryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

130. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(5- to 6-membered heteroaryl), wherein the 5- to 6-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

131. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(5-membered heteroaryl), wherein the 5-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

132. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(6-membered heteroaryl), wherein the 6-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

133. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(7-membered heteroaryl), wherein the 7-membered heteroaryl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

134. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-C_3$-C_8 cycloalkyl or $C(=O)-O-(CR_cR_d)_n-$(4- to 7-membered heterocyclyl), wherein the C_3-C_8 cycloalkyl or 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

135. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-C_3$-C_8 cycloalkyl, wherein the C_3-C_8 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

136. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-$(4- to 7-membered heterocyclyl), wherein the 4- to 7-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

137. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-C_3$-C_5 cycloalkyl, wherein the C_3-C_5 cycloalkyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

138. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-$(5- to 6-membered heterocyclyl), wherein the 5- to 6-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

139. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-$(5-membered heterocyclyl), wherein the 5-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

140. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-O-(CR_cR_d)_n-$(6-membered heterocyclyl), wherein the 6-membered heterocyclyl is unsubstituted or

substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

141. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is unsubstituted.

142. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

143. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 0.

144. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

145. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 1.

146. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) or $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the C_6-C_{10} aryl or 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

147. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is unsubstituted.

148. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

149. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is unsubstituted and further wherein n is 0.

150. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

151. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is unsubstituted and further wherein n is 1.

152. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) wherein the C_6-C_{10} aryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

153. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is unsubstituted.

154. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

155. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 0.

156. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

157. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is unsubstituted and further wherein n is 1.

158. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) wherein the 5- to 10-membered heteroaryl is substituted with one

or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

159. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is unsubstituted.

160. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

161. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is unsubstituted and further wherein n is 0.

162. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

163. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is unsubstituted and further wherein n is 1.

164. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) wherein the phenyl or 5- to 7-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

165. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is unsubstituted.

166. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

167. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is unsubstituted and further wherein n is 0.

168. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

169. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is unsubstituted and further wherein n is 1.

170. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(phenyl) or $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the phenyl or 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

171. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is unsubstituted.

172. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

173. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is unsubstituted and further wherein n is 0.

174. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

175. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is unsubstituted and further wherein n is 1.

176. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) wherein the 6-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

177. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is unsubstituted.

178. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

179. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is unsubstituted and further wherein n is 0.

180. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 0.

181. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is unsubstituted and further wherein n is 1.

182. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5-membered heteroaryl) wherein the 5-membered heteroaryl is substituted with one or more halogen, hydroxyl, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium and further wherein n is 1.

183. The compound according to any one of claims 1-182, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, unsubstituted C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with one or more halogen or deuterium.

184. The compound according to any one of claims 1-182, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H, halogen, or unsubstituted C_1-C_3 alkyl.

185. The compound according to any one of claims 1-182, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H or halogen.

186. The compound according to any one of claims 1-182, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H or fluorine.

187. The compound according to any one of claims 1-182, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is, independently, H or C_1-C_3 alkyl.

188. The compound according to any one of claims 1-182, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

189. The compound according to any one of claims 1-182, wherein R_3 and R_6, together, form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen.

190. The compound according to any one of claims 1-182, wherein R_4 and R_5, together, form an unsubstituted C_1-C_3 alkylene or a C_1-C_3 alkylene substituted with one or more halogen.

191. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-C_1-C_4 alkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

192. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-C_1-C_4 alkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl.

193. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-C_1-C_4 alkoxyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

194. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-C_1-C_4 alkoxyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl.

195. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

196. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H or unsubstituted C_1-C_3 alkyl.

197. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

198. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

199. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

200. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

201. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

202. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

203. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

204. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

205. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

206. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

207. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

208. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

209. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6-C_{10} aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

210. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6-C_{10} aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

211. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

212. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

213. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)-(CR_cR_d)_n-$(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

214. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

215. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

216. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5- to 7-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

217. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

218. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

219. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(5-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

220. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

221. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

222. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-$(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

223. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

224. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

225. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-O-$(CR_cR_d)_n$-C_3-C_8 cycloalkyl, n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

226. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

227. The compound according to any one of claims 1-113, wherein R_1 is C(=O)-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

228. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(4- to 7-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

229. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(5-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

230. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

231. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(5-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

232. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(6-membered heterocyclyl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

233. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(6-membered heterocyclyl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

234. The compound according to any one of claims 1-113, wherein R_1 is $C(=O)$-O-$(CR_cR_d)_n$-(6-membered heterocyclyl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

235. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 10-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

236. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(5- to 7-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

237. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

238. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

239. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(6-membered heteroaryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

240. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6-C_{10} aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

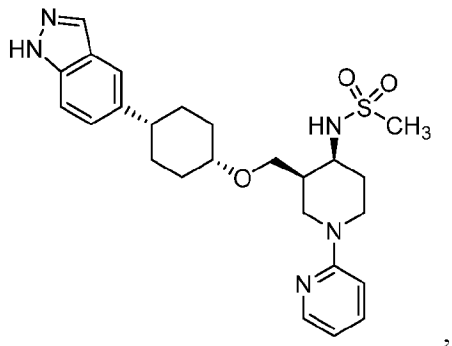
241. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6 aryl) and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

242. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 0, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

243. The compound according to any one of claims 1-113, wherein R_1 is $(CR_cR_d)_n$-(C_6 aryl), n is 1 or 2, and each of R_2, R_3, R_4, R_5, R_6, R_7, and R_8 is H.

244. The compound according to any one of claims 1-113, wherein R_1 is 3-pyridazinyl.

245. A compound or a pharmaceutically acceptable salt thereof selected from the group consisting of: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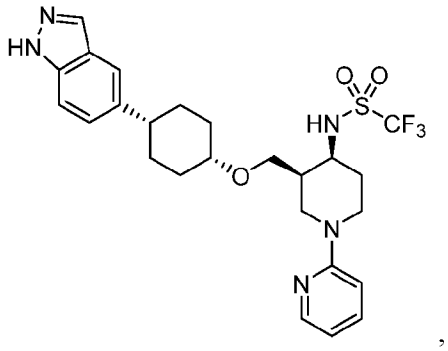
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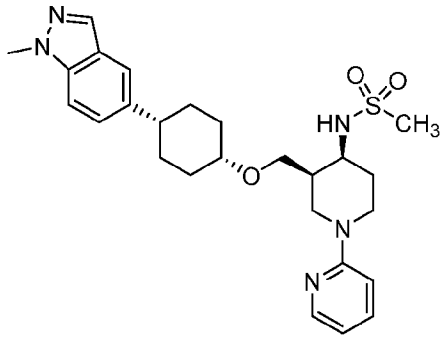
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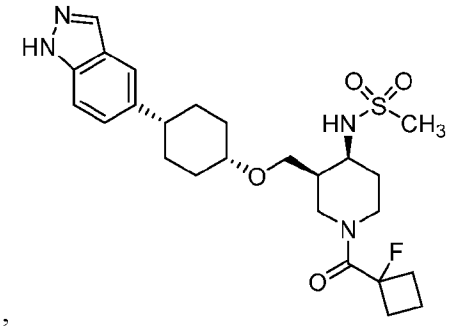
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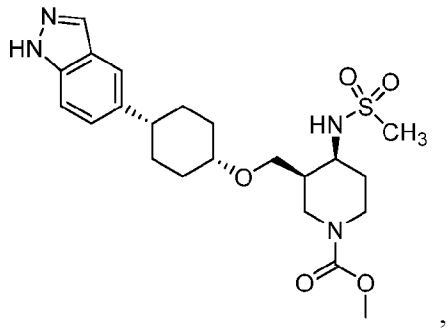
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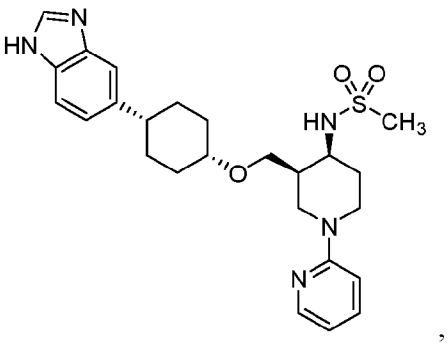
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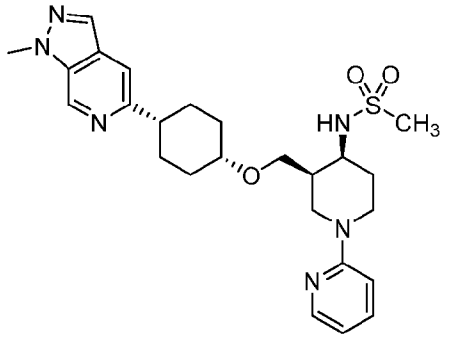
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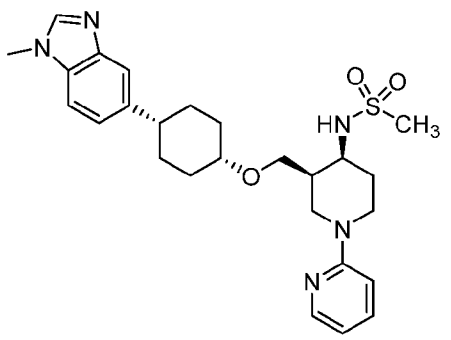
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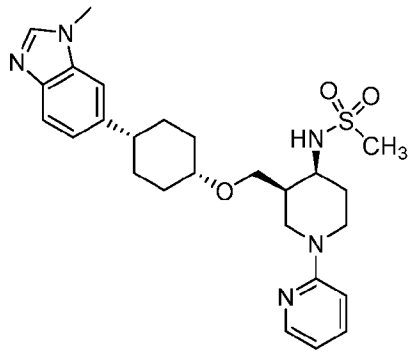
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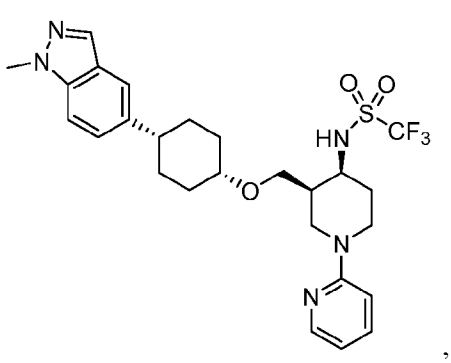
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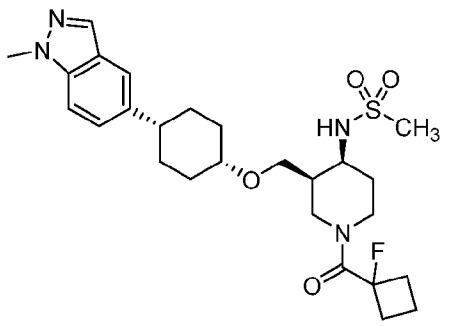
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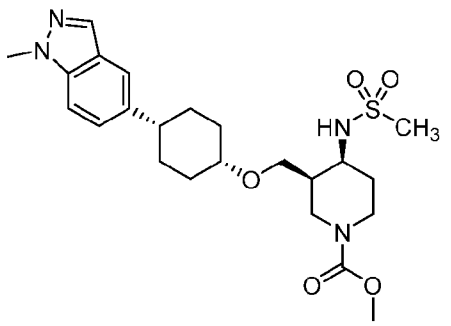
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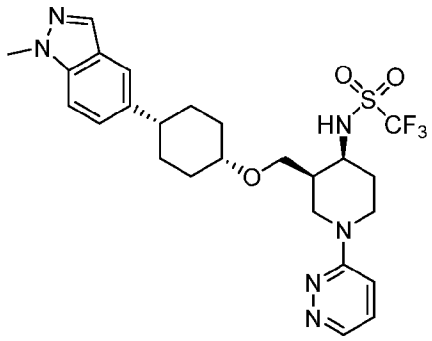
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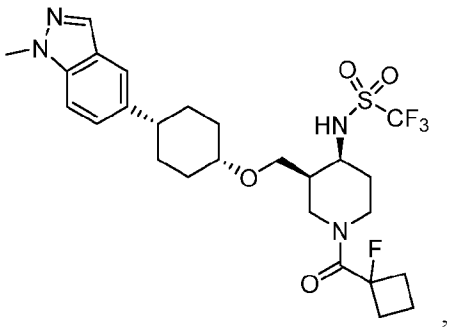
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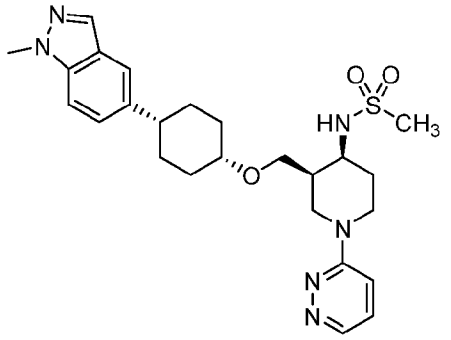
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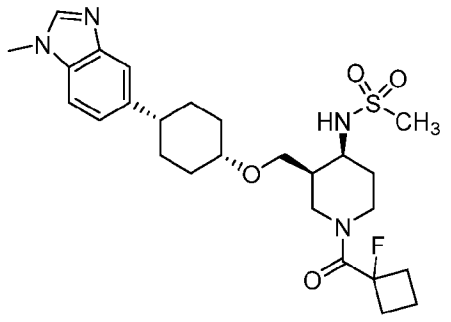
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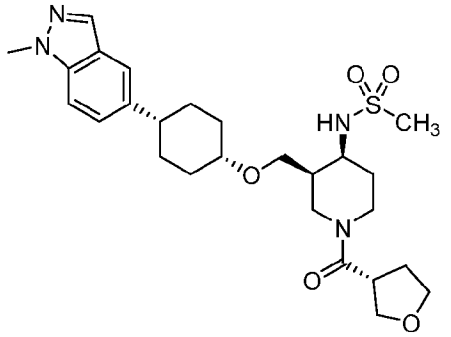
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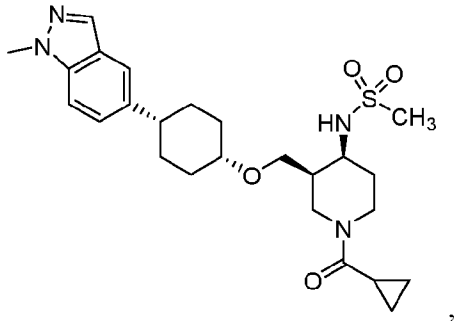
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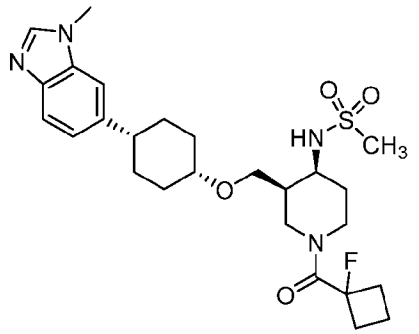
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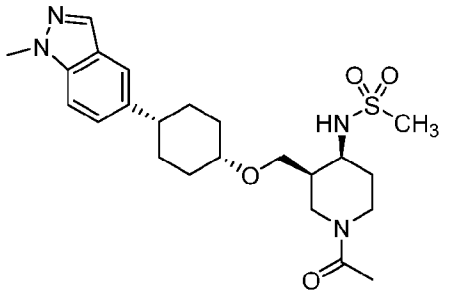
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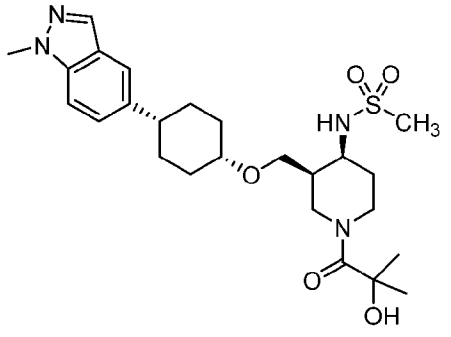
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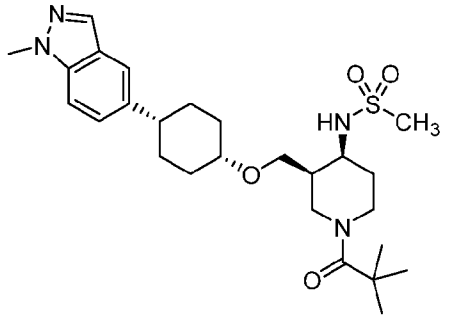
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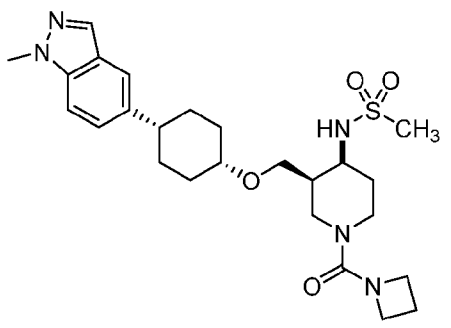
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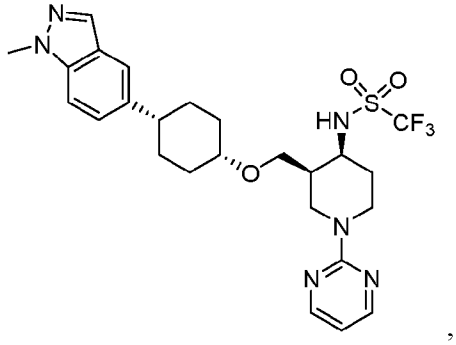
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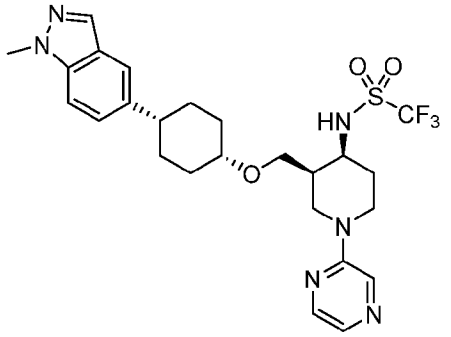
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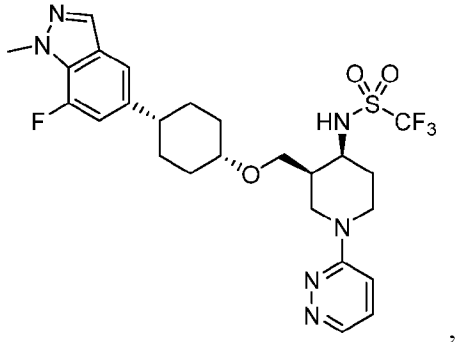
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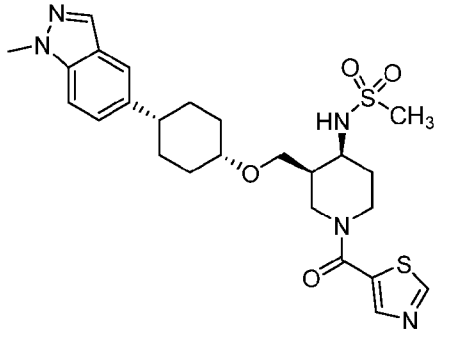
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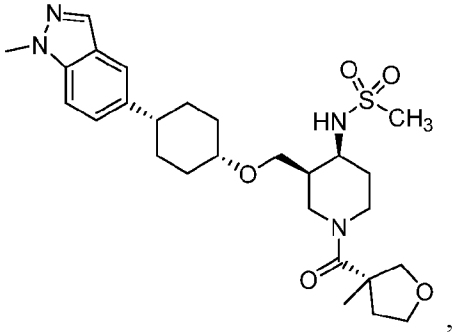
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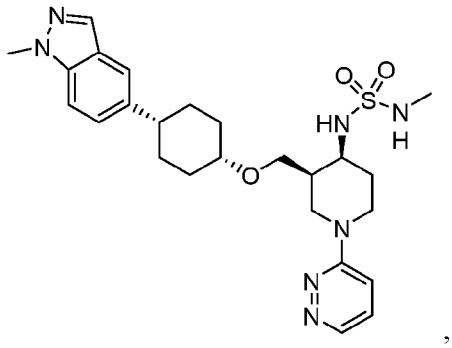
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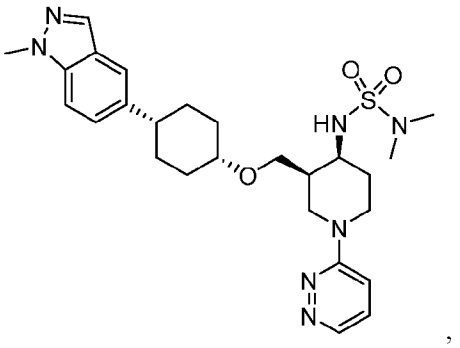
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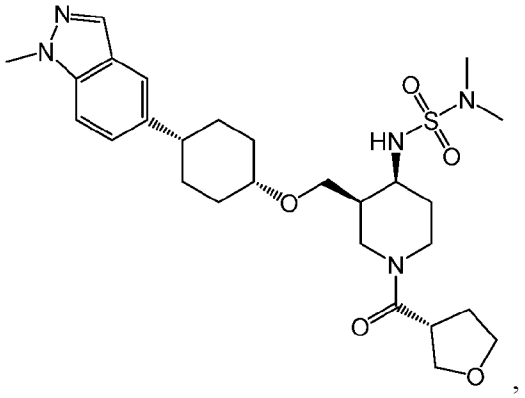
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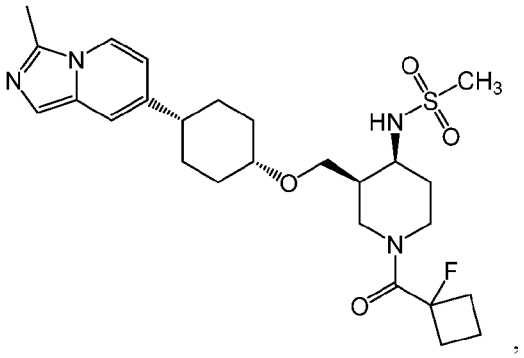
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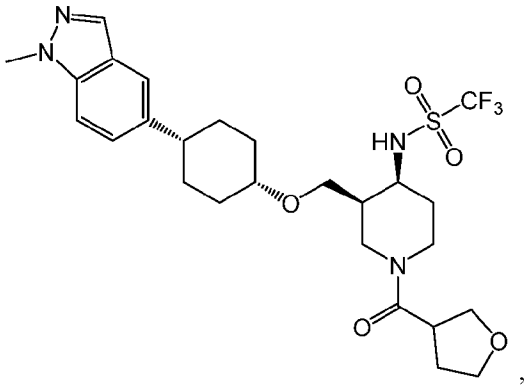
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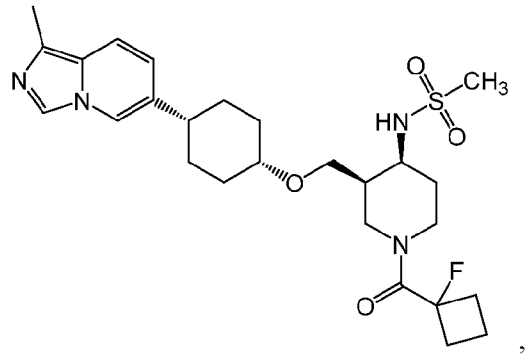
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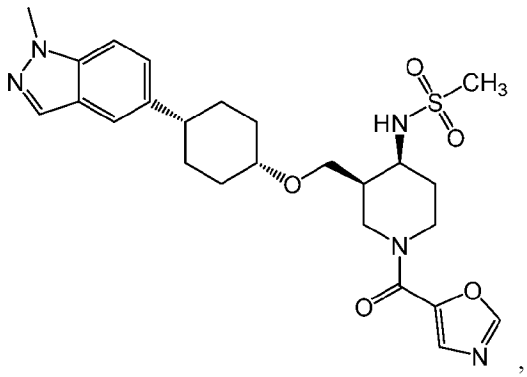
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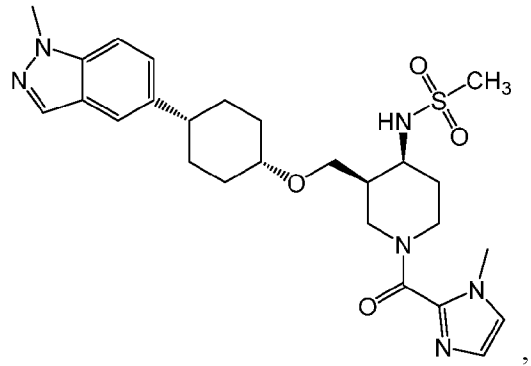
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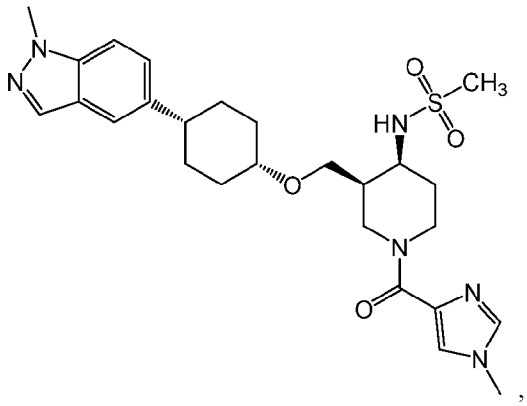
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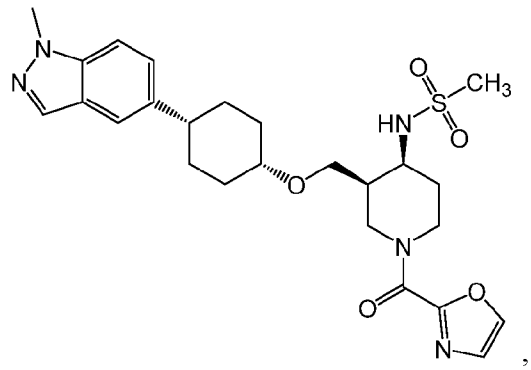
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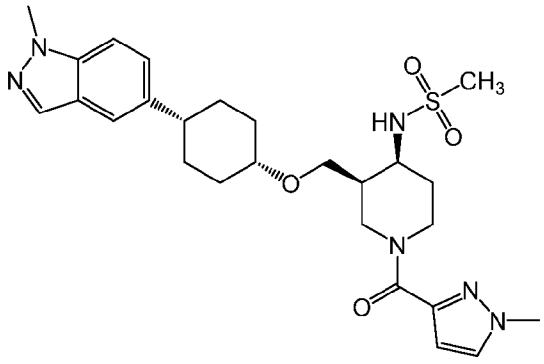
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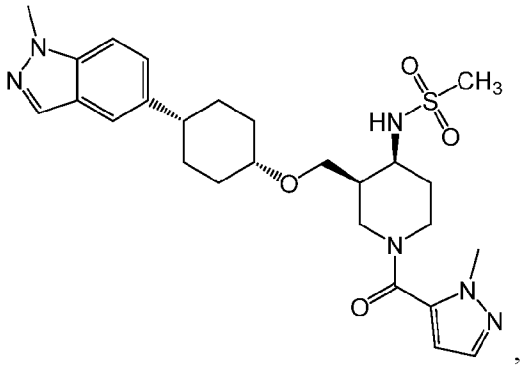
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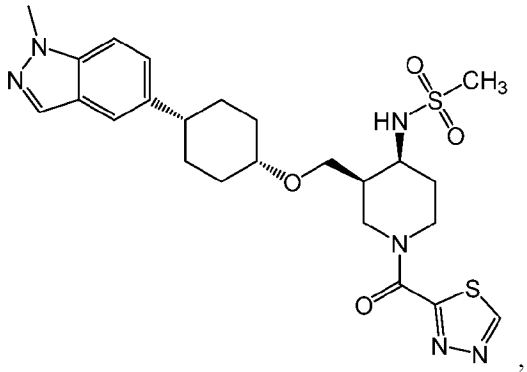
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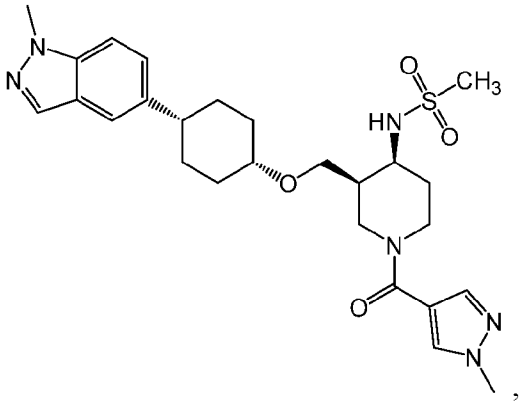
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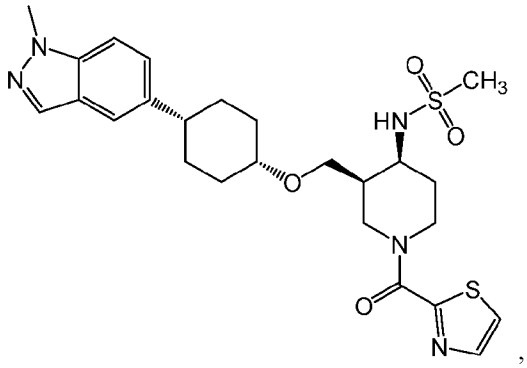
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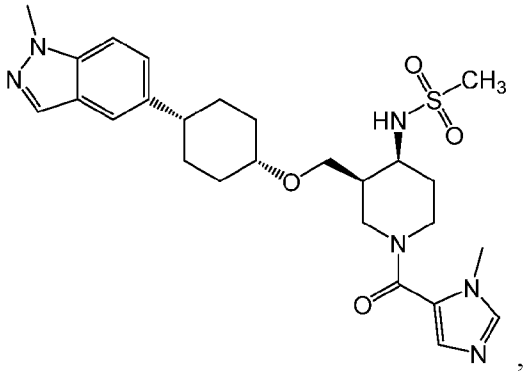
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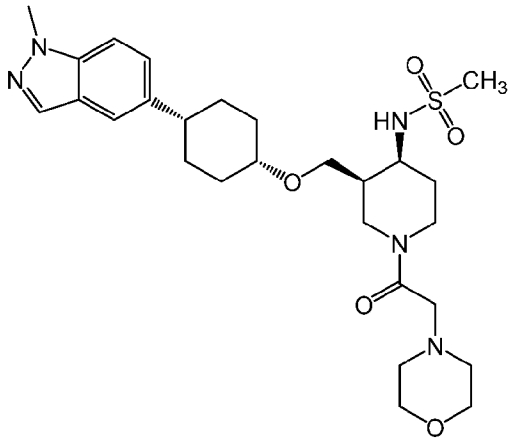
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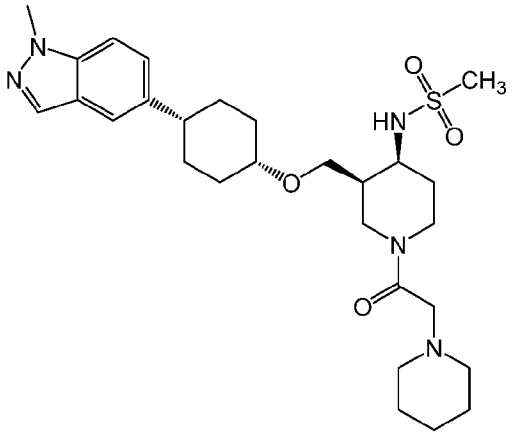
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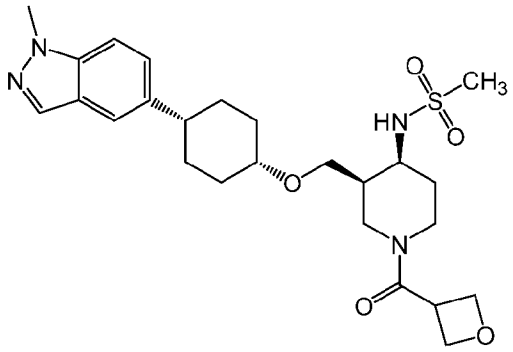
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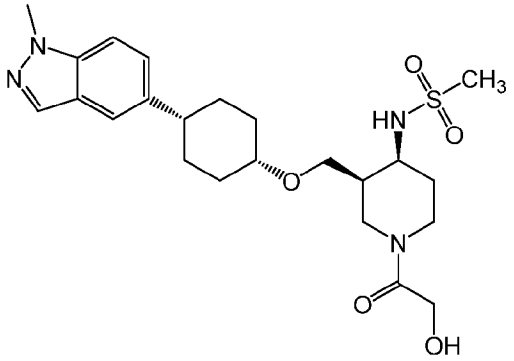
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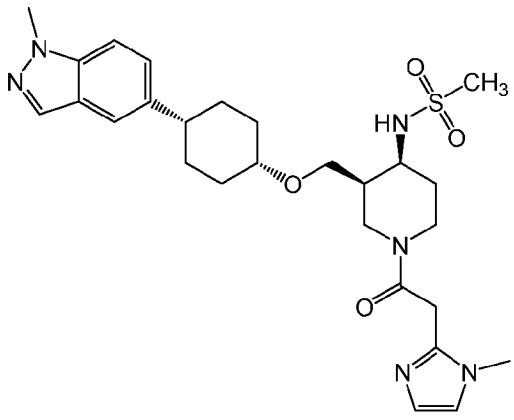
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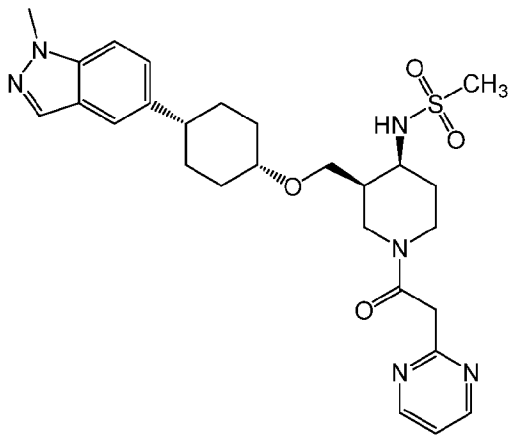
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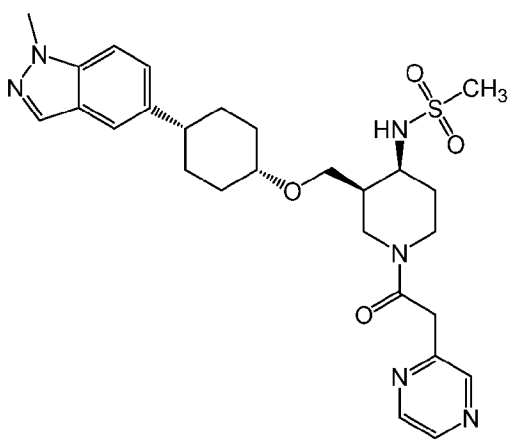
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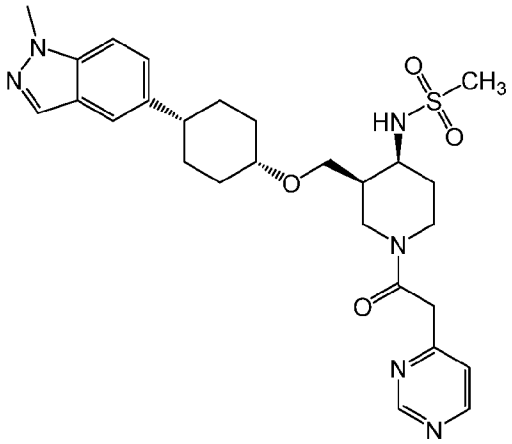
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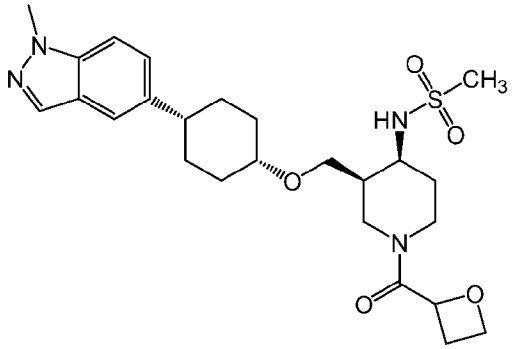
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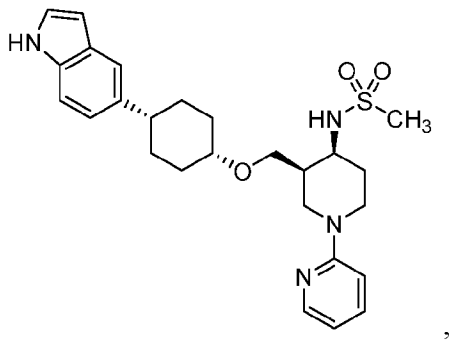
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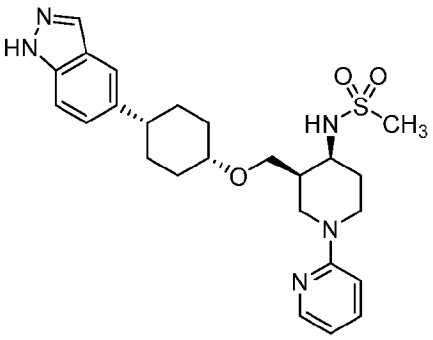
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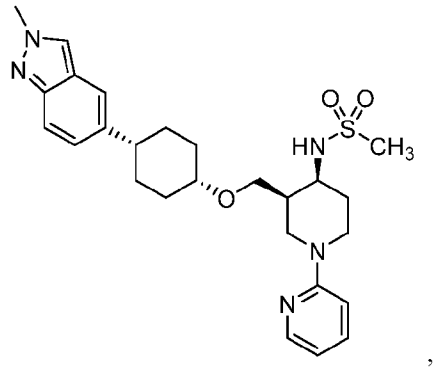
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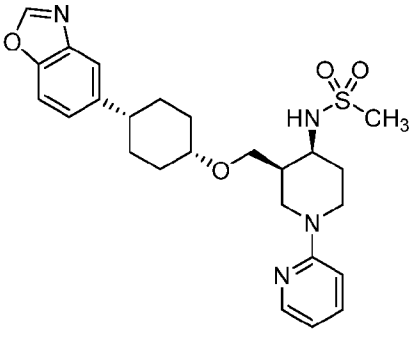
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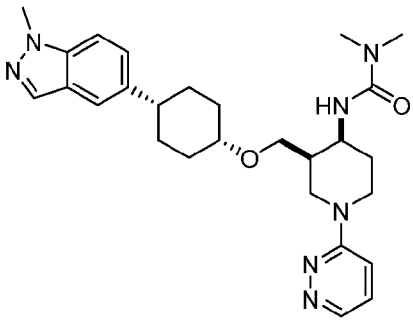

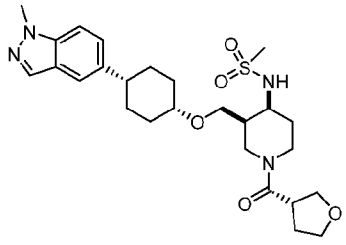
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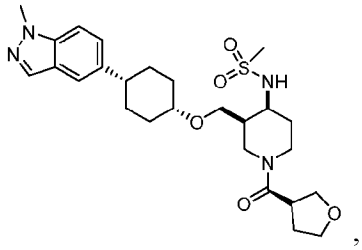
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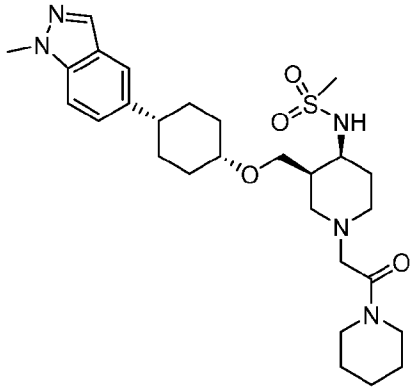
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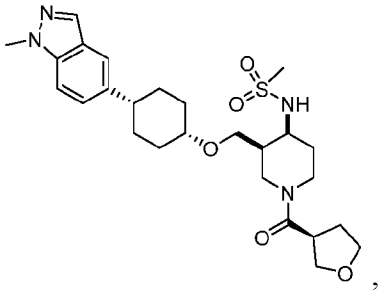
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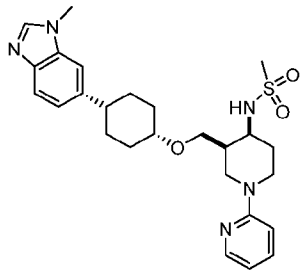
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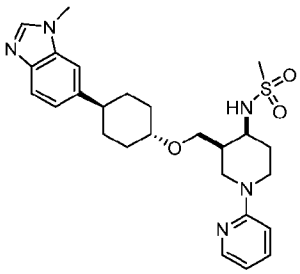
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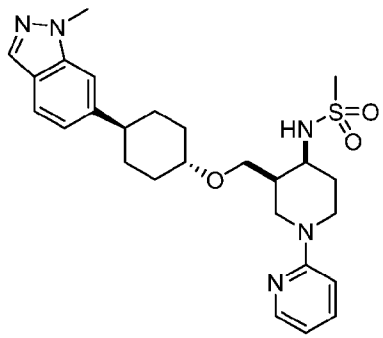
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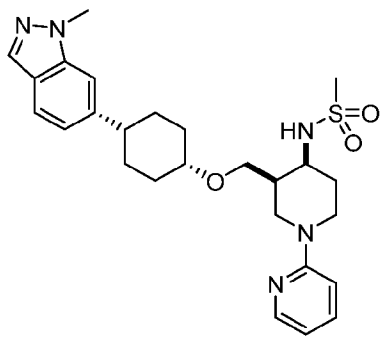
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246. A pharmaceutical composition comprising a compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

247. A method of treating narcolepsy in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, or a composition according to claim 246.

248. A method of treating cataplexy in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, or a composition according to claim 246.

249. Use of a compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, or a composition according to claim 246 for the manufacture of a medicament for narcolepsy.

250. Use of a compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, or a composition according to claim 246 for the manufacture of a medicament for cataplexy.

251. A compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, or a composition according to claim 246 for use in a method of treating narcolepsy in a subject in need thereof.

252. A compound of any one of claims 1-245 or a pharmaceutically acceptable salt thereof, or a composition according to claim 246 for use in a method of treating cataplexy in a subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/25385

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/445; A61K 31/4035; A61K 31/404; C07D 211/06; C07D 263/54 (2023.01)
ADD.

CPC - INV. A61K 31/445; A61K 31/4035; A61K 31/404; C07D 211/06; C07D 263/54
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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/135306 A1 (TAKEDA PHARMACEUTICAL COMPANY LIMITED) 10 August 2017; abstract; paragraphs [0190], [0231]	1-70, 245
A	US 2014/0024650 A1 (FUKUMOTO, S et al.) 23 January 2014; abstract; paragraphs [0047], [0052], [1983]; claim 4	1-70, 245
A	WO 2020/167701 A1 (MERCK SHARP AND DOHME CORP) 20 August 2020; page 7, lines 1-5; page 8, lines 5-15	1-70, 245
A	US 2009/0054489 A1 (HAUSKE, JR) 26 February 2009; abstract; figure 1	1-70, 245

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 2023 (19.08.2023)	SEP 13 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/25385

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 71-244, 246-252
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.