SOMATOSTATIN MODULATORS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/472,480 filed on March 16, 2017, which is incoporated herein by reference in its entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made partially with the support of the United States government under SBIR 1R44NS092231-01 by the National Institutes of Health.

FIELD OF THE INVENTION

[0003] Described herein are compounds that are somatostatin modulators, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds in the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

BACKGROUND OF THE INVENTION

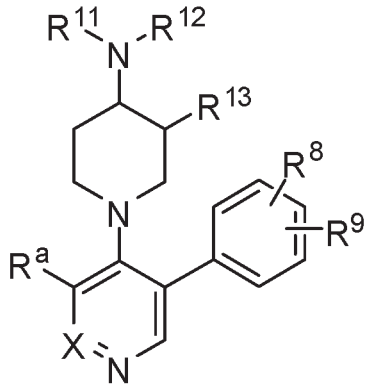
[0004] Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Six subtype somatostatin receptor proteins have been identified (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4, SSTR5) and are encoded by five different somatostatin receptor genes. Modulation of a particular subtype somatostatin receptor or combination thereof, is attractive for the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

SUMMARY OF THE INVENTION

[0005] Compounds described herein are somatostatin modulator compounds. In some embodiments, compounds described herein modulate one or more of the subtype somatostatin receptor proteins. In some embodiments, compounds described herein modulate one subtype somatostatin receptor. In some embodiments, compounds described herein modulate SSTR2 somatostatin receptor. Somatostatin peptide analogs, such as octreotide and pasireotide, formulated as depot injections, are routinely used to normalize hormone levels for the treatment of Growth Hormone (GH) secreting adenomas, pancreatic neuroendocrine tumors, and carcinoid tumors. Unfortunately, these analogs are only effective in about half of acromegalic patients with GH adenomas, and patients with carcinoid tumors frequently

become resistant to therapy due to internalization and desensitization of the SST2a receptor. In addition, these peptide drugs are extremely expensive and require frequent doctor's office visits for painful injections that can lead to injection site reactions. Compounds described herein are molecules that are structurally different from peptide analogs. The compounds described herein are somatostatin modulators that are potent inhibitors of hormone secretion.

[0006] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (I)

wherein:

X is C-R^1 or N;

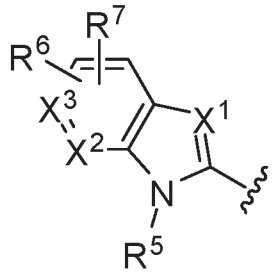
R^1 is -NR^2R^3, -OR^2, or R^4;

R^2 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

R^3 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring;

R^4 is F, Cl, Br, -CN, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4alkoxy, -SC_1-C_4alkyl, -S(=O)C_1-C_4alkyl , -$S(=O)_2$-C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, -CO_2R^{15}, -C(=O)$N(R^{15})_2$;

R^a is  or R^b-O-N=CH-;

R^b is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle,

R^5 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

each R^6 and R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, substituted or unsubstituted monocyclic heterocycle, -CN, $-OR^{15}$, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-C(=O)N(R^{15})OR^{15}$, $-N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-NR^{15}C(=O)OR^{15}$, $-OC(=O)N(R^{15})_2$, $-NR^{15}C(=O)N(R^{15})_2$, $-NR^{15}C(=O)NR^{15}OR^{15}$, $-C(R^{15})=N-OR^{15}$, $-SR^{15}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$;

or R^6 and an adjacent R^7 are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 5-membered or 6-membered ring;

R^8 and R^9 are independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, substituted or unsubstituted monocyclic heterocycle, -CN, $-OR^{15}$, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-C(=O)N(R^{15})OR^{15}$, $-N(R^{15})_2$, $-CH_2N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-NR^{15}C(=O)OR^{15}$, $-OC(=O)N(R^{15})_2$, $-NR^{15}C(=O)N(R^{15})_2$, $-NR^{15}C(=O)NR^{15}OR^{15}$, $-C(R^{15})=N-OR^{15}$, $-SR^{15}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$;

X^1 is N or C-R^{10};

R^{10} is hydrogen, F, Cl, Br, -CN, $-N(R^{15})_2$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4alkoxy, substituted or unsubstituted C_1-

C_4fluoroalkyl, substituted or unsubstituted C_1-C_4fluoroalkoxy, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted C_3-C_6cycloalkyl;

X^2 is C-R^7 or N;

X^3 is C-R^7 or N;

R^{11} and R^{12} are independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted N-containing heterocyclic ring;

R^{13} is hydrogen, -OR^{15}, -$N(R^{15})_2$, -CN, -CO_2R^{14}, -$C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6 alkyl, and substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle;

or R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted N-containing heterocyclic ring;

each R^{14} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^{15} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

or two R^{15} on the same N atom are taken together with the N atom to which they are attached to form an substituted or unsubstituted N-containing heterocycle.

[0007] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0008] Also described herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical

composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some embodiments, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some embodiments, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion. In some embodiments, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

[0009] Also described herein is a method of treating a disease or condition in a mammal that would benefit from the modulation of somatostatin receptor activity comprising administering a small molecule non-peptidyl compound, or pharmaceutically acceptable salt, or solvate thereof, to the mammal in need thereof. In some embodiments, the small molecule non-peptidyl compound is orally administered. In some embodiments, the small molecule non-peptidyl compound is a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof. . In some embodiments, the small molecule non-peptidyl compound is a SSTR2 modulator as described herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the disease or condition is acromegaly, a neuroendocrine tumor, an ophthalmic disease or condition, neuropathy, nephropathy, a respiratory disease or condition, cancer, pain, a neurodegenerative disease or condition, an inflammatory disease or condition, a psychiatric disease or condition, or combinations thereof.

[0010] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by inhalation; and/or (e) administered by nasal administration; or and/or (f) administered by injection to the mammal; and/or (g) administered topically to the mammal; and/or (h) administered by ophthalmic administration; and/or (i) administered rectally to the mammal; and/or (j) adminstered non-systemically or locally to the mammal.

[0011] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which the compound is administered once a day to the mammal or the compound is administered to the mammal multiple times over the span of one day. In some embodiments, the compound is administered on a continuous dosing schedule. In some embodiments, the compound is administered on a continuous daily dosing schedule.

[0012] In any of the embodiments disclosed herein, the mammal is a human.

[0013] In some embodiments, compounds provided herein are orally administered to a human.

[0014] Articles of manufacture, which include packaging material, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, tautomers, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for modulating one or more subtype somatostatin receptor proteins, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from modulating one or more subtype somatostatin receptor proteins, are provided.

[0015] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0016] Somatostatin (SST), also known as somatotropin release inhibiting factor (SRIF) was initially isolated as a 14-amino acid peptide from ovine hypothalamii (Brazeau *et al.*, *Science* 179, 77-79, 1973). An *N*-terminal extended 28-amino acid peptide with similar biological activity to 14-amino acid somatostatin was subsequently isolated (Pradayrol *et, al.*, *FEBS Letters*, 109, 55-58, 1980; Esch *et al.*, *Proc. Natl. Acad. Sci. U S A*, 77, 6827–6831, 1980). SST is a regulatory peptide produced by several cell types in response to other neuropeptides, neurotransmitters, hormones, cytokines, and growth factors. SST acts through both endocrine and paracrine pathways to affect its target cells. Many of these effects are related to the inhibition of secretion of other hormones, most notably growth hormone (GH). They are produced by a wide variety of cell types in the central nervous sstem (CNS) and gut and have multiple functions including modulation of secretion of growth hormone (GH), insulin, glucagon, as well as many other hormones that are anti-proliferative.

[0017] These pleotropic actions of somatostatins are mediated by six somatostatin receptor proteins (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4, SSTR5). The six somatostatin receptor

proteins are encoded by five different somatostatin receptor genes (Reisine and Bell, *Endocr Rev*. 16, 427-442, 1995; Patel and Srikant, *Trends Endocrinol Metab* 8, 398-405, 1997). All the receptors are members of the class-A subgroup of the GPCR superfamily. SST2a receptor is the most widely expressed subtype in human tumors and is the dominant receptor by which GH secretion is suppressed. Unless otherwise stated, the term SSTR2 means SSTR2a. .

[0018] It is possible to selectively modulate any one of the somatostatin receptor subtypes, or combination thereof. In some embodiments, selectively modulating any one of the somatostatin receptor subtypes relative to the other somatostatin receptor subtypes reduces unwanted side effects in a variety of clinical applications.

[0019] For example, selective modulation of SSTR2 activity mediates the inhibition of growth hormone (GH) release from the anterior pituitary and glucagon release from pancreas. SSTR2 is also implicated in many other biological functions such as, but not limited to, cell proliferation, nociception, inflammation, and angiogenesis. In some embodiments, a selective SSTR2 modulator is used in the treatment of acromegaly, neuroendocrine tumors, pain, neuropathies, nephropathies, and inflammation, as well as retinopathies resulting from aberrant blood vessel growth. In some other embodiments, a selective SSTR2 modulator is used in the treatment of arthritis, pain, cancer, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, Cushing's disease, acute lung injury, acute respiratory distress syndrome, and ophthalmic disorders such as age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema, and Graves ophthalmology, among others.

[0020] In one aspect, compounds described herein are modulators of SSTR2. In some embodiments, compounds described herein selectively modulate the activity of SSTR2 relatve to the other somatostatin receptors.

[0021] In some embodiments, compounds described here are amenable to oral administration to a mammal in need of treatment with a somatostatin modulator.

[0022] In some embodiments, somatostatin receptor modulators described herein have utility over a wide range of therapeutic applications. In some embodiments, somatostatin receptor modulators described herein are used in the treatment of a variety of diseases or conditions such as, but not limited to acromegaly, neuroendocrine tumors, retinopathies and other ophthalmic disorders, neuropathy, nephropathy, respiratory diseases, cancers, pain, neurodegenerative diseases, inflammatory diseases, as well as psychiatric and neurodegenerative disorders. In some embodiments, somatostatin receptor modulators described herein are used in the treatment of acromegaly in a mammal.

[0023] In some embodiments, somatostatin receptor modulators described herein inhibit the secretion of various hormones and trophic factors in mammals. In some embodiments, the compounds are used to suppress certain endocrine secretions, such as, but not limited to GH, insulin, glucagon and prolactin. The suppression of certain endocrine secretions is useful in the treatment of disorders such as acromegaly; endocrine tumors such as carcinoids, VIPomas, insulinomas and glucagonomas; or diabetes and diabetes-related pathologies, including retinopathy, neuropathy and nephropathy. In some embodiments, somatostatin receptor modulators described herein are used to suppress exocrine secretions in the pancreas, stomach and intestines, for the treatment of disorders such as pancreatitis, fistulas, bleeding ulcers and diarrhea associated with such diseases as AIDS or cholera. Disorders involving autocrine or paracrine secretions of trophic factors such as IGF-1 (as well as some endocrine factors) which may be treated by administration of the compounds described herein include cancers of the breast, prostate, and lung (both small cell and non-small cell epidermoids), as well as hepatomas, neuroblastomas, colon and pancreatic adenocarcinomas (ductal type), chondrosarcomas, and melanomas, diabetic retinopathy, and atherosclerosis associated with vascular grafts and restenosis following angioplasty.

[0024] In some embodiments, somatostatin receptor modulators described herein are used to suppress the mediators of neurogenic inflammation (e.g. substance P or the tachykinins), and may be used in the treatment of rheumatoid arthritis; psoriasis; topical inflammation such as is associated with sunburn, eczema, or other sources of itching; inflammatory bowel disease; irritable bowel syndrome; allergies, including asthma and other respiratory diseases In some other embodiments, the somatostatin receptor modulators described herein function as neuromodulators in the central nervous system and are useful in the treatment of Alzheimer's disease and other forms of dementia, pain, and headaches. In some embodiments, somatostatin receptor modulators described herein provide cytoprotection in disorders involving the splanchnic blood flow, including cirrhosis and oesophagal varices.

Compounds

[0025] Compounds of Formula (I), including pharmaceutically acceptable salts, prodrugs, active metabolites and pharmaceutically acceptable solvates thereof, are somatostatin receptor modulators. In some embodiments, the compounds of Formula (I), including pharmaceutically acceptable salts, prodrugs, active metabolites and pharmaceutically acceptable solvates thereof, are SSTR2 modulators. In some embodiments, the somatostatin receptor modulators are somatostatin receptor agonists.

[0026] In some embodiments, compounds described herein are at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 15 times, at least 20 times, at least 30 times, at least 40 times, at least 50 times, at least 100 times, at least 200 times, at least 300 times, or greater than 400 times more selective at modulating SSTR2 activity than SSTR4 receptor activity. In some embodiments, the R^1 group of the compounds described herein confers selectivity for modulating SSTR2 activity.

[0027] In some embodiments, it is desirable that SSTR2 modulators have reduced liability associated with CYP2D6 and/or hERG inhibitions. In some embodiments, compounds described herein reduced liability associated with CYP2D6 and/or hERG inhibitions. In some embodiments, compounds described herein reduced liability associated with CYP2D6 and hERG inhibitions. In some embodiments, the R^1 group of the compounds described herein reduced liability associated with CYP2D6 and/or hERG inhibitions.

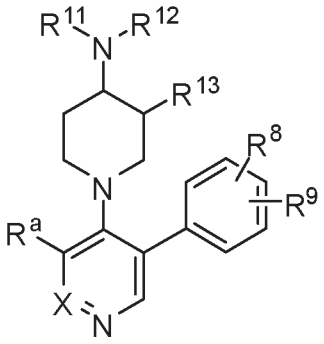
[0028] The CYP2D6 gene encodes an enzyme that is primarily expressed in the liver. CYP2D6 is a member of the cytochrome P450 family, and is one of the more important enzymes involved in the metabolism of xenobiotics in humans. Drugs may function as inhibitors of CYP2D6 activity or inducers of CYP2D6 enzyme expression which will lead to decreased or increased CYP2D6 activity, respectively. If such a drug is taken at the same time as a second drug that is metabolized by CYP2D6, the first drug may affect the elimination rate of the second through what is known as a drug-drug interaction. As such, the monitoring of and mininmizing of CYP2D6 inhibition during drug discovery and development has become an imporant selectivity assay in evaluating compounds that could move onto clinical development (Wolf & Smith, IARC Sci Publ 1999, 148, 209-229).

[0029] The hERG (the human Ether-à-go-go-Related Gene) gene encodes the alpha subunit of the $K_v11.1$ potassium ion channel. When this channel's capacity to conduct electrical current across the cell membrane is inhibited or compromised, either by drugs or mutation, it can result in a potentially fatal disorder called long QT syndrome. As such, the monitoring of and mininmizing of hERG inhibition during drug discovery and development has become an imporant selectivity assay in evaluating compounds that could move onto clinical development (Abbott et al., Cell 1999, 97, 175-187; Sanguinetti & Tristani-Firouzi, Nature 2006, 440, 463-9).

[0030] In some embodiments, the X group of compounds of Formula (I) improves properties of the compounds as compared to analogous compounds where X is CH. For example, as discussed herein, in some instances the X group of compounds of Formula (I)

confers selectivity for modulating SSTR2 activity, and/or reduces liability associated with CYP2D6 and/or hERG inhibitions. In some embodiments, when X is C-NR^2R^3 then water solubility at pH 7.4 buffer increases as compared to when X is CH.

[0031] In one aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, individual enantiomers or prodrug thereof:



Formula (I)

wherein:

X is C-R^1 or N;

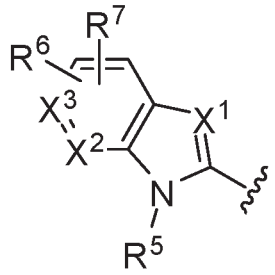
R^1 is -NR^2R^3, -OR^2, or R^4;

R^2 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

R^3 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring;

R^4 is F, Cl, Br, -CN, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4alkoxy, -SC_1-C_4alkyl, -S(=O)C_1-C_4alkyl , -$S(=O)_2$-C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, -CO_2R^{15}, -C(=O)$N(R^{15})_2$;



R^a is or R^b-O-N=CH-;

R^b is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle,

R^5 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

each R^6 and R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, substituted or unsubstituted monocyclic heterocycle, -CN, $-OR^{15}$, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-C(=O)N(R^{15})OR^{15}$, $-N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-NR^{15}C(=O)OR^{15}$, $-OC(=O)N(R^{15})_2$, $-NR^{15}C(=O)N(R^{15})_2$, $-NR^{15}C(=O)NR^{15}OR^{15}$, $-C(R^{15})=N-OR^{15}$, $-SR^{15}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$;

or R^6 and an adjacent R^7 are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 5-membered or 6-membered ring;

R^8 and R^9 are independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, substituted or unsubstituted monocyclic heterocycle, -CN, $-OR^{15}$, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-C(=O)N(R^{15})OR^{15}$, $-N(R^{15})_2$, $-CH_2N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-NR^{15}C(=O)OR^{15}$, $-OC(=O)N(R^{15})_2$, $-NR^{15}C(=O)N(R^{15})_2$, $-NR^{15}C(=O)NR^{15}OR^{15}$, $-C(R^{15})=N-OR^{15}$, $-SR^{15}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$;

X^1 is N or C-R^{10};

R^{10} is hydrogen, F, Cl, Br, -CN, $-N(R^{15})_2$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4alkoxy, substituted or unsubstituted C_1-

C_4fluoroalkyl, substituted or unsubstituted C_1-C_4fluoroalkoxy, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted C_3-C_6cycloalkyl;

X^2 is C-R^7 or N;

X^3 is C-R^7 or N;

R^{11} and R^{12} are independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted N-containing heterocyclic ring;

R^{13} is hydrogen, -OR^{15}, -$N(R^{15})_2$, -CN, -CO_2R^{14}, -$C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6 alkyl, and substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle;

or R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted N-containing heterocyclic ring;

each R^{14} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

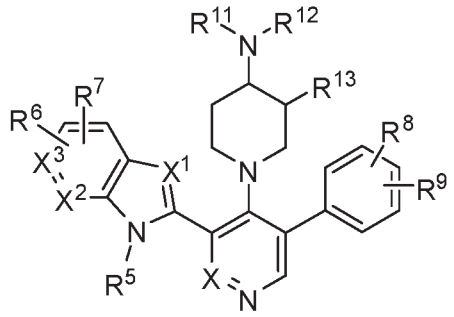
each R^{15} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

or two R^{15} on the same N atom are taken together with the N atom to which they are attached to form an substituted or unsubstituted N-containing heterocycle.

[0032] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments X is C-R^1 or N. In other embodiments, X is C-R^1. In some embodiments, X is N.

[0033] In some embodiments, R^1 is -NR^2R^3, -OR^2, or R^4. In some embodiments, R^1 is -NR^2R^3. In some embodiments, R^1 is -OR^2. In some embodiments, R^1 is R^4.

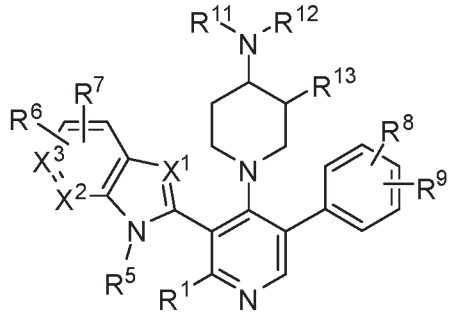
[0034] In some embodiments, the compound of Formula (I) has the structure of Formula (II), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (II).

[0035] In some embodiments, X is C-R^1.

[0036] In some embodiments, the compound of Formula (I) has the structure of Formula (III), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (III)

[0037] In some embodiments, R^1 is -NR^2R^3. In some embodiments, R^1 is -NHR^2. In some embodiments, R^1 is –NH_2.

[0038] In some embodiments, R^2 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl; R^3 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl; or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring. In some embodiments, R^2 is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, or -CH_2CN; R^3 is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -CH_2CN, or -CH_2CF_3; or R^2 and R^3 are taken together with the N atom to

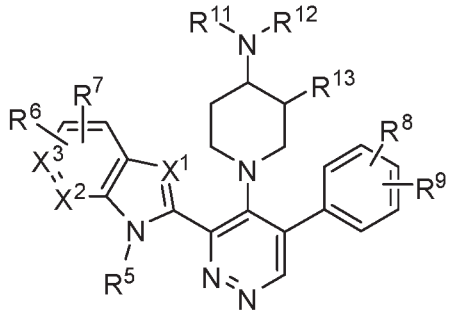
which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, or substituted or unsubstituted piperazinyl. In some embodiments, R^2 is hydrogen, or C_1-C_4alkyl; R^3 is hydrogen, or C_1-C_4alkyl. In some embodiments, R^3 is hydrogen.

[0039] In some embodiments, R^1 is $-OR^2$. In some embodiments, R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

[0040] In some embodiments, R^1 is R^4; R^4 is F, Cl, Br, -CN, C_1-C_4alkyl, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl , $-S(=O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, $-CO_2C_1$-C_4alkyl, or $-C(=O)N(R^{15})_2$. In some embodiments, R^4 is F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

[0041] In some embodiments, R^1 is $-NR^2R^3$, $-OR^2$, F, Cl, Br, -CN, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

[0042] In some embodiments, the compound of Formula (I) has the structure of Formula (IV), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (IV).

[0043] In some embodiments, R^{11} hydrogen; R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom; or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted *N*-containing heterocycloalkyl; R^{13} is hydrogen, $-OR^{15}$, $-N(R^{15})_2$, -CN, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl; or

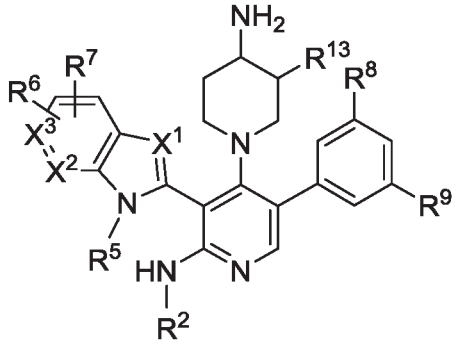
R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 4- to 7-membered saturated *N*-containing heterocyclic ring. In some embodiments, R^{11} hydrogen; R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom; or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted *N*-containing heterocycloalkyl; R^{13} is hydrogen.

[0044] In some embodiments, R^{11} hydrogen; R^{12} is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, cyclopropyl, $CH_2CH_2CH_2OCH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl; or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl; R^{13} is hydrogen, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -CN, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$; or R^{12} and R^{13} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted monocyclic 4- to 7-membered heterocyclic ring selected from substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl. In some embodiments, R^{11} hydrogen; R^{12} is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, cyclopropyl, $CH_2CH_2CH_2OCH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl; or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl; R^{13} is hydrogen.

[0045] In some embodiments, R^{11} hydrogen; R^{12} is hydrogen or -CH_3. In some embodiments, R^{11} hydrogen; R^{12} is hydrogen.

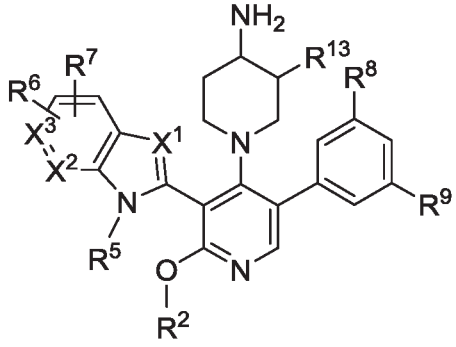
[0046] In some embodiements, R^{13} is hydrogen, -OH, -OCH_3 , -OCH_2CH_3, -OCF_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CN, -C(=O)OCH_3, -C(=O)NH_2, -C(=O)$NHCH_3$, -C(=O)$N(CH_3)_2$, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, or -CF_3. In some embodiments, R^{13} is hydrogen.

[0047] In some embodiments, the compound of Formula (I) has the structure of Formula (V), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (V)

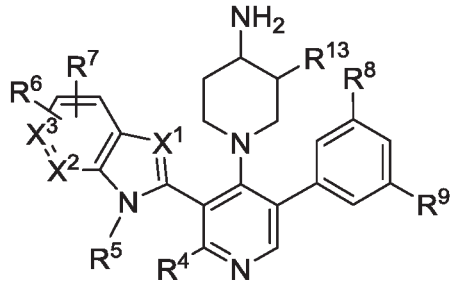
[0048] In some embodiments, the compound of Formula (I) has the structure of Formula (VI), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (VI)

[0049] In some embodiments, R^2 is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -CH_2CN, or-CH_2CF_3.

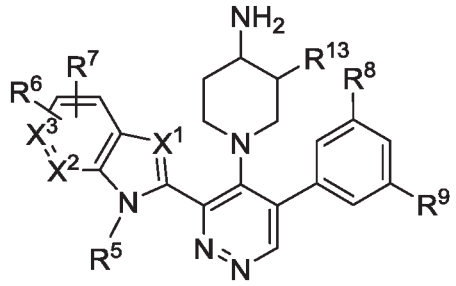
[0050] In some embodiments, the compound of Formula (I) has the structure of Formula (VII), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (VII)

[0051] In some embodiments, R^4 is F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-S(=O)_2CH_3$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, or $-C(=O)N(CH_3)_2$.

[0052] In some embodiments, the compound of Formula (I) has the structure of Formula (VIII), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (VIII)

[0053] In some embodiments, R^5 is hydrogen, or C_1-C_4alkyl; X^1 is N or C-R^{10}; R^{10} is hydrogen, F, Cl, Br, -CN, $-N(R^{15})_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy.

[0054] In some embodiments, R^{10} is hydrogen, F, Cl, Br, -CN, $-N(R^{15})_2$, or C_1-C_4alkyl.

[0055] In some embodiments, R^5 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, or $-CH_2CF_3$. In some embodiments, R^5 is hydrogen, $-CH_3$, or $-CH_2CH_3$. In some embodiments, R^5 is hydrogen.

[0056] In some embodiments, X^1 is N.

[0057] In some embodiments, X^1 is C-R^{10}; R^{10} is hydrogen, F, Cl, Br, -CN, $-CH_3$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, or $-C(CH_3)_3$.

[0058] In some embodiments, X^2 is C-R^7; and X^3 is C-R^7. In some embodiments, X^2 is C-H; and X^3 is C-R^7. In some embodiments, X^2 is C-R^7; and X^3 is C-H. In some embodiments, X^2 is C-H; and X^3 is C-H.

[0059] In some embodiments, X^2 is N; and X^3 is C-R^7. In some embodiments, X^2 is N; and X^3 is C-H.

[0060] In some embodiments, X^2 is C-R^7; and X^3 is N. In some embodiments, X^2 is C-H; and X^3 is N.

[0061] In some embodiments, each R^6 and R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, substituted or unsubstituted monocyclic C_1-C_5heteroaryl, -CN, -OR^{15}, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, -$C(=O)N(R^{15})OR^{15}$, -$N(R^{15})_2$, -$NR^{15}C(=O)R^{15}$, -$NR^{15}C(=O)OR^{15}$, -$OC(=O)N(R^{15})_2$, -$NR^{15}C(=O)N(R^{15})_2$, -$NR^{15}C(=O)NR^{15}OR^{15}$, -$C(R^{15})$=N-$OR^{15}$, -$SR^{15}$, -$S(=O)R^{14}$, -$SO_2R^{14}$, or -$SO_2N(R^{15})_2$.

[0062] In some embodiments, R^6 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, substituted or unsubstituted monocyclic C_1-C_5heteroaryl, -CN, -OR^{15}, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, -$C(=O)N(R^{15})OR^{15}$, -$N(R^{15})_2$, -$NR^{15}C(=O)R^{15}$, -$NR^{15}C(=O)OR^{15}$, -$OC(=O)N(R^{15})_2$, -$NR^{15}C(=O)N(R^{15})_2$, -$NR^{15}C(=O)NR^{15}OR^{15}$, -$C(R^{15})$=N-$OR^{15}$, -$SR^{15}$, -$S(=O)R^{14}$, -$SO_2R^{14}$, or -$SO_2N(R^{15})_2$; each R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -O-(substituted or unsubstituted C_1-C_4alkyl), or -O-(substituted or unsubstituted C_1-C_4fluoroalkyl).

[0063] In some embodiments, R^6 is hydrogen, F, Cl, Br, -CH_3, -CH_2CH_3, -CH_2OH, -CH_2CH_2OH, -CH_2CN, -CH_2CO_2H, -$CH_2CO_2CH_3$, -$CH_2CO_2CH_2CH_3$, -$CH_2C(=O)NH_2$, -$CH_2C(=O)NHCH_3$, -$CH_2C(=O)N(CH_3)_2$, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CH_2F, -CHF_2, -CF_3, -$CH=CH_2$, -C≡CH, -CN, -OH, -OCH_3, -OCH_2CH_3, -OCF_3, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, oxetanyloxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, azetidinyl, pyrrolidinyl, tetrazolyl, -CN, -OH, -OCH_3, -OCH_2CH_3, -OCH_2CH_2OH, -

OCH_2CN, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, or $-SO_2N(CH_3)_2$; each R^7 is independently hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, or $-OCF_3$.

[0064] In some embodiments, R^6 is hydrogen, F, Cl, $-CH_3$, $-CF_3$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCF_3$, azetidinyl, pyrrolidinyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, or $-SO_2NH_2$; each R^7 is independently hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$.

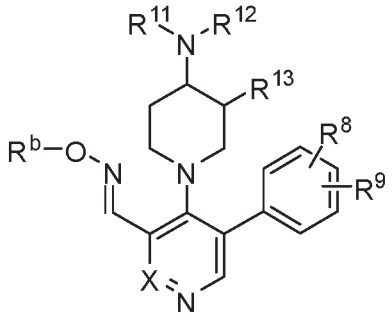
[0065] In some embodiments, R^6 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -O-(substituted or unsubstituted C_1-C_4alkyl), or -O-(substituted or unsubstituted C_1-C_4fluoroalkyl); each R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, substituted or unsubstituted monocyclic C_1-C_5heteroaryl, -CN, $-OR^{15}$, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-C(=O)N(R^{15})OR^{15}$, $-N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-NR^{15}C(=O)OR^{15}$, $-OC(=O)N(R^{15})_2$, $-NR^{15}C(=O)N(R^{15})_2$, $-NR^{15}C(=O)NR^{15}OR^{15}$, $-C(R^{15})=N-OR^{15}$, $-SR^{15}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$.

[0066] In some embodiments, R^6 is hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, or $-OCF_3$; each R^7 is independently hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH,

$-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, oxetanyloxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, azetidinyl, pyrrolidinyl, tetrazolyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, or $-SO_2N(CH_3)_2$.

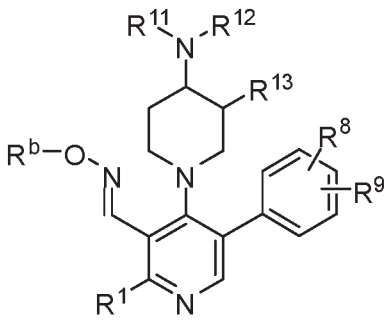
[0067] In some embodiments, R^6 is hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$; each R^7 is independently hydrogen, F, Cl, $-CH_3$, $-CF_3$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCF_3$, azetidinyl, pyrrolidinyl, tetrazolyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, or $-SO_2NH_2$.

[0068] In some embodiments, the compound of Formula (I) has the structure of Formula (IX), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (IX).

[0069] In some embodiments, the compound of Formula (I) has the structure of Formula (X), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (X)

[0070] In some embodiments, R^b is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle. In some embodiments, R^b is hydrogen or substituted or unsubstituted C_1-C_6alkyl. In some embodiments, R^b is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)(CH_2CH_3)$, or -$CH_2C(CH_3)_3$. In some embodiments, R^b is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, or -$C(CH_3)_3$.

[0071] In some embodiments, R^1 is -NR^2R^3; R^2 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl; R^3 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl; or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring.

[0072] In some embodiments, R^2 is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -CH_2CN or -CH_2CF_3; R^3 is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -CH_2CN, or -CH_2CF_3; or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, or substituted or unsubstituted piperazinyl. In some embodiments, R^2 is hydrogen, or -CH_3; R^3 is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, -CH_2CN, or -CH_2CF_3; or R^2

and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, or substituted or unsubstituted piperazinyl. In some embodiments, R^2 is hydrogen, $-CH_3$, or $-CH_2CH_3$; R^3 is hydrogen, $-CH_3$, or $-CH_2CH_3$. In some embodiments, R^3 is hydrogen. In some embodiments, R^2 is hydrogen; R^3 is hydrogen. In some embodiments, R^2 is hydrogen.

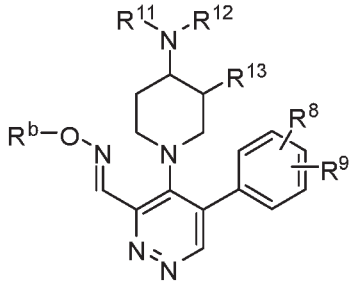
[0073] In some embodiments, R^1 is $-OR^2$; R^2 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl. In some embodiments, R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

[0074] In some embodiments, R^1 is R^4; R^4 is F, Cl, Br, -CN, C_1-C_4alkyl, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl , $-S(=O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, $-CO_2C_1$-C_4alkyl, or $-C(=O)N(R^{15})_2$.

[0075] In some embodiments, R^4 is F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-S(=O)_2CH_3$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, or $-C(=O)N(CH_3)_2$.

[0076] In some embodiments, R^1 is $-NR^2R^3$, $-OR^2$, F, Cl, Br, -CN, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

[0077] In some embodiments, the compound of Formula (I) has the structure of Formula (XI), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (XI).

[0078] In some embodiments, R^{11} hydrogen; R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom; or R^{11} and R^{12} are taken together with the nitrogen

atom to which they are attached to form a substituted or unsubstituted *N*-containing heterocycloalkyl; R^{13} is hydrogen, $-OR^{15}$, $-N(R^{15})_2$, -CN, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl; or R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 4- to 7-membered saturated *N*-containing heterocyclic ring.

[0079] In some embodiments, R^{11} hydrogen; R^{12} is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, cyclopropyl, $CH_2CH_2CH_2OCH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl; or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl; R^{13} is hydrogen, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -CN, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$; or R^{12} and R^{13} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted monocyclic 4- to 7-membered heterocyclic ring selected from substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl.

[0080] In some embodiments, R^{11} hydrogen; R^{12} is hydrogen or $-CH_3$.

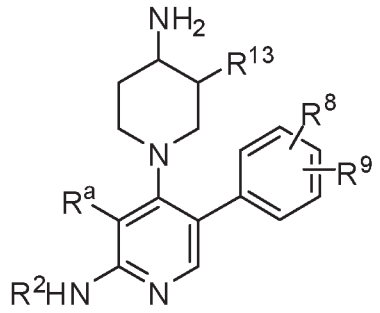
[0081] In some embodiments, R^8 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, -CN, -OH, $-OR^{14}$, $-CO_2R^{15}$, $-CH_2CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-CH_2C(=O)N(R^{15})_2$, $-N(R^{15})_2$, $-CH_2N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-CH_2NR^{15}C(=O)R^{14}$, $-SR^{14}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$; and R^9 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, -CN, -OH, -O-(substituted or unsubstituted C_1-C_4alkyl), or -O-(substituted or unsubstituted C_1-C_4fluoroalkyl).

[0082] In some embodiments, R^8 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, or pyrrolidinyl; R^9 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CN$, or $-OCF_3$.

[0083] In some embodiments, R^8 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, azetidinyl, or pyrrolidinyl; R^9 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$.

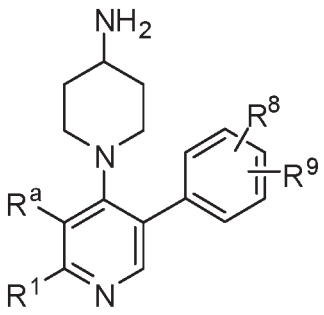
[0084] In some embodiments, R^8 is hydrogen, F, Cl, Br, $-CH_3$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$; R^9 is hydrogen, F, Cl, Br, $-CH_3$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$.

[0085] In some embodiments, the compound of Formula (I) has the following structure, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



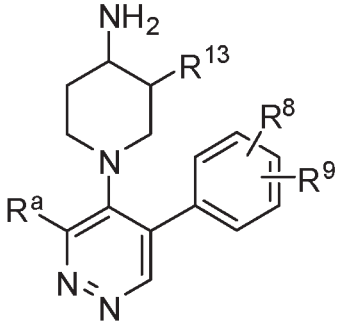
[0086] In some embodiments, R^a, R^{13}, R^8, and R^9 are as described in Table 1, Table 2, or Table 3. In some embodiments, R^2 is as described in Table 1. In some embodiments, R^a, R^2, R^{13}, R^8, and R^9 are as described in Table 1. In some embodiments, R^a, R^8, and R^9 are as described in Table 1, Table 2, Table 3, or Table 4.

[0087] In some embodiments, the compound of Formula (I) has the following structure, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



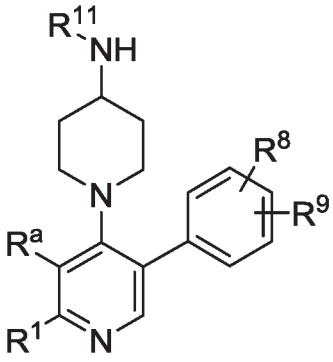
[0088] In some embodiments, R^a, R^8, and R^9 are as described in Table 1, Table 2, or Table 3. In some embodiments, R^1 is as described in Table 2. In some embodiments, R^a, R^1, R^8, and R^9 are as described in Table 2. In some embodiments, R^a, R^8, and R^9 are as described in Table 1, Table 2, Table 3, or Table 4.

[0089] In some embodiments, the compound of Formula (I) has the following structure, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



[0090] In some embodiments, R^a, R^{13}, R^8, and R^9 are as described in Table 1, Table 2, or Table 3. In some embodiments, R^a, R^{13}, R^8, and R^9 are as described in Table 3. In some embodiments, R^a, R^8, and R^9 are as described in Table 1, Table 2, Table 3, or Table 4.

[0091] In some embodiments, the compound of Formula (I) has the following structure, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:

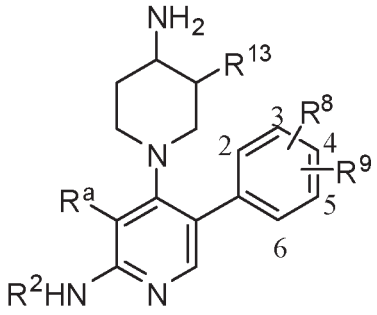


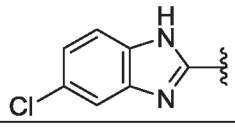
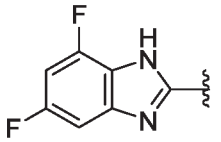
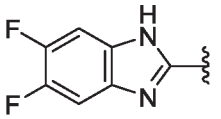
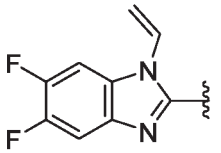
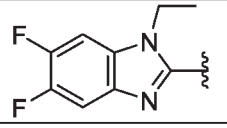
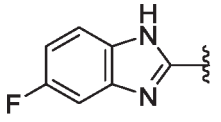
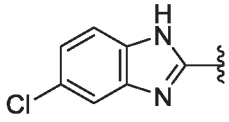
[0092] In some embodiments, R^a, R^1, R^{11}, R^8, and R^9 are as described in Table 4. In some embodiments, R^a, R^8, and R^9 are as described in Table 1, Table 2, Table 3, or Table 4. In some embodiments, R^{11} is as described in Table 4. .

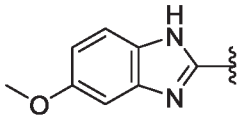
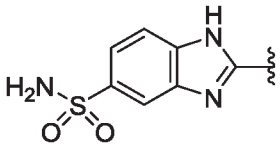
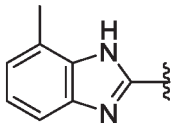
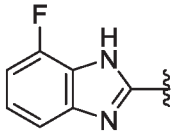
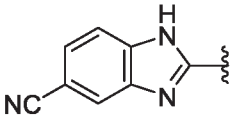
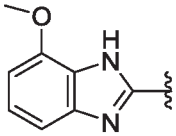
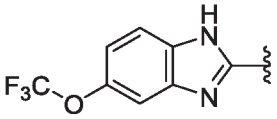
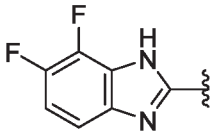
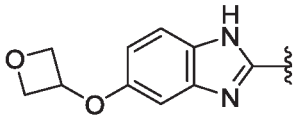
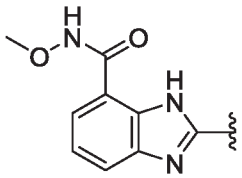
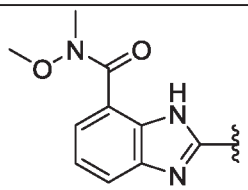
[0093] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

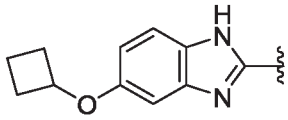
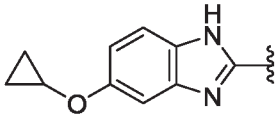
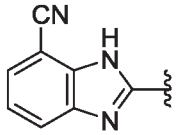
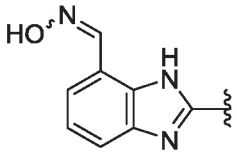
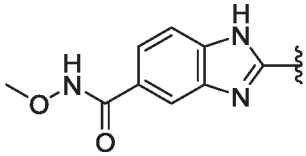
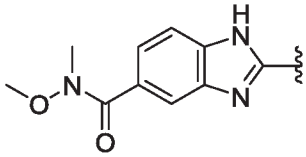
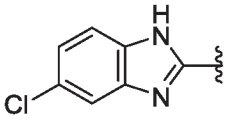
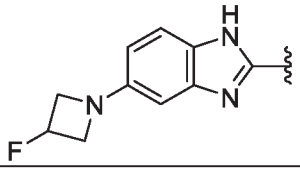
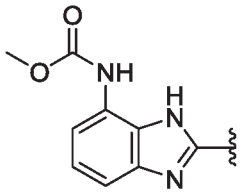
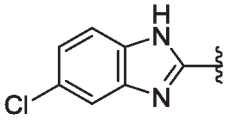
[0094] Exemplary compounds described herein include the compounds described in the following Tables:

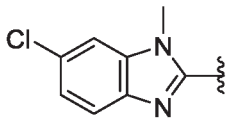
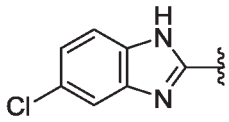
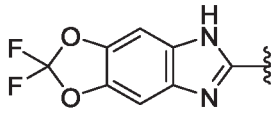
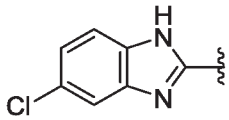
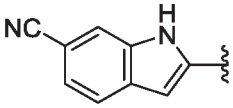
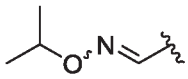
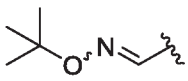
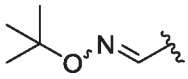
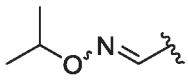
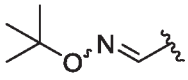
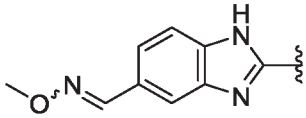
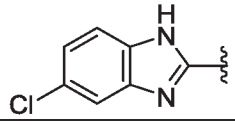
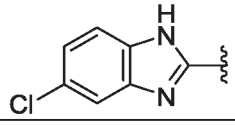
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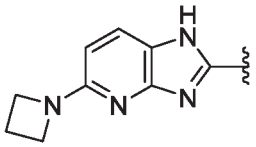
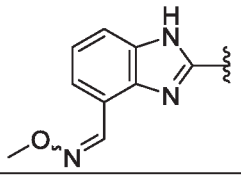
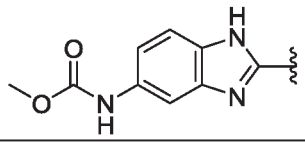
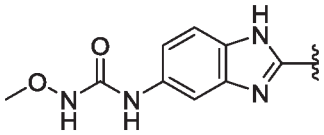
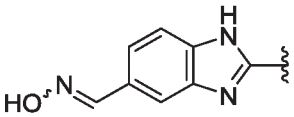
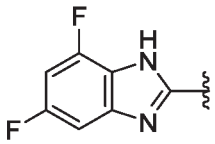
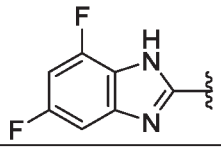
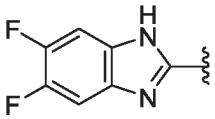
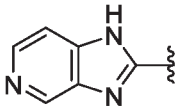
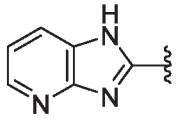
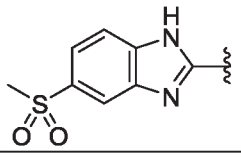
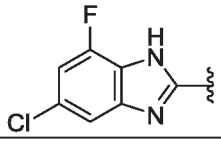


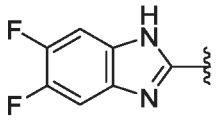
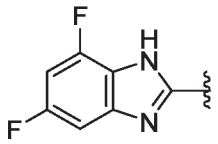
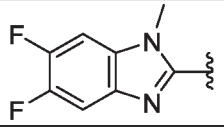
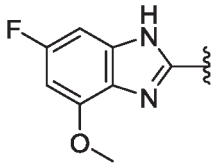
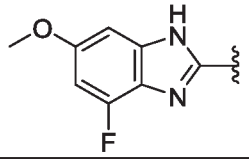
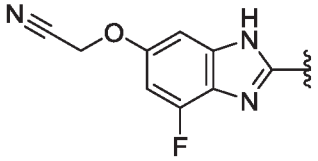
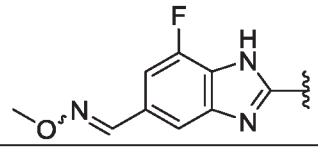
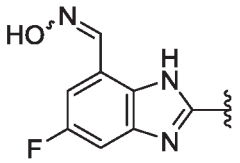
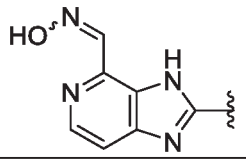
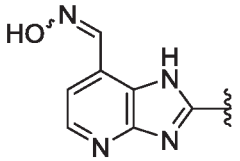
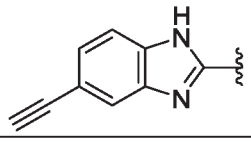
Cpd No.	R^a	R^{13}	R^2	R^8	R^9
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1-2		H	H	3-F	5-CH_3
1-3		H	H	3-F	5-CH_3
1-4		H	H	3-F	5-CH_3
1-5		H	H	3-F	5-CH_3
1-6		H	H	3-F	5-CH_3
1-7		OCH_3 (trans-racamic)	H	3-F	5-CH_3

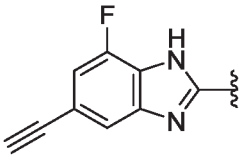
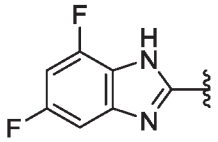
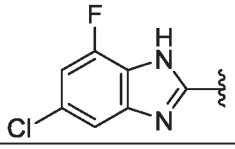
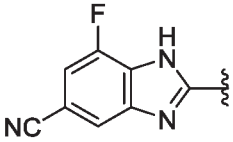
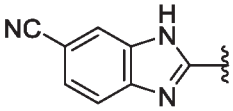
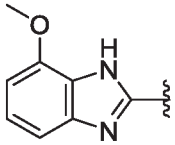
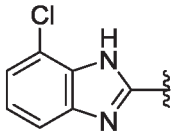
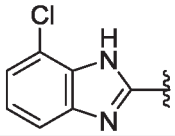
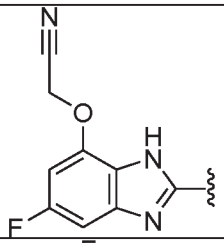
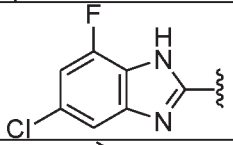
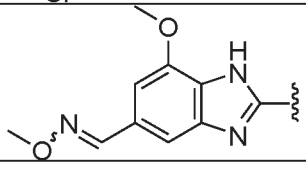
Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-8		H	H	3-F	5-CH_3
1-9		H	H	3-F	5-CH_3
1-10		H	H	3-F	5-CH_3
1-11		H	H	3-F	5-CH_3
1-12		H	H	3-F	5-CH_3
1-13		H	H	3-F	5-CH_3
1-14		H	H	3-F	5-CH_3
1-15		H	H	3-F	5-CH_3
1-16		H	H	3-F	5-CH_3
1-17		H	H	3-F	5-CH_3
1-18		H	H	3-F	5-CH_3

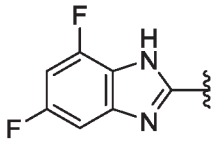
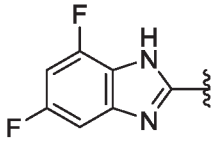
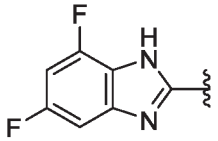
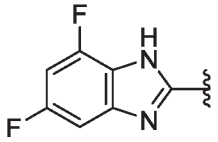
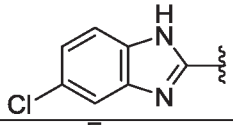
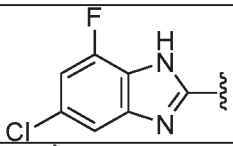
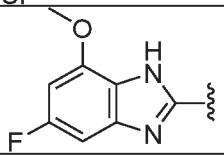
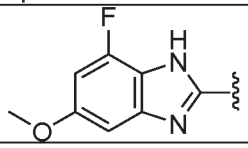
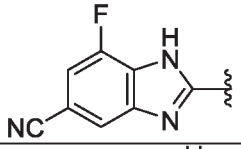
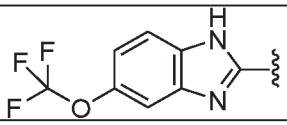
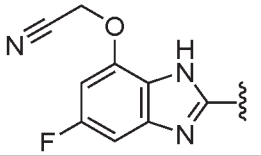
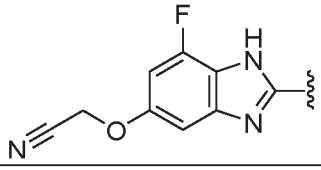
Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-19		H	H	3-F	5-CH_3
1-20		H	H	3-F	5-CH_3
1-21		H	H	3-F	5-CH_3
1-22		H	H	3-F	5-CH_3
1-23		H	H	3-F	5-CH_3
1-24		H	H	3-F	5-CH_3
1-25		H	H	3-CN	5-CH_3
1-26		H	H	3-F	5-CH_3
1-27		H	H	3-F	5-CH_3
1-28		H	CH_3-	3-F	5-CH_3

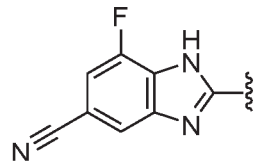
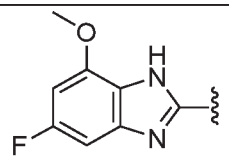
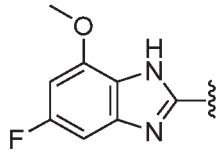
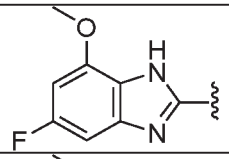
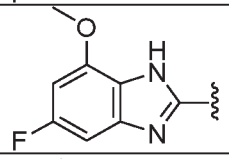
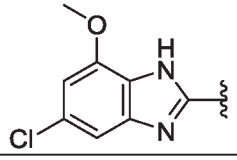
Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-29		H	H	3-F	5-CH_3
1-30		H	CH_3CH-	3-F	5-CH_3
1-31		H	H	3-F	5-CH_3
1-32		H	H	3-CN	5-F
1-33		H	H	3-F	5-CH_3
1-34		H	H	3-F	5-CH_3
1-35		H	H	3-F	5-CH_3
1-36		H	H	3- CH_3	5-CH_3
1-37		H	H	3-Cl	5-CH_3
1-38		H	H	3-Cl	5-CH_3
1-39		H	H	3-Cl	5-CH_3
1-40		H	H	3-F	5-CH_3
1-41		CN (trans-racamic)	H	3- CH_3	5-CH_3
1-42		CN (trans-racamic)	H	3-F	5-CH_3

Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-43		H	H	3-F	5-CH_3
1-44		H	H	3-F	5-CH_3
1-45		H	H	3-F	5-CH_3
1-46		H	H	3-F	5-CH_3
1-47		H	H	3-F	5-CH_3
1-48		H	CH_3-	3-F	5-CH_3
1-49		H	CH_3CH_2-	3-F	5-CH_3
1-50		H	CH_3CH_2-	3-F	5-CH_3
1-51		H	H	3-F	5-CH_3
1-52		H	H	3-F	5-CH_3
1-53		H	H	3-F	5-CH_3
1-54		H	H	3-F	5-CH_3

Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-55		H	CH_3-	3-F	5-CH_3
1-56		H	$CH_3OCH_2CH_2$-	3-F	5-CH_3
1-57		H	H	3-F	5-CH_3
1-58		H	H	3-F	5-CH_3
1-59		H	H	3-F	5-CH_3
1-60		H	H	3-F	5-CH_3
1-61		H	H	3-F	5-CH_3
1-62		H	H	3-F	5-CH_3
1-63		H	H	3-F	5-CH_3
1-64		H	H	3-F	5-CH_3
1-65		H	H	3-F	5-CH_3

Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-66		H	H	3-F	5-CH_3
1-67		H	H	3-F	5-OCH_3
1-68		H	H	3-F	5-OCH_3
1-69		H	H	3-F	5-CH_3
1-70		H	CH_3-	3-F	5-CH_3
1-71		H	CH_3-	3-F	5-CH_3
1-72		H	CH_3-	3-F	5-CH_3
1-73		H	H	3-F	5-CH_3
1-74		H	H	3-F	5-CH_3
1-75		H	CH_3-	3-F	5-CH_3
1-76		H	H	3-F	5-CH_3

Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-77		H	H	3-F	5-Cl
1-78		H	H	3-CH_3	5-CH_3
1-79		H	H	3-Cl	5-CH_3
1-80		H	H	3-CH_3	5-OCH_3
1-81		H	H	3-F	5-F
1-82		H	H	3-F	5-F
1-83		H	H	3-CH_3	5-CH_3
1-84		H	H	3-CH_3	5-CH_3
1-85		H	H	3-F	5-Cl
1-86		H	H	3-F	5-F
1-87		H	H	3-F	5-Cl
1-88		H	H	3-F	5-Cl

Cpd No.	R^a	R^{13}	R^2	R^8	R^9
1-89		H	CH_3-	3-F	5-CH_3
1-90		H	H	3-Cl	5-F
1-91		H	H	3-CH_3	4-F
1-92		H	H	3-Cl	H
1-93		H	H	3-CH_3	H
1-94		H	H	3-F	5-CH_3

[0095] Compounds in Table 1 are named:

1-1: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-2: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-3: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-4: 4-(4-aminopiperidin-1-yl)-3-(1-ethenyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-5: 4-(4-aminopiperidin-1-yl)-3-(1-ethyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-6: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-7: 4-[*trans*-4-amino-3-methoxypiperidin-1-yl]-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-8: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(5-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-9: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-5-sulfonamide;

1-10: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methyl-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-11: 4-(4-aminopiperidin-1-yl)-3-(7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-12: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-5-carbonitrile;

1-13: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-14: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[5-(trifluoromethoxy)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-15: 4-(4-aminopiperidin-1-yl)-3-(6,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amineine;

1-16: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[5-(oxetan-3-yloxy)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-17: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-1H-1,3-benzodiazole-7-carboxamide;

1-18: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-N-methyl-1H-1,3-benzodiazole-7-carboxamide;

1-19: 4-(4-aminopiperidin-1-yl)-3-(5-cyclobutoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-20: 4-(4-aminopiperidin-1-yl)-3-(5-cyclopropoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-21: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-7-carbonitrile;

1-22: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-[(hydroxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-23: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-1H-1,3-benzodiazole-5-carboxamide;

1-24: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-N-methyl-1H-1,3-benzodiazole-5-carboxamide;

1-25: 3-[6-amino-4-(4-aminopiperidin-1-yl)-5-(5-chloro-1H-1,3-benzodiazol-2-yl)pyridin-3-yl]-5-methylbenzonitrile;

1-26: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[5-(3-fluoroazetidin-1-yl)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-27: methyl N-{2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazol-7-yl}carbamate;

1-28: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-29: 4-(4-aminopiperidin-1-yl)-3-(6-chloro-1-methyl-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-30: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-N-ethyl-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-31: 4-(4-aminopiperidin-1-yl)-3-{5,5-difluoro-4,6-dioxa-10,12-diazatricyclo[7.3.0.0^{3,7}]dodeca-1,3(7),8,10-tetraen-11-yl}-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-32: 3-[6-amino-4-(4-aminopiperidin-1-yl)-5-(5-chloro-1H-1,3-benzodiazol-2-yl)pyridin-3-yl]-5-fluorobenzonitrile;

1-33: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-indole-6-carbonitrile;

1-34: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-2-amine;

1-35: 4-(4-aminopiperidin-1-yl)-3-[(tert-butoxy)imino]methyl]-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-36: 4-(4-aminopiperidin-1-yl)-3-[(tert-butoxy)imino]methyl]-5-(3,5-dimethylphenyl)pyridin-2-amine;

1-37: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-2-amine;

1-38: 4-(4-aminopiperidin-1-yl)-3-[(tert-butoxy)imino]methyl]-5-(3-chloro-5-methylphenyl)pyridin-2-amine;

1-39: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-[(hydroxyimino)methyl]pyridin-2-amine;

1-40: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{5-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-41: *trans*-4-amino-1-[2-amino-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3,5-dimethylphenyl)pyridin-4-yl]piperidine-3-carbonitrile;

1-42: *trans*-4-amino-1-[2-amino-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidine-3-carbonitrile;

1-43: 4-(4-aminopiperidin-1-yl)-3-[5-(azetidin-1-yl)-1H-imidazo[4,5-b]pyridin-2-yl]-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-44: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{4-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-45: methyl N-{2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazol-5-yl}carbamate;

1-46: 1-{2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazol-5-yl}-3-methoxyurea;

1-47: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{5-[(hydroxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-48: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-49: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-N-ethyl-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-50: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-N-ethyl-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-51: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{1H-imidazo[4,5-c]pyridin-2-yl}pyridin-2-amine;

1-52: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{1H-imidazo[4,5-b]pyridin-2-yl}pyridin-2-amine;

1-53: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(5-methanesulfonyl-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-54: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-55: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-56: 3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-(2-methoxyethyl)-4-(4-methylpiperidin-1-yl)pyridin-2-amine;

1-57: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1-methyl-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-58: 4-(4-aminopiperidin-1-yl)-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-59: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(4-fluoro-6-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine.

1-60: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-4-fluoro-1H-1,3-benzodiazol-6-yl}oxy)acetonitrile;

1-61: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-fluoro-5-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-62: 4-(4-aminopiperidin-1-yl)-3-{6-fluoro-4-[(hydroxyimino)methyl]-1H-1,3-benzodiazol-2-yl}-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-63：4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{4-[(hydroxyimino)methyl]-1H-imidazo[4,5-c]pyridin-2-yl}pyridin-2-amine；

1-64：4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-[(hydroxyimino)methyl]-3H-imidazo[4,5-b]pyridin-2-yl}pyridin-2-amine；

1-65: 4-(4-aminopiperidin-1-yl)-3-(5-ethynyl-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-66: 4-(4-aminopiperidin-1-yl)-3-(5-ethynyl-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-67: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methoxyphenyl)pyridin-2-amine;

1-68: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methoxyphenyl)pyridin-2-amine;

1-69: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

1-70: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylamino)pyridin-3-yl]-1H-1,3-benzodiazole-6-carbonitrile;

1-71: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methoxy-1H-1,3-benzodiazol-2-yl)-N-methylpyridin-2-amine;

1-72: 4-(4-aminopiperidin-1-yl)-3-(7-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-73: 4-(4-aminopiperidin-1-yl)-3-(7-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-74: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-5-fluoro-1H-1,3-benzodiazol-7-yl}oxy)acetonitrile;

1-75: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-76: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-methoxy-5-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-77: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-78: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3,5-dimethylphenyl)pyridin-2-amine;

1-79: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-80: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-methoxy-5-methylphenyl)pyridin-2-amine;

1-81: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3,5-difluorophenyl)pyridin-2-amine;

1-82: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3,5-difluorophenyl)pyridin-2-amine;

1-83: 4-(4-aminopiperidin-1-yl)-5-(3,5-dimethylphenyl)-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-84: 4-(4-aminopiperidin-1-yl)-5-(3,5-dimethylphenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-85: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

1-86: 4-(4-aminopiperidin-1-yl)-5-(3,5-difluorophenyl)-3-[5-(trifluoromethoxy)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-87: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)pyridin-3-yl]-5-fluoro-1H-1,3-benzodiazol-7-yl}oxy)acetonitrile;

1-88: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazol-5-yl}oxy)acetonitrile;

1-89: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylamino)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

1-90: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-91: 4-(4-aminopiperidin-1-yl)-5-(4-fluoro-3-methylphenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

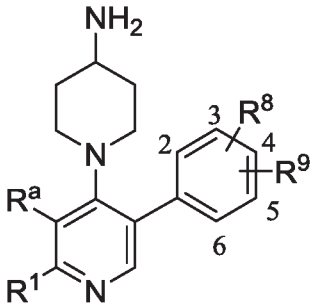
1-92: 4-(4-aminopiperidin-1-yl)-5-(3-chlorophenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

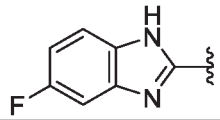
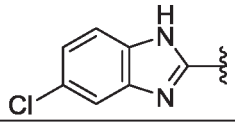
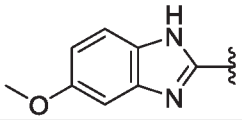
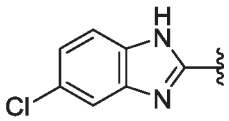
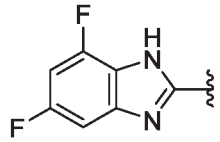
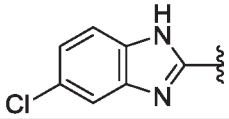
1-93: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-methylphenyl)pyridin-2-amine;

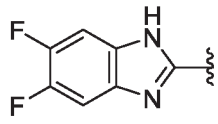
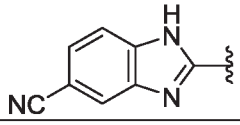
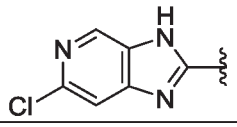
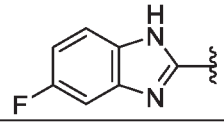
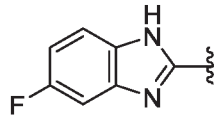
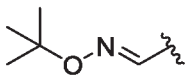
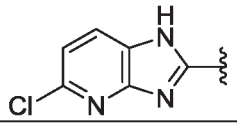
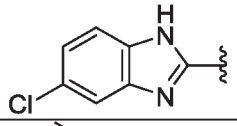
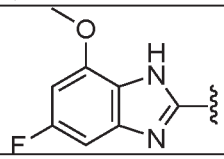
1-94: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine.

[0096] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 1.

Table 2:



Cpd No.	R^a	R^1	R^8	R^9
2-1		$-OCH_3$	3-F	$5-CH_3$
2-2		$-OCH_3$	3-F	$5-CH_3$
2-3		$-OCH_3$	3-F	$5-CH_3$
2-4		-OH	3-F	$5-CH_3$
2-5		$-OCH_3$	3-F	$5-CH_3$
2-6		$-OCH_3$	3-CN	$5-CH_3$

Cpd No.	R^a	R^1	R^8	R^9
2-7		-OH	3-F	5-CH_3
2-8		-OCH_3	3-F	5-CH_3
2-9		-OCH_3	3-F	5-CH_3
2-10		-OH	3-F	5-CH_3
2-11		-Cl	3-F	5-CH_3
2-12		-OCH_3	3-Cl	5-CH_3
2-13		-OCH_3	3-F	5-CH_3
2-14		-OCH_3	3-F	5-F
2-15		-CH_3	3-F	5-CH_3

[0097] Compounds in Table 2 are named:

2-1: 1-[3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-2: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-3: 1-[5-(3-fluoro-5-methylphenyl)-2-methoxy-3-(5-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-4-yl]piperidin-4-amine;

2-4: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol;

2-5: 1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-6: 3-[4-(4-aminopiperidin-1-yl)-5-(5-chloro-1H-1,3-benzodiazol-2-yl)-6-methoxypyridin-3-yl]-5-methylbenzonitrile;

2-7: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol;

2-8: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-3-yl]-1H-1,3-benzodiazole-5-carbonitrile;

2-9: 1-(3-{6-chloro-3H-imidazo[4,5-c]pyridin-2-yl}-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl)piperidin-4-amine;

2-10: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol;

2-11: 1-[2-chloro-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-amine;

2-12: 1-{3-[(1E)-[(tert-butoxy)imino]methyl]-5-(3-chloro-5-methylphenyl)-2-methoxypyridin-4-yl}piperidin-4-amine;

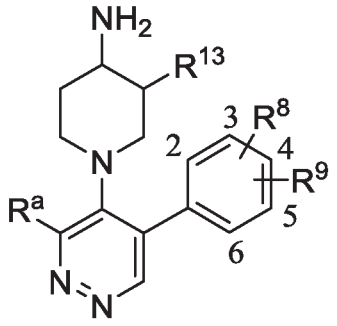
2-13: 1-(3-{5-chloro-1H-imidazo[4,5-b]pyridin-2-yl}-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl)piperidin-4-amine;

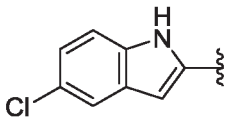
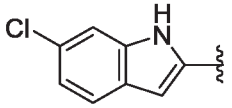
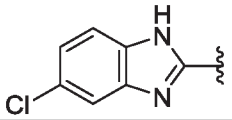
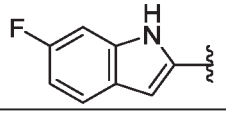
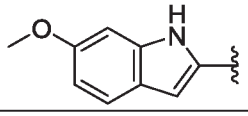
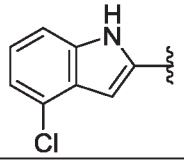
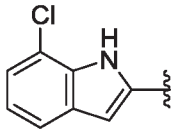
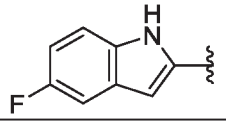
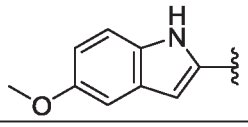
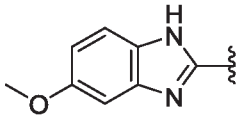
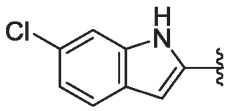
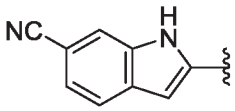
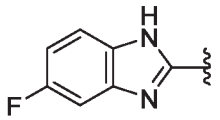
2-14: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3,5-difluorophenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

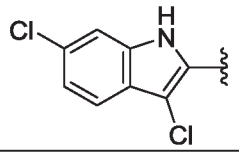
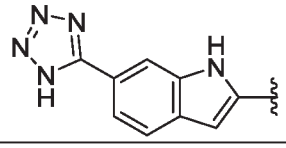
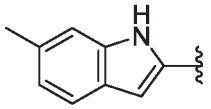
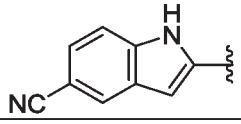
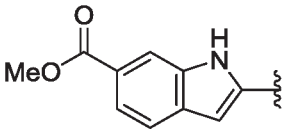
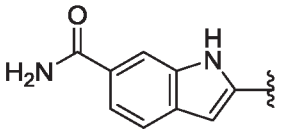
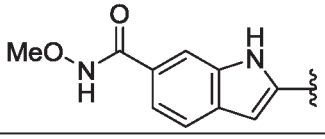
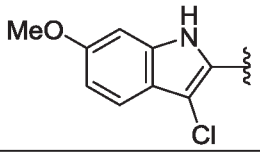
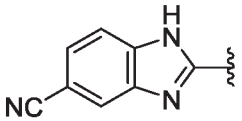
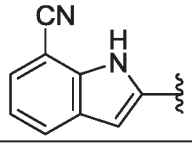
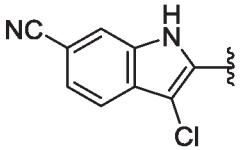
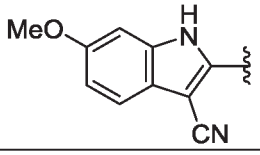
2-15: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methylpyridin-4-yl]piperidin-4-amine.

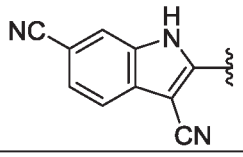
[0098] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 2.

Table 3:



Cpd No.	R^a	R^{13}	R^8	R^9
3-1		H	3-F	5-CH_3
3-2		H	3-F	5-CH_3
3-3		H	3-F	5-CH_3
3-4		H	3-F	5-CH_3
3-5		H	3-F	5-CH_3
3-6		H	3-F	5-CH_3
3-7		H	3-F	5-CH_3
3-8		H	3-F	5-CH_3
3-9		H	3-F	5-CH_3
3-10		H	3-F	5-CH_3
3-11		OCH_3 (trans-racamic)	3-F	5-CH_3
3-12		H	3-F	5-CH_3
3-13		H	3-F	5-CH_3

Cpd No.	R^a	R^{13}	R^8	R^9
3-14		H	3-F	5-CH_3
3-15		H	3-F	5-CH_3
3-16		H	3-F	5-CH_3
3-17		H	3-F	5-CH_3
3-18		H	3-F	5-CH_3
3-19		H	3-F	5-CH_3
3-20		H	3-F	5-CH_3
3-21		H	3-F	5-CH_3
3-22		H	3-F	5-CH_3
3-23		H	3-F	5-CH_3
3-24		H	3-F	5-CH_3
3-25		H	3-F	5-CH_3

Cpd No.	R^a	R^{13}	R^8	R^9
3-26		H	3-F	5-CH_3

[0099] Compounds in Table 3 are named:

3-1: 1-[3-(5-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-2: 1-[3-(6-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-3: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-4: 1-[3-(6-fluoro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-5: 1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1H-indol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-6: 1-[3-(4-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-7: 1-[3-(7-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-8: 1-[3-(5-fluoro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-9: 1-[5-(3-fluoro-5-methylphenyl)-3-(5-methoxy-1H-indol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-10: 1-[5-(3-fluoro-5-methylphenyl)-3-(5-methoxy-1H-1,3-benzodiazol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-11: *trans*-1-[3-(6-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]-3-methoxypiperidin-4-amine;

3-12: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-6-carbonitrile;

3-13: 1-[3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-14: 1-[3-(3,6-dichloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-15: 1-[5-(3-fluoro-5-methylphenyl)-3-[6-(2H-1,2,3,4-tetrazol-5-yl)-1H-indol-2-yl]pyridazin-4-yl]piperidin-4-amine;

3-16: 1-[5-(3-fluoro-5-methylphenyl)-3-(6-methyl-1H-indol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-17: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-5-carbonitrile;

3-18: methyl 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-6-carboxylate;

3-19: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-6-carboxamide;

3-20: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-N-methoxy-1H-indole-6-carboxamide;

3-21: 1-[3-(3-chloro-6-methoxy-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-22: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-1,3-benzodiazole-5-carbonitrile;

3-23: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-7-carbonitrile;

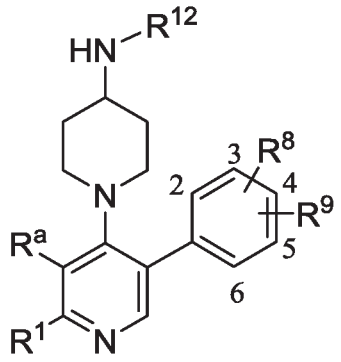
3-24: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-3-chloro-1H-indole-6-carbonitrile;

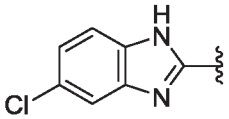
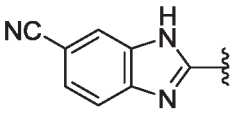
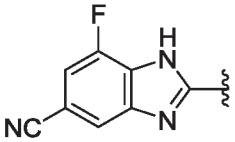
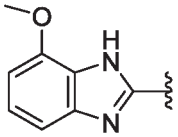
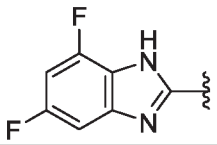
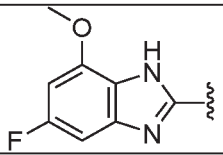
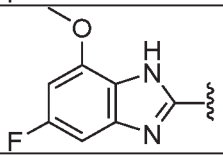
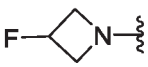
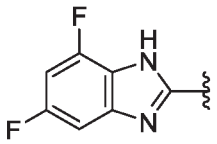
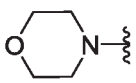
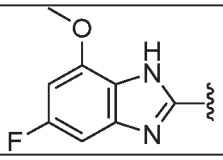
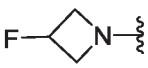
3-25: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-6-methoxy-1H-indole-3-carbonitrile;

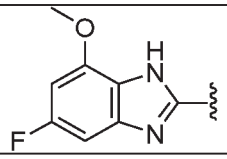
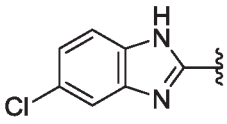
3-26: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-3,6-dicarbonitrile.

[00100] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 3.

Table 4:



Cpd No.	R^a	R^1	R^{12}	R^8	R^9
4-1			CH_3	3-F	5-CH_3
4-2			CH_3	3-F	5-CH_3
4-3			CH_3	3-F	5-CH_3
4-4			H	3-F	5-CH_3
4-5			H	3-F	5-CH_3
4-6			H	3-F	5-CH_3
4-7			H	3-F	5-CH_3
4-8			H	3-F	5-CH_3
4-9			H	3-F	5-H

Cpd No.	R^a	R^1	R^{12}	R^8	R^9
4-10			CH_3	3-F	5-CH_3
4-11			H	3-F	5-CH_3

[00101] Compounds in Table 4 are named:

4-1: 3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methyl-4-[4-(methylamino)piperidin-1-yl]pyridin-2-amine;

4-2: 2-[2-amino-5-(3-fluoro-5-methylphenyl)-4-[4-(methylamino)piperidin-1-yl]pyridin-3-yl]-1H-1,3-benzodiazole-6-carbonitrile;

4-3: 2-[2-amino-5-(3-fluoro-5-methylphenyl)-4-[4-(methylamino)piperidin-1-yl]pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

4-4: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methoxy-1H-1,3-benzodiazol-2-yl)-N,N-dimethylpyridin-2-amine;

4-5: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N,N-dimethylpyridin-2-amine;

4-6: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N,N-dimethylpyridin-2-amine;

4-7: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(3-fluoroazetidin-1-yl)pyridin-4-yl]piperidin-4-amine;

4-8: 1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-amine;

4-9: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-2-(3-fluoroazetidin-1-yl)-5-(3-fluorophenyl)pyridin-4-yl]piperidin-4-amine;

4-10: 3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-4-[4-(methylamino)piperidin-1-yl]pyridin-2-amine;

4-11: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl]piperidin-4-amine.

[00102] In some embodiments, provided herein is a pharmaceutically acceptable salt of a compound that is described in Table 4.

[00103] In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00104] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is 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.

[00105] The term "pharmaceutically acceptable salt" refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible and this capability can be manipulated as one aspect of delayed and sustained release behaviours. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

[00106] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I) with an acid. In some embodiments, the compound of Formula (I) (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid);

caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; proprionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[00107] In some embodiments, a compound of Formula (I) is prepared as a chloride salt, sulfate salt, bromide salt, mesylate salt, maleate salt, citrate salt or phosphate salt.

[00108] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I) with a base. In some embodiments, the compound of Formula (I) is acidic and is reacted with a base. In such situations, an acidic proton of the compound of Formula (I) is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt.

[00109] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00110] The methods and formulations described herein include the use of *N*-oxides (if appropriate), or pharmaceutically acceptable salts of compounds having the structure of Formula (I), as well as active metabolites of these compounds having the same type of activity.

[00111] In some embodiments, sites on the organic radicals (e.g. alkyl groups, aromatic rings) of compounds of Formula (I) are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the organic radicals will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium, an alkyl group, a haloalkyl group, or a deuteroalkyl group.

[00112] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00113] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine chlorine, iodine, phosphorus, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{32}P and ^{33}P. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00114] In some embodiments, the compounds of Formula (I) possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. In some embodiments, the compound of Formula (I) exists in the R configuration. In some embodiments, the compound of Formula (I) exists in the S configuration. The compounds presented herein include all diastereomeric, individual enantiomers, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00115] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, compounds of Formula (I) are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of steroisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00116] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. Further or alternatively, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") but then is metabolically hydrolyzed to provide the active entity. A further example of a prodrug is a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00117] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, N-alkyloxyacyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, and sulfonate esters. See for example Design

of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like. In some embodiments, a hydroxyl group in the compounds disclosed herein is a prodrug wherein the hydroxyl is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, a carboxyl group is used to provide an ester or amide (i.e. the prodrug), which is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, compounds described herein are prepared as alkyl ester prodrugs.

[00118] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I) as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds is a prodrug for another derivative or active compound.

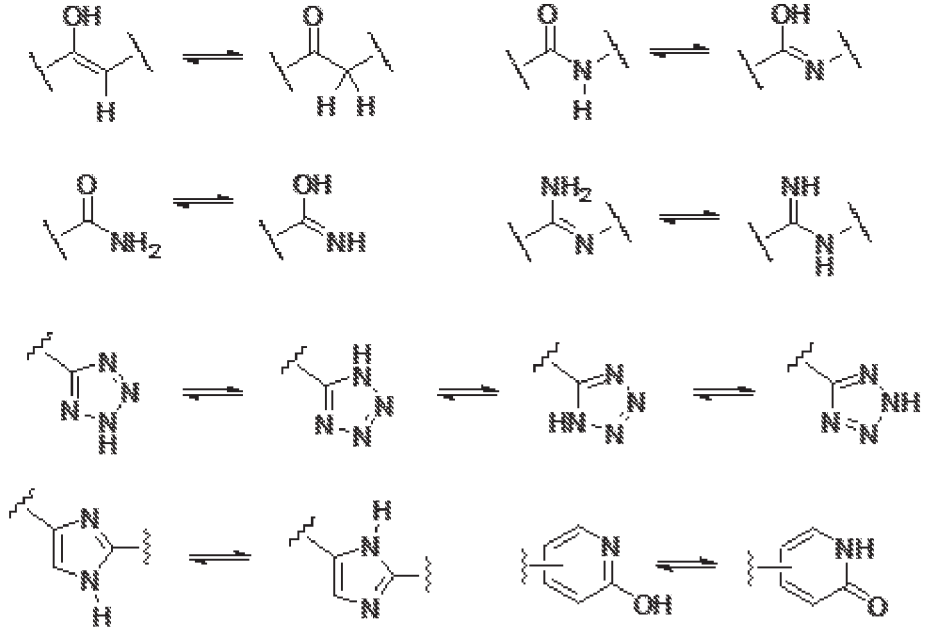
[00119] In some embodiments, any one of the hydroxyl group(s), amino group(s) and/or carboxylic acid group(s) are functionalized in a suitable manner to provide a prodrug moiety. In some embodiments, the prodrug moiety is as described above.

[00120] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

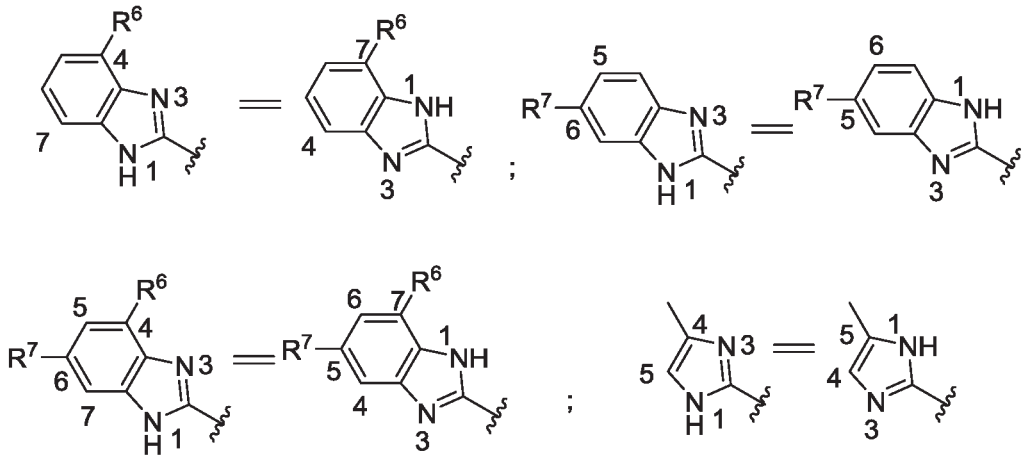
[00121] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and

analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00122] In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[00123] In some instances, heterocyclic rings may exist in tautomeric forms. In such situtations, it is understood that the structures of said compounds are illustrated or named in one tautomeric form but could be illustrated or named in the alternative tautomeric form. The alternative tautomeric forms are expressly included in this disclosure, such as, for example, the structures illustrated below. For example, benzimidazoles or imidazoles could exist in the following tautomeric forms:



Synthesis of Compounds

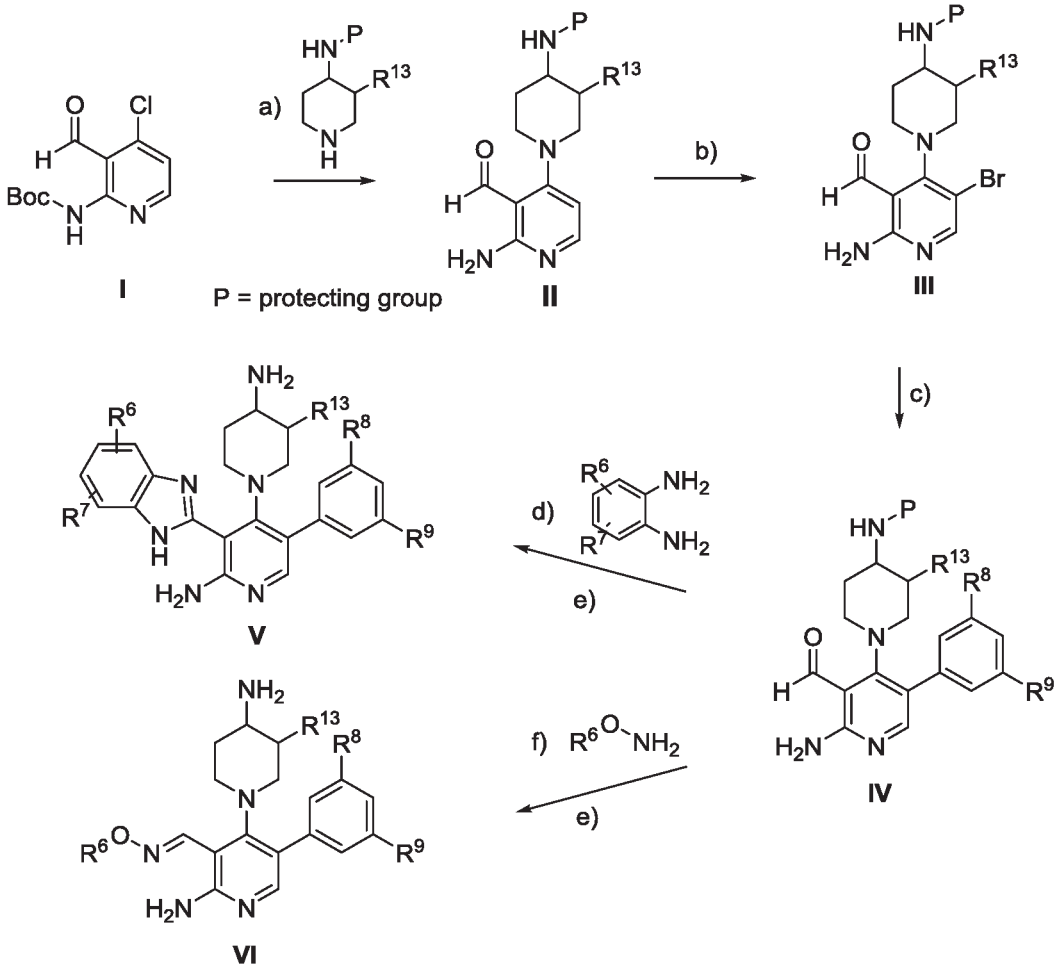
[00124] Compounds of Formula (I) described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein.

[00125] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed.

[00126] Compounds are prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions.

[00127] In some other embodiments, compounds described herein are prepared as described in **Scheme A.**

Scheme A

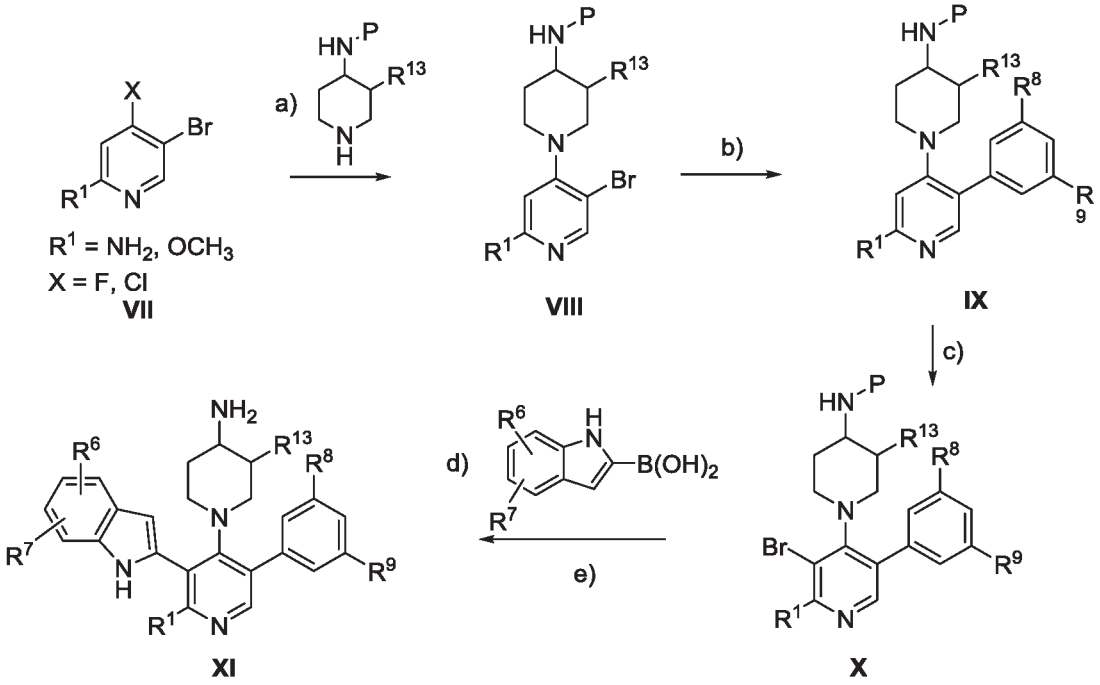


a) DIEA, ACN, b) NBS, ACN, c) $ArR^8R^9B(OH)_2$, Pd, d) DMF/H_2O, e) deprotection, f) EtOH

[00128] Nucleophilic substitution of **I** by 4-Boc aminopiperidine afforded intermediate **II**. Compound **II** was treated with NBS to yield intermediate **III** which was subsequently converted to intermediate **IV** by an organometallic coupling reaction such as Suzuki–Miyaura reaction with $ArR^8R^9B(OH)_2$. Benzimidazole formation between **IV** and corresponding 1,2-diaminobenzenes was achieved by heating in wet DMF or NMP or DMSO or other solvent with or without $Na_2S_2O_5$ under atmospheric oxygen. Subsquent removal of a protecting group using appropriate deprotection methods yielded the compound **V**. Intermediate **IV** was also converted to **VI** by an oxime formation with R^8O-NH_2 in the presence of pyridine and subsequent removal of the protectiong group in an appropriate acid condition.

[00129] In some other embodiments, compounds described herein are prepared as described in **Scheme B**.

Scheme B

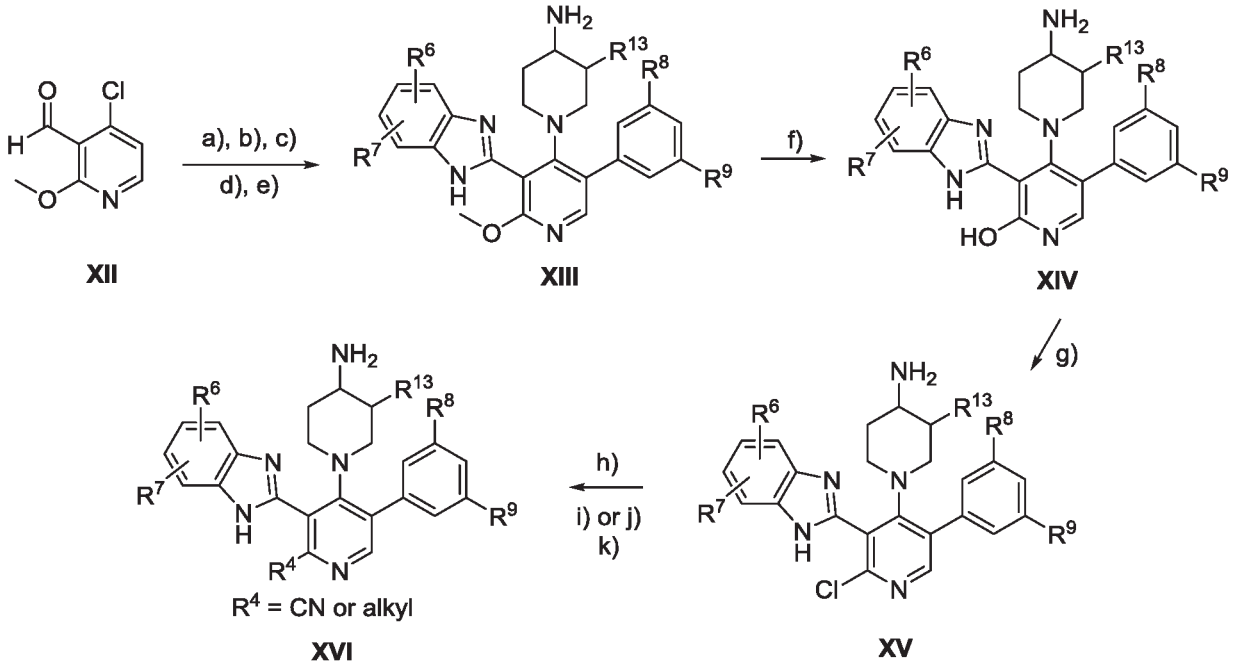


a) DIEA, DMSO, b) $Ar(R^8R^9)B(OH)_2$, Pd, c) NBS, ACN, d) Pd, e) deprotection

[00130] Commercially available **VII** underwent SN2 reaction with 4-Boc aminopiperidine to produce intermediate **VIII** which was transformed to **IX** by Suzuki–Miyaura reactions with $ArR^8R^9B(OH)_2$. Subsequently, selective bromination to intermediate **X** was achieved by treating with NBS. Then, compound **X** was converted to **XI** by Suzuki–Miyaura reactions with corresponding indole-2-boronic acids and subsquent removal of the protecting group using an appropriate deprotection method.

[00131] In some other embodiments, compounds described herein are prepared as described in **Scheme C.**

Scheme C

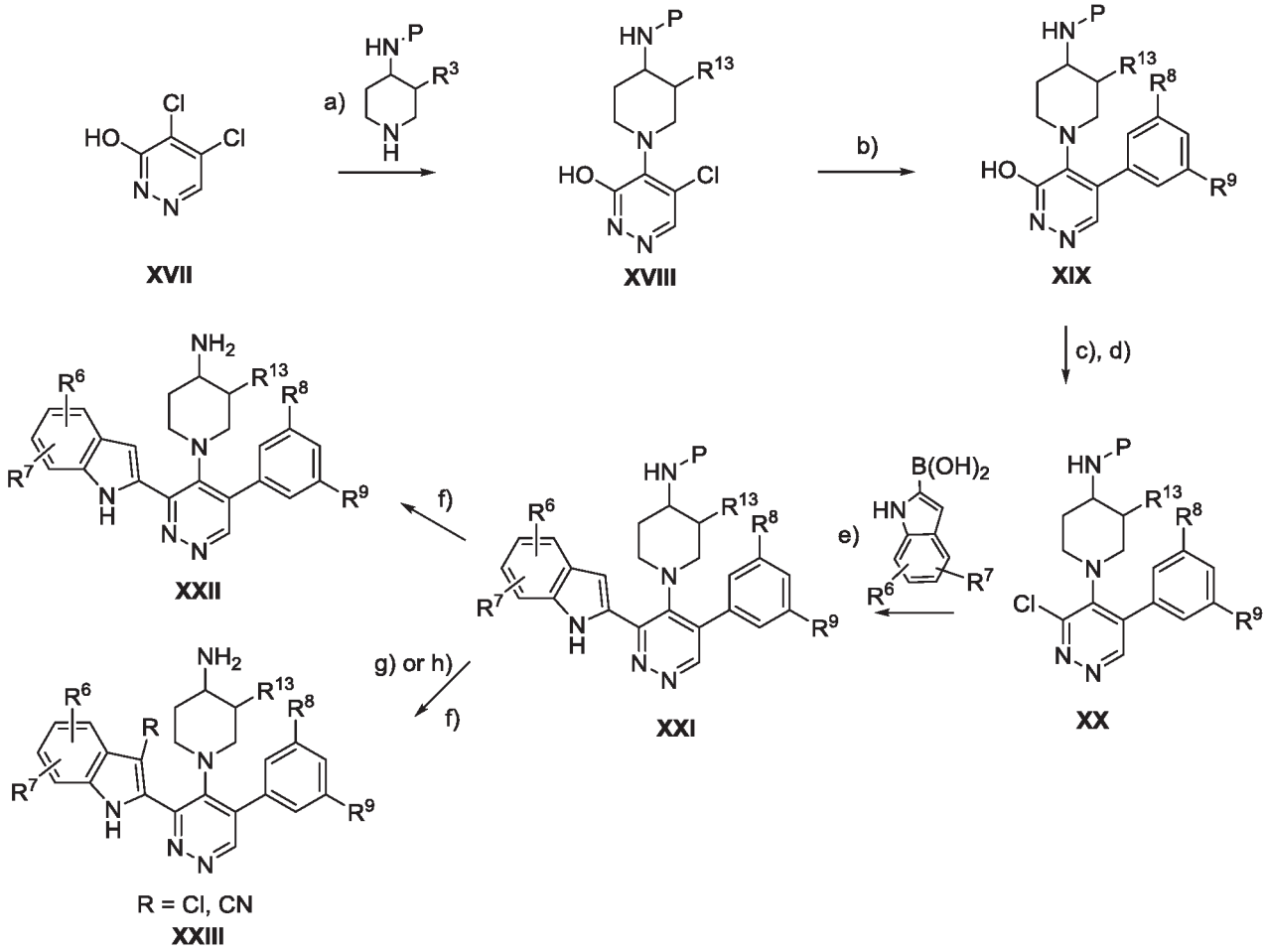


a) DIEA, ACN, b) NBS, ACN, c) $ArR^8R^9B(OH)_2$, Pd, d) DMF/H_2O, e) TFA, f) HCl, g) $POCl_3$, h) $(Boc)_2O$ i) $Zn(CN)_2$, Pd, j) $RSnBu_3$, Pd, k) deprotection

[00132] Compound **XIII** was prepared by a similar manner described in Step a) to Step e) in **Scheme A** starting from commercially available **XII**. Transformation to **XIV** was achieved by an acid catalyzed demethylation of **XIII**. The hydroxyl pyridine was converted to **XV** by refluxing in $POCl_3$. The cyano analogs (**XVI**) are obtained *via* three steps, protection of the primary amine, replacement of Cl with CN, and deprotection in an acidic condition. Introduction of alkyl groups at the 2-position can be also achieved by a Stille coupling reaction.

[00133] In some other embodiments, compounds described herein are prepared as described in **Scheme D.**

Scheme D

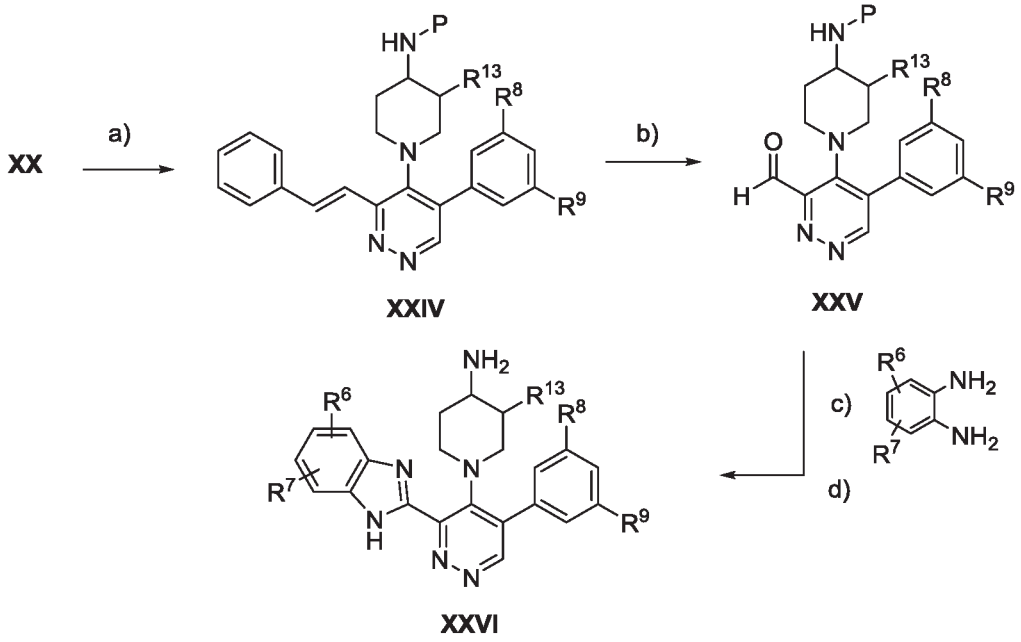


a) $NaHCO_3$, b) $ArR^8R^9B(OH)_2$, Pd, c) $POCl_3$, d) NaOH, $(Boc)_2O$, e) Pd, f) deprotection, g) NCS, h) $ClSO_2NCO$

[00134] The SN2 reaction between **XVII** and 4-Boc aminopiperidine in the presence of an iorganic base such as $NaHCO_3$ or $KHCO_3$ produced a mixture of two regioisomers (~1/1 ratio) which was separated to yield intermediate **XVIII**. Subsequently, **XVIII** was converted to **XIX** by Suzuki–Miyaura reactions with $ArR^8R^9B(OH)_2$. Compound **XXI** was obtained *via* two steps from **XIX**, chlorination with $POCl_3$ and Suzuki–Miyaura reaction with corresponding indole-2-boronic acids. Removal of the protecting group using an appropriate deprotection method gave compound **XXII**, and also chlorination at the 3-position of indole by treating with NCS and deprotection with an acid produced compound **XXIII** (R= Cl). Cyanation of the 3-position of indole (**XXIII**, R = CN) was achieved by treating with chlorosulfonyl isocyanate (CSI).

[00135] In some other embodiments, compounds described herein are prepared as described in **Scheme E.**

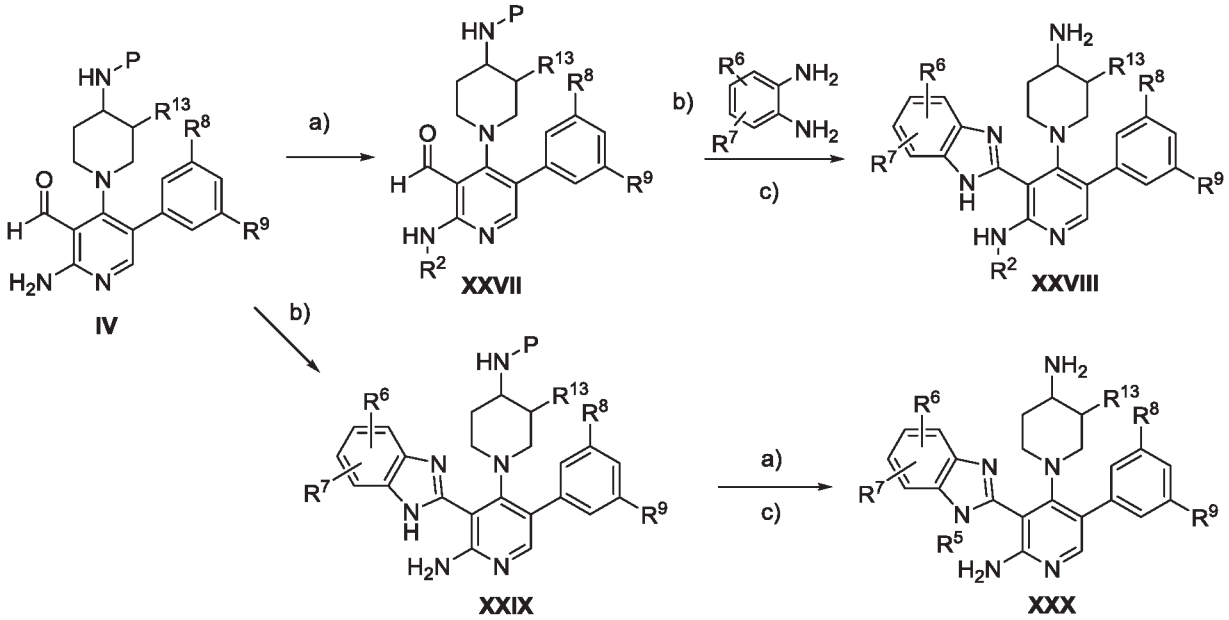
Scheme E



[00136] Intermediate **XX** was converted to **XXIV** by Suzuki–Miyaura reaction with 2-phenylvinylboronic acid. The olefin smoothly underwent oxidative cleavage by Lemieux–Johnson oxidation to form **XXV**. Benzimidazole formation with corresponding 1,2-diaminobenzenes was achieved by heating in wet DMF or DMSO or other solvents under atmospheric oxygen. Subsquent removal of a protecting group using appropriate deprotection methods yielded compound **XXVI**.

[00137] In some other embodiments, compounds described herein are prepared as described in **Scheme F.**

Scheme F

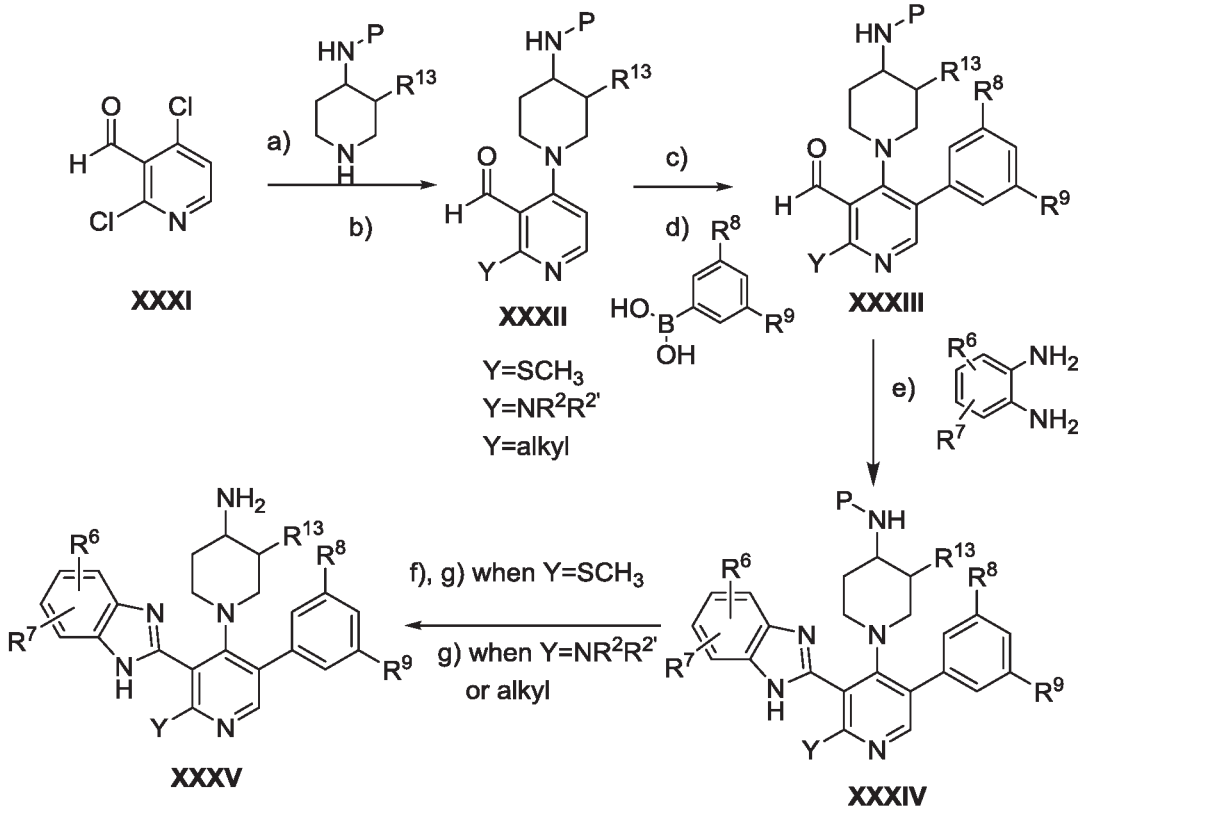


a) Alkyl halide, NaOH, DMF, b) DMF/H_2O, c) deprotection

[00138] The amino pyridine **IV** was alkylated to **XXVII** using the corresponding alkyl halide (R^2-X) and a base. Benzimidazole formation and deprotection by a similar manner described in Scheme A gave compound **XXVIII**. *N*-alkylation of **XXIX** with an alkyl halid (R^5-X) can be regioselectively achived and deprotection of the amino protection group also produced compound **XXX**.

[00139] In some embodiments, compounds are prepared as described in **Scheme G**.

Scheme G

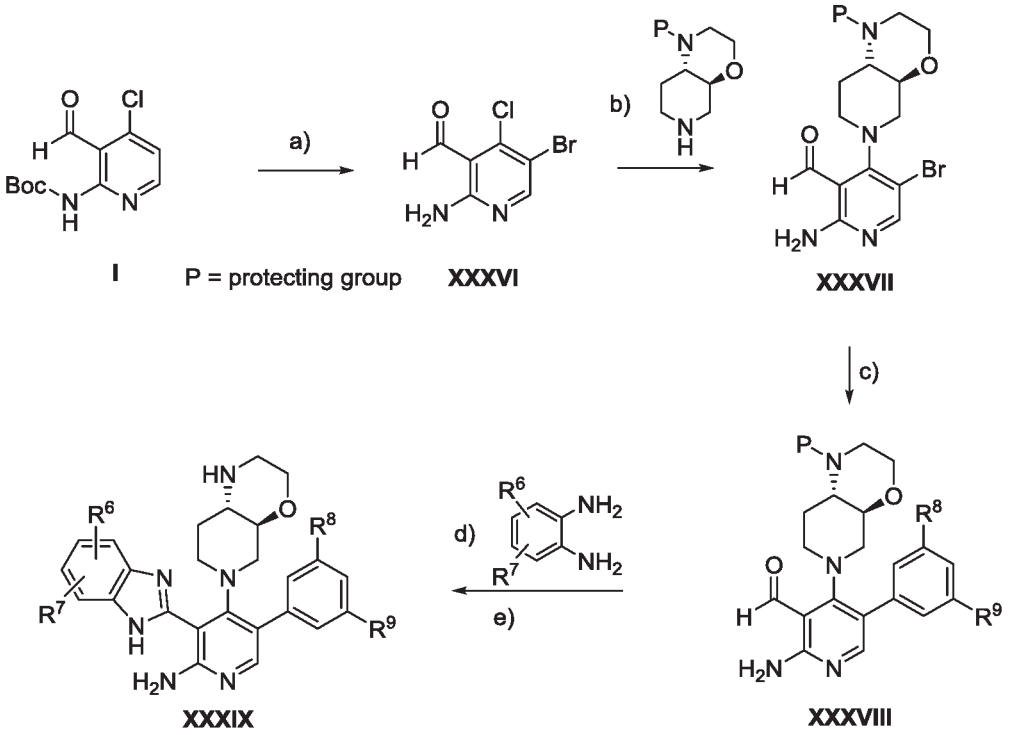


a) DMF, TEA; b) $R^2R^{2'}NH$, 100°C, or MeSNa, THF, 70°C or alkylboronic acid, $Pd(DTBPF)Cl_2$, $CsCO_3$, dioxane, water, 100°C ; c) NBS, DCE;
d) Pd_2dba^3, $P(t\text{-}Bu)_3$; e) $Na_2S_2O_5$, NMP, 120°C; f) m-CPBA, DCM, then $R^2R^{2'}NH$, 100°C;
g) TFA or HCl

The stepwise replacement of 2,4-dichloropyridine-3-carboxaldehyde **XXXI** with a protected 4-amino piperadine analog (step a), followed by the replacement reaction with either another amine ($R^2R^{2'}NH$) or methanethiol sodium salt or alkylboronic acid (step b) produced **XXXII**. Subsequent bromination (step c) and followed by a Suzuki coupling (step d) yielded compound **XXXIII,** which underwent benzimidazole formation with a phenylenediamine to afford **XXXIV** (step e). Subsequent deprotection by a similar manner described in Scheme A (step g) gave compound **XXXV** when $Y=NR^2R^{2'}$ or alkyl. In case $Y=SCH_3$, **XXXIV** was subject to an oxidating reagent such as m-CPBA to yield the corresponding sulfoxide which was then replaced with $R^2R^{2'}NH$, followed by deprotection of the protecting group on the amine to yield the desired product **XXXV**.

[00140] In some other embodiments, compounds described herein are prepared as described in **Scheme H.**

Scheme H

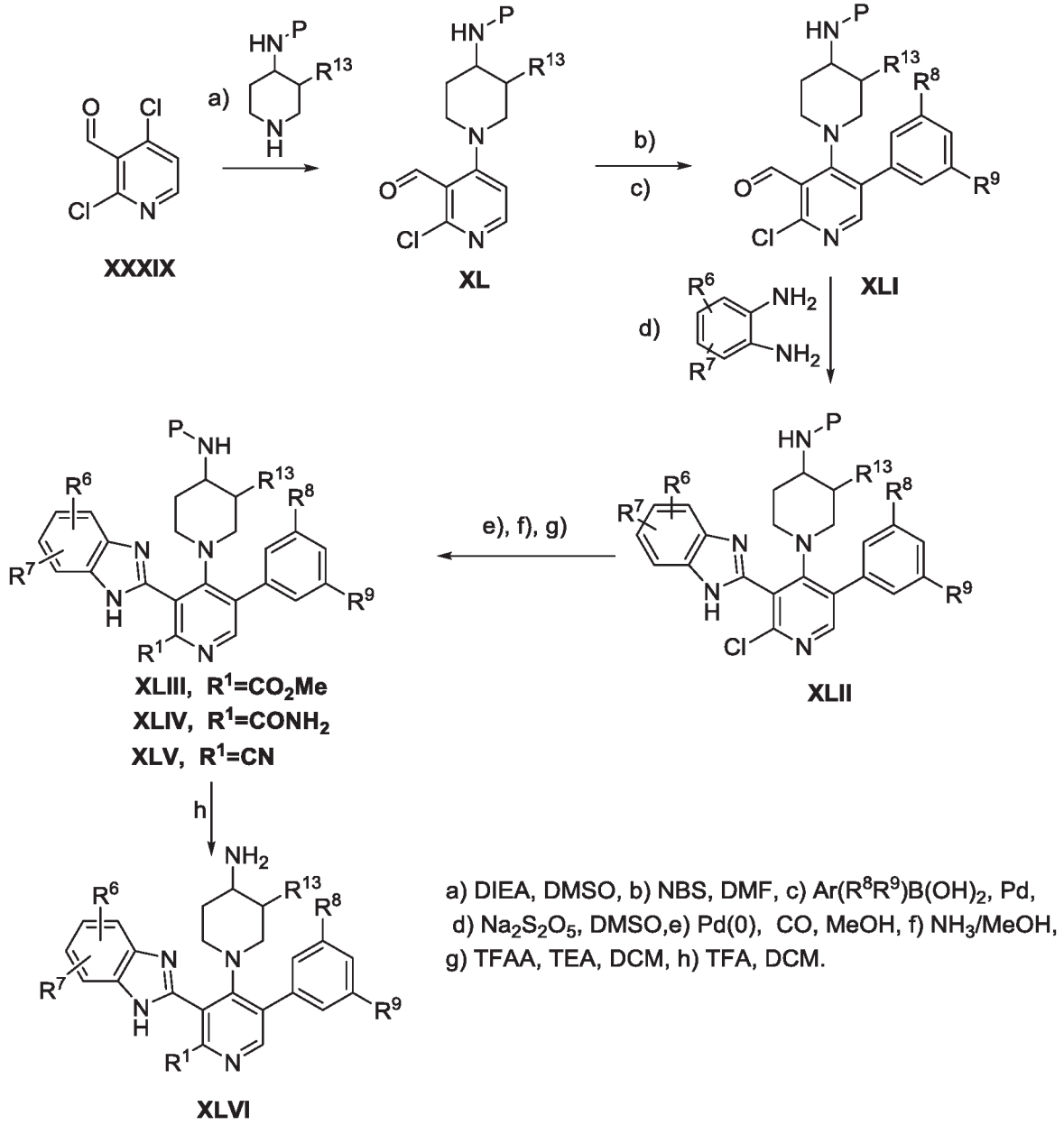


a) NBS, DCE, b) DIEA, ACN, c) $ArR^8R^9B(OH)_2$, Pd, d) DMF/H_2O, e) deprotection

[00141] Regioselective bromination of **I** with NBS afforded intermediate **XXXVI**. The conversion of **XXXVI** to **XXXIX** wascompleted by the similar manner described in **Scheme A**.

[00142] In some other embodiments, compounds described herein are prepared as described in **Scheme I.**

Scheme I



[00143] Compound **XXXIX** reacted with an amine to form **XL**. Bromination of **XL** and followed by Suzuki coupling reaction resulted in **XLI**, which was heated with a aryl-diamine to produce **XLII**. A carbon monoxide insertion in the presence of an alcohol led to formation of **XLIII**, which can be converted to **XLIVI** by ammonia, further dehydralation to afford **XLV**. Deprotection of **XLIII**, or **XLVI** or **XLV** yielded **XLVI**.

Certain Terminology

[00144] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are

for organizational purposes only and are not to be construed as limiting the subject matter described.

[00145] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_6" indicates that there are one to six carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[00146] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the "alkyl" group has 1 to 10 carbon atoms, i.e. a C_1-C_{10}alkyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, an alkyl is a C_1-C_6alkyl. In one aspect the alkyl is methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, or hexyl.

[00147] An "alkylene" group refers refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an alkelene is a C_1-C_6alkylene. In other embodiments, an alkylene is a C_1-C_4alkylene. Typical alkylene groups include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and the like. In some embodiments, an alkylene is -CH_2-.

[00148] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00149] The term "alkylamine" refers to the –N(alkyl)$_x$H$_y$ group, where x is 0 and y is 2, or where x is 1 and y is 1, or where x is 2 and y is 0.

[00150] An "hydroxyalkyl" refers to an alkyl in which one hydrogen atom is replaced by a hydroxyl. In some embodiments, a hydroxyalkyl is a C_1-C_4hydroxyalkyl. Typical hydroxyalkyl groups include, but are not limited to, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2OH$, and the like.

[00151] An "aminoalkyl" refers to an alkyl in which one hydrogen atom is replaced by an amino. In some embodiments, aminoalkyl is a C_1-C_4aminoalkyl. Typical aminoalkyl groups

include, but are not limited to, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, and the like.

[00152] The term "alkenyl" refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula $-C(R)=CR_2$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $-C(CH_3)=CHCH_3$, and $-CH_2CH=CH_2$.

[00153] The term "alkynyl" refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula -C≡C-R, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non-limiting examples of an alkynyl group include -C≡CH, $-C\equiv CCH_3$ $-C\equiv CCH_2CH_3$, $-CH_2C\equiv CH$.

[00154] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6heteroalkyl.

[00155] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00156] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycles include aryls and cycloalkyls.

[00157] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In one aspect, aryl is phenyl or a naphthyl. In some

embodiments, an aryl is a phenyl. In some embodiments, an aryl is a phenyl, naphthyl, indanyl, indenyl, or tetrahyodronaphthyl. In some embodiments, an aryl is a C_6-C_{10}aryl. Depending on the structure, an aryl group is a monoradical or a diradical (i.e., an arylene group).

[00158] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. In some embodiments, a cycloalkyl is a C_3-C_6cycloalkyl.

[00159] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[00160] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkyl is a C_1-C_6fluoroalkyl.

[00161] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-

dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[00162] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include monocyclic heteroaryls and bicyclcic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Monocyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C_1-C_9heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C_6-C_9heteroaryl.

[00163] A “heterocycloalkyl” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a

heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[00164] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00165] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00166] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2(C_1$-C_4alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4alkyl), $-C(=O)N(C_1$-C_4alkyl$)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1$-C_4alkyl), $-S(=O)_2N(C_1$-C_4alkyl$)_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, and $-S(=O)_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[00167] In some embodiments, each substituted alkyl, substituted fluoroalkyl, substituted heteroalkyl, substituted carbocycle, and substituted heterocycle is substituted with one or more R^s groups independently selected from the group consisting of halogen, C_1-C_6alkyl, monocyclic carbocycle, monocyclic heterocycle, -CN, -OR^{16}, -CO_2R^{16}, -$C(=O)N(R^{16})_2$, -$N(R^{16})_2$, -$NR^{16}C(=O)R^{17}$, -SR^{16}, -$S(=O)R^{17}$, -SO_2R^{17}, or -$SO_2N(R^{16})_2$; each R^{16} is independently selected from hydrogen, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl and 6-membered heteroaryl; or two R^{16} groups are taken together with the N atom to which they are attached to form a N-containing heterocycle; each R^{17} is independently selected from C_1-C_6alkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, benzyl, 5-membered heteroaryl and 6-membered heteroaryl.

[00168] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00169] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00170] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an agonist.

[00171] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[00172] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00173] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[00174] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00175] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00176] The terms "article of manufacture" and "kit" are used as synonyms.

[00177] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00178] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Pharmaceutical compositions

[00179] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00180] In some embodiments, the compounds described herein are administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for example the condition and disorder of the recipient. By way of example only, compounds described herein can be administered locally to the area in need of treatment, by for example, local infusion during surgery, topical application such as creams or ointments, injection,

catheter, or implant. The administration can also be by direct injection at the site of a diseased tissue or organ.

[00181] In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[00182] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[00183] In some embodiments, pharmaceutical compositions are formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-

dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[00184] Pharmaceutical compositions for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[00185] Pharmaceutical compositions may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00186] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[00187] Pharmaceutical compositions may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[00188] Pharmaceutical compositions suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation

such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation.

[00189] Pharmaceutical compositions for administration by inhalation are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, pharmaceutical preparations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[00190] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Methods of Dosing and Treatment Regimens

[00191] In one embodiment, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from modulation of somatostatin activity. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound of Formula (I) or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00192] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight,

and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00193] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00194] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00195] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00196] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00197] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-2000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00198] In one embodiment, the daily dosages appropriate for the compound of Formula (I), or a pharmaceutically acceptable salt thereof, described herein are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00199] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00200] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00201] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00202] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is

administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

Combination Treatments

[00203] In certain instances, it is appropriate to administer at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents.

[00204] In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00205] In one specific embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is co-administered with a second therapeutic agent, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[00206] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient is simply be additive of the two therapeutic agents or the patient experiences a synergistic benefit.

[00207] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00208] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If

administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

[00209] The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, as well as combination therapies, are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject.

EXAMPLES

[00210] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

Abbreviations:

$Pd(PPh_3)_4$: tetrakis(triphenylphosphine)palladium(0);

$Pd(dppf)Cl_2$: [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride;

$Pd(PPh_3)_2Cl_2$: bis(triphenylphosphine)palladium(II) dichloride;

PdAMphos or Pd (amphos)Cl_2: bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II);

$Pd(DTBPF)Cl_2$: [1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II);

$P(t\text{-}Bu)_3$: tri-tert-buytlphosphine;

HBF_4: tetrafluoroboric acid;

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;

DIEA: N,N-diisopropylethylamine;

Prep-HPLC: preparative high performance liquid chromatography;

LC-MS: Liquid chromatography–mass spectrometry;

MS: mass spectrometry;

AcOH : acetic acid;

TFA: trifluoroacetic acid;

HCl : hydrochloric acid or hydrochloride;

MeCN or CH_3CN or ACN: acetonitrile;

m-CPBA: 3-chloroperbenzoic acid;

H_2O: water;

DMSO: dimethyl sulfoxide;

DMF : dimethylformamide

DCM : dichloromethane

NBS: N-bromosuccinimide;

Br_2: bromine;

NCS : N-Chlorosuccinimide ;

rt: room temperature;

SST: somatostatin;

SSTR: somatostatin receptor;

TBAF: tetrabutylammonium fluoride;

hrs: hours;

h or hr: hour;

min : minute

N_2 : nitrogen gas;

mg: milligrams;

mL : milliliter;

eq. : equivalents;

mmol: millimole

ppts: precipitates;

K_2CO_3 : potassium carbonate

$NaHCO_3$: sodium bicarbonate

OsO_4 : osmium tetraoxide

t-BuOH : *tert*-butyl alcohol

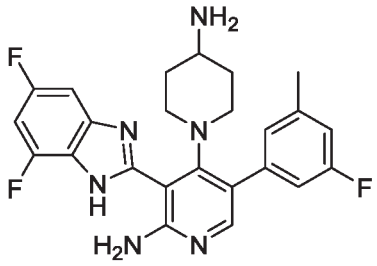
EtOAc : ethyl acetate

Na_2SO_4 : sodium sulfate

[00211] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Synthesis of Compounds

Example 1. 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine (compound 1-2).



[00212] Step 1-1, preparation of *tert*-butyl *N*-[1-(2-amino-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: A mixture of *tert*-butyl *N*-(4-chloro-3-formylpyridin-2-yl)carbamate (0.81 g, 3.16 mmol), 4-Boc aminopiperidine (1.2 g, 1.9 eq.), and DIEA (1.6 mL, 2.5 eq.) in ACN (20 mL) was stirred at 85 °C for 16 hrs. The reaction was cooled to rt, and concentrated to remove the volatile solvent. The residue was purified by column chromatography to afford the title compound (0.48 g, 48%). MS $(M+H)^+ = 321.3$.

[00213] Step 1-2, preparation of *tert*-butyl *N*-[1-(2-amino-5-bromo-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: To a solution of *tert*-butyl *N*-[1-(2-amino-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (2.2 g, 6.87 mmol) in ACN (50 mL) was added NBS (1.6 g, 1.3 eq.) at room temperature. The reaction was stirred for 15 min at rt, and concentrated. The residue was purified by column chromatography to afford the title compound (1.7 g, 63 %). MS $(M+H)^+ = 399.1$.

[00214] Step 1-3, preparation of *tert*-butyl *N*-{1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl)]piperidin-4-yl}carbamate: A mixture of *tert*-butyl *N*-[1-(2-amino-5-bromo-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (1.6 g, 4.0 mmol), 3-fluoro-5-methylboronic acid (1,0 g, 1.7 eq.), $PdCl_2(t\text{-}Bu_2PPhNMe_2)_2$ (280 mg, 0.4 mmol), and K_2CO_3 (1.1 g, 2 eq.) in dioxane/H_2O (10/1 = 20 mL/2.0 mL) was degassed with N_2 for 5 min, and then sealed. The reaction mixture was stirred for 1.2 h at 80 °C and cooled to room temperature. The reaction was filtered through a pad of celite, and the volatile solvent was removed under vacuum. The residue was purified by column chromatography to afford the title compound (1.35 g, 79 %). MS $(M+H)^+ = 429.4$.

[00215] Step 1-4, preparation of *tert*-butyl *N*-{1-[2-amino-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl}carbamate: A mixture of *tert*-butyl *N*-{1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl)]piperidin-4-yl}carbamate (1.7 g, 3.97 mmol) and 3,5-difluoro -1,2-diaminobenzene (0.69

g, 1.2 eq.) in DMF/H_2O (9/1 = 15 mL/1.7 mL) was stirred at 100°C for 5 days under atmospheric oxygen. The reaction was cooled to rt, diluted with H_2O (~120 mL) to form precipitates which were filtered, washed with H_2O and hexane, and dried. The solid was purified from a reverse phase C18 column chromatography to afford the title compound (0.81 g, 37%). MS $(M+H)^+$ = 553.4.

[00216] Step 1-5, preparation of 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine: To a solution of *tert*-butyl *N*-{1-[2-amino-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl}carbamate (0.8 g, 1.44 mmol) in DCM (15 mL) was added TFA (4 mL) at rt. The reaction was stirred at rt for 1 h, and then concentrated to remove the volatile solvent. The residue was purified from a reverse phase C18 column chromatography using ACN/H_2O with 0.1% TFA. The pure fractions were combined and basified to pH ~10 with sat-$NaHCO_3$. The product was precipitated in the aqueous layer during removal of the volatile ACN. The solid ppts were collected, washed with H_2O and hexane, and dried to afford the title compound (0.46 g, 70 %) as a white powder. MS $(M+H)^+$ = 453.2.

[00217] Step 1-6, preparation of HCl salt: The product described in Step 1-5 was dissolved in dioxane or DCM. The resulting solution was treated with 4N-HCl in dioxane (~2.5 eq.) and stirred for 10 min at rt. The solution was concentrated under high vacuum to give the final product as two HCl salt.

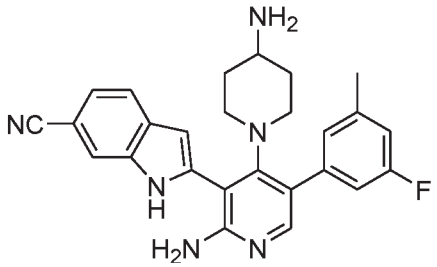
[00218] The following compounds were prepared similarly to **Example 1** with appropriate substituting reagents, solvents and substrates at different steps and they may require additional functional group modifications on benzimidazoyl side chain via well known chemistry with appropriate reagents, and different salt such as TFA or formic acid maybe obtained.

Compound no.	MS $(M+H)^+$
1-1	451.3
1-3	453.1
1-6	435.4
1-7	481.2
1-8	447.3
1-9	496.5
1-10	431.2
1-11	435.2
1-12	442.2
1-13	477.2
1-14	501.2
1-15	453.2

Compound no.	MS $(M+H)^+$
1-16	489.4
1-17	490.2
1-18	504.3
1-19	487.5
1-20	473.3
1-21	442.1
1-23	490.2
1-24	504.3
1-25	458.3
1-26	490.4
1-27	490.2
1-31	497.2
1-32	462.4
1-41	472.2
1-42	476.2
1-45	490.3
1-46	505.3
1-51	418.4
1-52	418.2
1-53	495.5
1-54	469.2
1-59	465.2
1-60	490.2
1-61	492.3
1-66	459.2
1-67	469.4
1-73	451.1
1-74	490.2
1-76	504.3
1-77	473.3
1-78	449.2
1-79	469.2
1-80	465.3
1-81	455.1
1-82	473.1
1-83	461.2
1-84	461.2
1-85	480.1
1-86	505.2
1-87	510.1
1-88	510.2
1-90	485.2
1-91	465.5
1-92	467.5
1-93	447.5
1-94	481.2
4-2	456.2

Compound no.	MS $(M+H)^+$
4-3	474.2
4-10	479.3

Example 2. 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-indole-6-carbonitrile (Compound 1-33)



[00219] Step 2-1, preparation of *tert*-butyl *N*-[1-(2-amino-5-bromopyridin-4-yl)piperidin-4-yl]carbamate: A mixture of 2-amino-5-bromo-4-fluoropyridine (0.15 g, 0.78 mmol), 4-Boc aminopiperidine (0.31 g, 2.0 eq.), and DIEA (0.33 mL, 2.5 eq.) in DMSO (3 mL) was stirred at 120 °C for 16h. The reaction was cooled to rt, and diluted with H_2O to form solid. The solid were collected, washed with H_2O and ~10% AcOH in H_2O, and dried to afford the title compound (0.23 g, 79 %). MS $(M+H)^+ = 371.1$.

[00220] Step 2-2, preparation of *tert*-butyl *N*-{1-[2-amino-5-(3-fluoro-5-methylphenyl)lpyridin-4-yl]piperidin-4-yl}carbamate: A mixture of *tert*-butyl *N*-[1-(2-amino-5-bromopyridin-4-yl)piperidin-4-yl]carbamate (0.11 g, 0.29 mmol), 3-fluoro-5-methylboronic acid (91 mg, 2.0 eq.), $PdCl_2(t\text{-}Bu_2PPhNMe_2)_2$ (21 mg, 0.03 mmol), and K_2CO_3 (82 mg, 2 eq.) in dioxane/H_2O (10/1 = 3 mL/0.3 mL) was degassed with N_2 for 5 min, and then sealed. The reaction mixture was stirred for 1.5 h at 75 °C and cooled to room temperature. The reaction was filtered through a pad of celite, and the volatile solvent was removed under vacuum. The residue was purified by column chromatography to afford the title compound (0.1 g, 83 %). MS $(M+H)^+ = 401.5$.

[00221] Step 2-3, preparation of *tert*-butyl *N*-{1-[2-amino-3-bromo-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)]piperidin-4-yl}carbamate: To a solution of *tert*-butyl *N*-{1-[2-amino-5-(3-fluoro-5-methylphenyl)lpyridin-4-yl]piperidin-4-yl}carbamate (0.1 g, 0.25 mmol) in ACN (2 mL) was added NBS (60 mg, 1.3 eq.) at room temperature. The reaction was stirred for 10 min at rt, and concentrated. The residue was purified by reverse phase C18 column chromatography to afford the title compound (73 mg, 61 %). MS $(M+H)^+ = 479.0$.

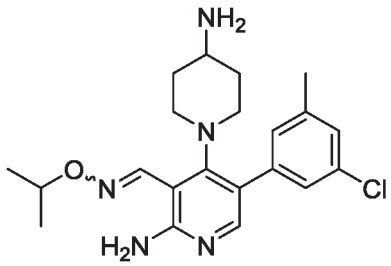
[00222] Step 2-4, preparation of *tert*-butyl *N*-{1-[2-amino-3-(6-cyano-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl}carbamate: A mixture of *tert*-butyl *N*-{1-

[2-amino-3-bromo-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)]piperidin-4-yl}carbamate (70 mg, 0.15 mmol), (6-cyano-1H-indol-2-yl)boronic acid (55 mg, 2.0 eq.), $PdCl_2$(t-$Bu_2PPhNMe_2)_2$ (21 mg, 0.029 mmol), and K_2CO_3 (42 mg, 2 eq.) in dioxane/H_2O (10/1 = 2.5 mL/0.25 mL) was degassed with N_2 for 5 min, and then sealed. The reaction mixture was stirred for 1.0 h at 80 °C and cooled to rt. The reaction was filtered through a pad of celite, and the volatile solvent was removed under vacuum. The residue was purified by column chromatography to afford the title compound (40 mg, 51 %). MS $(M+H)^+$ = 541.3.

[00223] Step 2-5, preparation of 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-indole-6-carbonitrile: To a solution of *tert*-butyl *N*-{1-[2-amino-3-(6-cyano-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl}carbamate (38 mg, 0.07 mmol) in DCM (1.5 mL) was added TFA (0.3 mL) at rt. The reaction was stirred for 1.5 h at rt, and then concentrated. The residue was purified by reverse phase C18 column chromatography to afford the title compound (16 mg, 53 %). MS $(M+H)^+$ = 441.5.

[00224] Step 2-6, preparation of HCl salt: The product described in Step 2-5 was dissolved in dioxane or DCM. The resulting solution was treated with 4N-HCl in dioxane (~2.5 eq.) and stirred for 10 min at rt. The solution was concentrated under high vacuum to give the final product as two HCl salt.

Example 3. 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-2-amine (Compound 1-37).



[00225] Step 3-1, preparation of benzyl N-[1-[2-amino-5-(3-chloro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-4-yl]piperidin-4-yl]carbamate: Into a 50-mL round-bottom flask, was placed benzyl N-[1-[2-amino-5-(3-chloro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate (45 mg, 0.09 mmol, 1.00 equiv) obtained from a similar manner described in Step 1-1 to Step 1-3 in **Example 1**, methanol (2 mL), O-(propan-2-yl)hydroxylamine hydrochloride (13 mg, 0.12 mmol, 1.20 equiv), pyridine (9 mg, 0.11 mmol, 1.20 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was

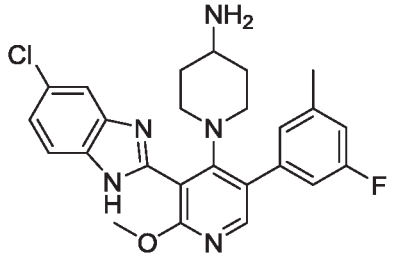
concentrated under vacuum resulting in 50 mg (99%) of the title compound as a yellow solid. MS $(M+H)^+$ = 536.2.

[00226] Step 3-2, preparation of 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-2-amine trifluoroacetate: Into a 50-mL round-bottom flask, was placed benzyl N-[1-[2-amino-5-(3-chloro-5-methylphenyl)-3-[(1E)-[(propan-2-yloxy)imino]methyl]pyridin-4-yl]piperidin-4-yl]carbamate (50 mg, 0.09 mmol, 1.0 equiv), trifluoroacetic acid (2 mL). The resulting solution was stirred for 2 hrs at 50°C in an oil bath. The resulting mixture was concentrated under vacuum. The crude product (50 mg) was purified by Prep- HPLC with the following conditions (Waters-2767): Column, X-bridge RP18, 5μm, 19 x100mm; mobile phase, A is 0.03% trifluoroacetic acid in water and B is CH_3CN (25% CH3CN up to 80% in 15 min); Detector, UV 220&254nm. This resulted in 32.6 mg (68%) of the title compound as a light yellow solid. MS $(M+H)^+$= 402.2

[00227] The following compounds either as a mixture of cis/trans isomers or only trans isomer or only cis isomer were prepared similarly to **Example 3** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
1-34	386.2
1-35	400.2
1-36	396.3
1-38	416.3
1-39	360.2
2-12	431.2

Example 4: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine (Compound 2-2)



[00228] Step 4-1, preparation of *tert*-butyl *N*-[1-(3-formyl-2-methoxypyridin-4-yl)piperidin-4-yl]carbamate: A mixture of 4-chloro-3-formyl-2-methoxypyridine (0.43 g, 2.51 mmol), 4-Boc-aminopiperidine (0.7 g, 3.5 mmol), and DIEA (1.0 mL, 2.5 eq.) in ACN (14 mL) was stirred at 100 °C for 40 min. After removal of the volatile solvent, the residue was purified by column chromatography to afford the title compound (0.84 g, 100%). MS $(M+H)^+$: 336.5.

[00229] Step 4-2, preparation of *tert*-butyl *N*-[1-(5-bromo-3-formyl-2-methoxypyridin-4-yl)piperidin-4-yl]carbamate: To a solution of *tert*-butyl *N*-[1-(3-formyl-2-methoxypyridin-4-yl)piperidin-4-yl]carbamate (0.29 g, 0.86 mmol) in ACN (12 mL) was added NBS (0.2 g, 1.13 mmol) at room temperature. The reaction was completed within 20 min, and the product was formed as precipitates during the course of reaction. The solid was filtered, washed with ACN and hexane, and dried to afford the title compound (0.27 g, 77%). MS $(M+H)^+$ = 414.2.

[00230] Step 4-3, preparation of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-methoxypyridin-4-yl)]piperidin-4-yl}carbamate: The title compound was prepared by a similar manner described in Step 1-3 in **Example 1**. MS $(M+H)^+$= 444.4.

[00231] Step 4-4, preparation of N-[1-[3-(3-fluoro-5-methylphenyl)-5-[[(2-methylpropoxy)imino] methyl]pyridin-4-yl]piperidin-4-yl]carbamate: A mixture of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-methoxypyridin-4-yl)]piperidin-4-yl}carbamate (85 mg, 0.19 mmol), 4-chloro-1,2-diaminobenzene (30 mg, 1.1 eq.) in DMF/H_2O (9/1 = 1.5 mL/0.16 mL) was stirred at 90 °C overnight under atmospheric oxygen. The reaction was directly purified by reverse phase C18 column chromatography to afford the title compound (75 mg, 75%). MS $(M+H)^+$= 566.4.

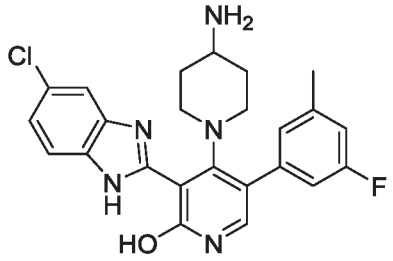
[00232] Step 4-5, preparation of 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine: The title compound was prepared by a similar manner described in Step 1-5 for **Example 1**. MS $(M+H)^+$= 466.3.

[00233] Step 4-6, preparation of AcOH salt: The product as free base described in Step 4-5 was dissolved in ACN or DCM. The resulting solution was treated with AcOH (~2.0 eq.) and stirred for 10 min at room temperature. The solution was concentrated under high vacuum to give the final product as AcOH salt.

[00234] The following compounds were prepared similarly to **Example 4** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
2-1	450.2
2-3	462.4
2-5	468.4
2-6	473.2
2-8	457.2
2-9	467.0
2-13	467.4
2-14	470.2

Example 5: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol (Compound 2-4)

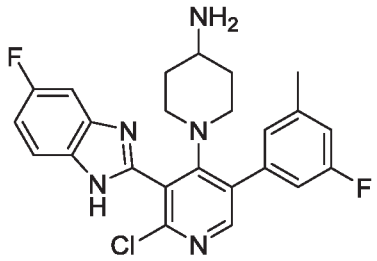


[00235] Step 5-1, preparation of 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol: To a solution of 1-[3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine (20 mg, 0.04 mmol) in dioxane (1 mL) was added 4N HCl (53 μL, 5 eq.). The reaction was stirred for 2hrs at 70 °C. After removal of the volatile solvent, the residue was purified by reverse phase C18 column chromatography to afford the title compound (6.5 mg, 34 %). MS $(M+H)^+$= 452.3.

[00236] The following compounds were prepared similarly to **Example 5** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
2-7	454.2
2-10	436.3

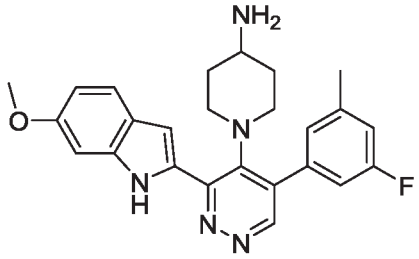
Example 6: 1-[2-chloro-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-amine (Compound 2-11)



[00237] Step 6-1, preparation of 1-[2-chloro-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5- methylphenyl)pyridin-4-yl]piperidin-4-amine: A suspension of 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol (180 mg, 0.41 mmol) in $POCl_3$ (3.5 mL) was refluxed for 2.5 h. The reaction was cooled to rt and carefully poured into an ice. The reaction was bascified with 50%-NaOH and extracted with DCM (3x). The combined organic layers were washed

with brine (1x), dried, and concentrated. The residue was purified by reverse phase C18 column chromatography to afford the title compound (26 mg, 14 %). MS $(M+H)^+$= 454.3.

Example 7: 1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-amine (Compound 3-5)



[00238] Step 7-1, preparation *tert*-butyl *N*-[1-(5-chloro-3-hydroxypyridazin-4-yl)piperidin-4-yl]carbamate: To a mixture of 4,5-dichloropyridazin-3-ol (10.00 g, 60.61 mmol) and *tert*-butyl *N*-(piperidin-4-yl)carbamate (14.57 g, 72.73 mmol) under nitrogen was added dioxane (200 mL) and $NaHCO_3$ (7.64 g, 90.92 mmol). The mixture was heated at reflux for 1 d. The mixture was concentrated *in vacuo* and the residue (slurry) was triturated with DCM. The first solid was collected by vacuum filtration to give more polar undesired *tert*-butyl *N*-[1-(5-chloro-6-hydroxypyridazin-4-yl)piperidin-4-yl]carbamate. The filtrate was concentrated *in vacuo* to dryness and triturated with MeOH. The second solid was collected by vacuum filtration to give less polar desired product. With filtrate, the above DCM or MeOH trituration procedure was repeated to obtain more product. The reaction overall afforded desired product (9.81 g, 49.2 % yield) as a light yellow solid. MS $(M+H)^+$= 329.3.

[00239] Step 7-2, preparation of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-hydroxypyridazin-4-yl]piperidin-4-yl}carbamate: To a mixture of *tert*-butyl *N*-[1-(5-chloro-3-hydroxypyridazin-4-yl)piperidin-4-yl]carbamate (4.00 g, 12.17 mmol), (3-fluoro-5-methylphenyl)boronic acid (3.748 g, 24.34 mmol), $Pd[t\text{-}Bu_2P(4\text{-}NMe_2C_6H_4)]_2Cl_2$) (0.86 g, 1.22 mmol), and K_2CO_3 (5.41 g, 39.12 mmol) in a sealed tube was added dioxane (40 mL) and water (4.0 mL). The mixture was bubbled with N_2 (g) for 10 min and then heated at 100°C for 2 hrs. The mixture was concentrated *in vacuo* to dryness and purified by silica gel column chromatography to afford the title compound (2.81 g, 57.3 % yield) as an off-white solid. MS $(M+H)^+$= 403.5.

[00240] Step 7-3, preparation of *tert*-butyl *N*-{1-[3-chloro-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-yl}carbamate: To *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-hydroxypyridazin-4-yl]piperidin-4-yl}carbamate (2.81 g, 6.97 mmol) was added $POCl_3$ (20 mL, 0.214 mol) and the mixture was heated at reflux for 2 hrs. The mixture

was carefully poured into an ice and stirred overnight. The mixture was then basified with NaOH (ca. 45 g) in an ice bath, followed by the addition of MeOH (20 mL) and Boc_2O (3 mL). After stirring at rt for 30 min, the mixture was concentrated in vacuo to dryness and purified by silica gel column chromatography to give the title compound (1.36 g, 46.2 % yield) as a light yellow solid. MS $(M+H)^+$= 421.3.

[00241] Step 7-4, preparation of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-yl}carbamate: To a mixture of *tert*-butyl *N*-{1-[3-chloro-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-yl}carbamate (100.0 mg, 0.24 mmol), 6-methoxy-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (130.0 mg, 0.48 mmol), $Pd[t\text{-}Bu_2P(4\text{-}NMe_2C_6H_4)]_2Cl_2$) (16.9 mg, 0.024 mmol), and K_2CO_3 (98.7 mg, 0.71 mmol) in a sealed tube was added dioxane (5 mL) and water (0.5 mL). The mixture was bubbled with N_2 for 10 min and then heated at 100°C for 1 h. The mixture was concentrated and purified by silica gel column chromatography to give the title compound (59.2 mg, 46.6 % yield) as a yellow solid. MS $(M+H)^+$= 532.3.

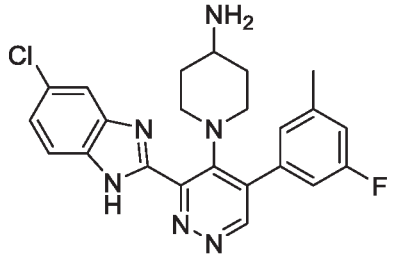
[00242] Step 7-5, preparation of 1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-amine dihydrochloride: To a solution of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-yl}carbamate (59.2 mg, 0.111 mmol) in DCM (0.8 mL) was added TFA (0.2 mL). The mixture was stirred at RT for 30 min. The mixture was concentrated in vacuo and the residue was purified by C_{18} reversed-phase column chromatography. Pure fractions were combined, basified with saturated $NaHCO_3$ (aq) and concentrated to remove MeCN. The aqueous residue was extracted with DCM (3X) and the combined organics were dried over anhydrous Na_2SO_4 and concentrated to give neutral product which was triturated with 2 *N* HCl in ether (0.2 mL) to give 2 HCl salt of the title compound (47.1 mg, 0.0934 mmol, 84.1 % yield) as a golden yellow solid. MS $(M+H)^+$= 432.4.

[00243] The following compounds were prepared similarly to **Example 7** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
3-1	436.4
3-2	436.3
3-4	420.4
3-6	436.1
3-7	435.8
3-8	420.3
3-9	431.9
3-11	466.1

Compound no.	MS $(M+H)^+$
3-12	427.1
3-15	470.5
3-16	415.9
3-17	427.4
3-18	460.1
3-19	445.3
3-20	475.2
3-23	427.2

Example 8: 1-[3-(5-chloro-1*H*-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine (compound 3-3)



[00244] Step 8-1, preparation of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-[(*E*)-2-phenylethenyl]pyridazin-4-yl]piperidin-4-yl}carbamate: The title compound was prepared as a yellow solid using a similar method to the one described in **Example 7**, Step 7-3. MS $(M+H)^+$= 489.4.

[00245] Step 8-2, preparation of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-formylpyridazin-4-yl]piperidin-4-yl}carbamate: To a solution of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-[(*E*)-2-phenylethenyl]pyridazin-4-yl]piperidin-4-yl}carbamate (161.9 mg, 0.33 mmol) in a mixed solvent of dioxane (5 mL) and water (1 mL) was added a solution of OsO_4 (8.4 mg, 0.03 mml) in *t*-BuOH (0.4 mL), followed by sodium periodate (389.4 mg, 1.82 mmol). The mixture was stirred at RT overnight. The mixture was diluted with water and extracted with EtOAc (2X). The combined organics were concentrated in vacuo to dryness and the residue was purified by silica gel column chromatography to give the title compound (120.0 mg, 87.6 % yield) as a brown gum.

[00246] Step 8-3, preparation of *tert*-butyl *N*-{1-[3-(5-chloro-1*H*-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-yl}carbamate: To a solution of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-formylpyridazin-4-yl]piperidin-4-yl}carbamate (120.0 mg, 0.29 mmol) in a mixed solvent of DMF (6 mL) and water (0.6 mL) was added 4-chlorobenzene-1,2-diamine (62.0 mg, 0.435 mmol). The mixture was heated at 80°C over the weekend. The mixture was concentrated to a half volume and purified by C18 reversed-phase

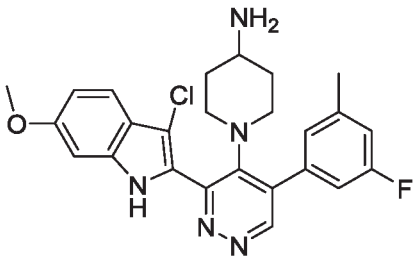
column chromatography. Pure fractions were combined, basified with saturated $NaHCO_3$ (aq) and concentrated to remove MeCN. The aqueous residue was extracted with DCM (3X) and the combined organics were dried over anhydrous Na_2SO_4 and concentrated to give the title compound (86.4 mg, 55.5 % yield) as a light brown solid. MS $(M+H)^+$= 537.5.

[00247] Step 8-4, preparation of 1-[3-(5-chloro-1*H*-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine dihydrochloride: The title compound was prepared as a yellow solid using a similar method to the one described in **Example 7**, Step 7-5. MS $(M+H)^+$= 437.3.

[00248] The following compounds were prepared similarly to **Example 8** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
3-10	433.2
3-13	420.8
3-22	428.3

Example 9: 1-[3-(3-chloro-6-methoxy-1*H*-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine (compound 3-21)



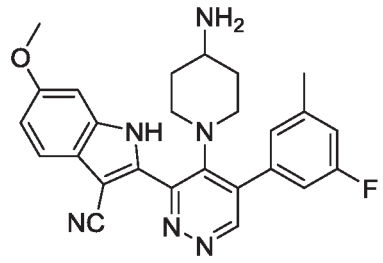
[00249] Step 9-1, preparation of *tert* -butyl *N*-{1-[3-(3-chloro-6-methoxy-1*H*-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-yl}carbamate: To a solution of *tert*-butyl *N*-{1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-yl}carbamate (from Example 6, Step 6-4) (126.0 mg, 0.24 mmol) in DMF (4 mL) was added NCS (63.3 mg, 0.47 mmol). The mixture was stirred at for 10 min. Very little product was shown and thus more NCS (31.6 mg, 0.24 mmol) were added and the reaction was continued to stir at rt for 10 min. Unreacted starting material was still remained but the reaction was stopped by quenching with water and saturated $Na_2S_2O_3$ (aq). The mixture was extracted with EtOAc (2X) and the combined organics were concentrated in vacuo to dryness. The residue was purified by silica gel column chromatography to give the title compound (69.5 mg, 51.9 % yield). MS $(M+H)^+$= 566.5.

[00250] Step 9-2, preparation of 1-[3-(3-chloro-6-methoxy-1*H*-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine dihydrochloride: The title compound was prepared as a yellow solid using a similar method to the one described in **Example 7**, Step 7-5. MS $(M+H)^+$= 466.2.

[00251] The following compounds were prepared similarly to **Example 9** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
3-14	470.1
3-24	461.2

Example 10: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-6-methoxy-1*H*-indole-3-carbonitrile (Compound 3-25)



[00252] Step 10-1, preparation of 2-[1-(5-chloro-3-hydroxypyridazin-4-yl)piperidin-4-yl]-2,3-dihydro-1*H*-isoindole-1,3-dione: The title compound was prepared as a light yellow solid using a similar method to the one described in **Example 6**, Step 6-1. MS $(M+H)^+$= 358.8.

[00253] Step 9-2, preparation of 2-{1-[5-(3-fluoro-5-methylphenyl)-3-hydroxypyridazin-4-yl]piperidin-4-yl}-2,3-dihydro-1*H*-isoindole-1,3-dione: The title compound was prepared as a light yellow solid using a similar method to the one described in **Example 7**, Step 7-2. MS $(M+H)^+$= 433.2.

[00254] Step 10-3, preparation of 2-{1-[3-chloro-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-yl}-2,3-dihydro-1*H*-isoindole-1,3-dione: To 2-{1-[5-(3-fluoro-5-methylphenyl)-3-hydroxypyridazin-4-yl]piperidin-4-yl}-2,3-dihydro-1*H*-isoindole-1,3-dione (325 mg, 0.91mmol) was added $POCl_3$ (3 mL) and the mixture was heated at reflux for 1 hr. The mixture was carefully poured into an ice and the solid was collected by vacuum filtration and washed with water to give the title compound (379.4 mg, 92.8 %) as a yellow solid. MS $(M+H)^+$= 451.1.

[00255] Step 10-4, preparation of 2-{1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-yl}-2,3-dihydro-1*H*-isoindole-1,3-dione: The title

compound was prepared as a brown solid using a similar method to the one described in **Example** 7, Step 7-4. MS $(M+H)^+$= 562.4.

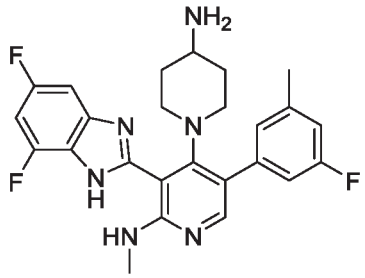
[00256] Step 10-5, preparation of 2-{4-[4-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)piperidin-1-yl]-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl}-6-methoxy-1*H*-indole-3-carbonitrile: To a suspension of 2-{1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-yl}-2,3-dihydro-1*H*-isoindole-1,3-dione (48.0 mg, 0.09 mmol) in a mixed solvent of DMF (0.5 mL) and MeCN (5 mL) at 0°C was added a solution of chlorosulfonylisocyanate (0.020 mL) in MeCN (0.2 mL). The mixture was stirred at rt for 30 min. The mixture was poured into ice-water, basified with saturated $NaHCO_3$ (aq) and extracted with EtOAc (2X). The combined organics were concentrated in vacuo and the residue was purified by silica gel column chromatography to give the title compound (21.8 mg, 43.5 %) as a brown solid. MS $(M+H)^+$= 586.6.

[00257] Step 10-6, preparation of 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-6-methoxy-1*H*-indole-3-carbonitrile dihydrochloride: To a suspension of 2-{1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1*H*-indol-2-yl)pyridazin-4-yl]piperidin-4-yl}-2,3-dihydro-1*H*-isoindole-1,3-dione (21.8 g, 0.0372 mmol) in EtOH (2 mL) in a sealed tube was added hydrazine monohydrate (5 drops) and the mixture was heated at 80°C for 30 min. The mixture was cooled to rt and concentrated. The residue was purified by C18 reversed-phase column chromatography. Pure fractions were combined, basified with saturated $NaHCO_3$ (aq) and concentrated to remove MeCN. The aqueous residue was extracted with DCM (3X) and the combined organics were dried over anhydrous Na_2SO_4 and concentrated to give the neutral compound which was triturated with 2 *N* HCl in ether (0.2 mL) to give 2 HCl salt of the title compound (9.0 mg, 45.7 %) as a yellow solid. MS $(M+H)^+$= 457.4.

[00258] The following compounds were prepared similarly to **Example 10** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
3-26	452.3

Example 11 : 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine (Compound 1-48)



[00259] Step 11-1, preparation of tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-(methylamino)pyridin-4-yl]piperidin-4-yl]carbamate: into a 50-mL round-bottom flask, was placed tert-butyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate (500 mg, 1.17 mmol, 1.00 equiv), sodium hydroxide (140 mg, 3.50 mmol, 3.00 equiv), N,N-dimethylformamide (5 mL), CH_3I (200 mg, 1.41 mmol, 1.20 equiv). The resulting solution was stirred for 30 min at 50 °C. The crude product was further purified by Prep-HPLC with the following conditions (Waters I): Column, X bridge Prep C18 OBD column, 5μm, 19x150mm; mobile phase, Water with 0.1% NH_4OH and CH_3CN (45% CH_3CN up to 85% in 13 min); Detector, UV 220 & 254 nm, which resulted in 165 mg (32%) of the title compound as a light yellow solid. MS $(M+H)^+$= 443.2. The position of methylation was confirmed by a NMR NOE experiment.

[00260] Step 11-2, preparation of tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylamino)pyridin-4-yl]piperidin-4-yl]carbamate: into a 50-mL round-bottom flask, was placed tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-(methylamino)pyridin-4-yl]piperidin-4-yl]carbamate (165 mg, 0.37 mmol, 1.00 equiv), $Na_2S_2O_5$ (142 mg, 2.00 equiv), NMP (3 mL), water(0.3 mL), 3,5-difluorobenzene-1,2-diamine (165 mg, 1.14 mmol, 3.00 equiv). The resulting solution was stirred for 8 h at 100 °C. The crude product was further purified by Prep-HPLC with the following conditions (Waters I): Column, X bridge Prep C18 OBD column, 5um, 19 x150mm; mobile phase, Water (0.05% TFA) and CH_3CN (5% CH_3CN up to 55% in 12 min); Detector, UV 220 & 254 nm to afford 60 mg (28%) of the title compound as a brown solid. MS $(M+H)^+$= 567.5.

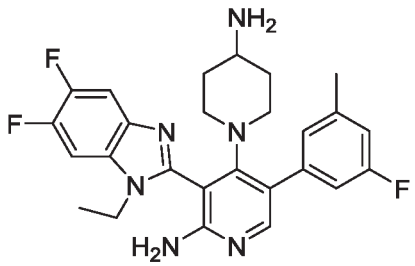
[00261] Step 11-3, preparation of 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine hydrochloride: into a 50-mL round-bottom flask, was placed tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylamino)pyridin-4-yl]piperidin-4-yl]carbamate (60 mg, 0.11 mmol, 1.00 equiv), dichloromethane (1.5 mL), trifluoroacetic acid (0.5 mL). The resulting solution was stirred for 1 h at 25 °C and then concentrated under vacuum. 5 mL 1M HCl was added to the residue and the mixture was freeze-dried, which

resulted in 49.0 mg (92%) of the title compound as a brown solid. MS $(M+H)^+$= 467.2. H^1-NMR (300 MHz, CD_3OD, ppm): δ 7.64 (s, 1H), 7.37 (d, 1H), 7.18 (s, 1H), 7.14 – 7.06 (m, 3H), 3.37 – 3.34 (m, 1H), 3.28 – 3.24 (m, 1H), 3.03 (m, 4H), 2.61 – 2.52 (m, 2H), 2.48 (s, 3H), 1.64 – 1.57 (m, 2H), 1.25 – 1.18 (m, 2H).

[00262] The following compounds were prepared similarly to **Example 11** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
1-28	465.2
1-30	479.2
1-49	481.3
1-50	481.3
1-55	467.2
1-70	456.2
1-71	461.2
1-72	465.1
1-75	483.2
1-89	474.2
4-1	479.2

Example 12: 4-(4-aminopiperidin-1-yl)-3-(1-ethyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine (compound 1-5)



[00263] Step 12-1, preparation of tert-butyl N-(4-chloro-3-formylpyridin-2-yl)carbamate: into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl N-(4-chloropyridin-2-yl)carbamate (15.0 g, 65.60 mmol, 1.00 equiv), anhydrous tetrahydrofuran (300 mL). This was followed by the addition of n-BuLi (2.5 M, 55.1 mL, 2.00 equiv) dropwise with stirring at -78 °C in 30 min, followed by addition of N,N-dimethylformamide (15.1 mL, 3.00 equiv) dropwise with stirring at -78 °C in 5 min. The resulting solution was stirred for another 1 h at -78 °C and then carefully quenched with 300 mL of ammonium chloride saturated solution. The mixture was extracted with 3x300 mL of ethyl acetate and combined organics were washed with 3x100 mL of water and dried over anhydrous sodium sulfate. After filtration to remove the solid, the solution was concentrated under vacuum and the residue was purified by silica gel column

chromatography eluted with ethyl acetate/petroleum ether to give 12.0 g (71%) of the title compound as a light yellow solid. MS $(M+H)^+$= 257.1.

[00264] Step 12-2, preparation of benzyl N-[1-(2-amino-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: into a 250-mL round-bottom flask, was placed tert-butyl N-(4-chloro-3-formylpyridin-2-yl)carbamate (8.1 g, 31.56 mmol, 1.00 equiv), benzyl N-(piperidin-4-yl)carbamate (8.1 g, 34.57 mmol, 1.10 equiv), DIEA (12.2 g, 94.40 mmol, 3.00 equiv), ACN (100 mL). The resulting solution was stirred for 16 h at 85 °C and then concentrated under vacuum. The residue was purified by a silica gel column chromatagraph elted with ethyl acetate/petroleum ether (1:3) to afford 4.6 g (41%) of the title compound as a yellow solid. MS $(M+H)^+$= 355.2.

[00265] Step 12-3, preparation of benzyl N-[1-(2-amino-5-bromo-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: into a 100-mL round-bottom flask, was placed benzyl N-[1-(2-amino-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (4.5 g, 12.70 mmol, 1.00 equiv), NBS (2.9 g, 16.29 mmol, 1.30 equiv), DCE (50 mL). The resulting solution was stirred for 40 min at 85 °C and then concentrated. The residue was purified by silica gel column chromatography eluted with ethyl acetate/petroleum ether to afford 3.9 g (71%) of the title compound as a yellow solid. MS $(M+H)^+$= 433.1/435.1.

[00266] Step 12-4, preparation of benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate: into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed benzyl N-[1-(2-amino-5-bromo-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (3.9 g, 9.00 mmol, 1.00 equiv), (3-fluoro-5-methylphenyl)boronic acid (2.8 g, 18.19 mmol, 2.00 equiv), $Pd_2(dba)_3$ (200 mg, 0.22 mmol, 0.02 equiv), *t*-Bu_3P (400 mg), K_3PO_4 (5.7 g, 3.00 equiv), THF (50 mL), water(10 mL). The resulting solution was stirred for 2 hrs at 30 °C, diluted with 200 mL of H_2O and then extracted with 3x200 mL of ethyl acetate. The organics were dried over anhydrous sodium sulfate. After filtration to remove the solids, the solution was concentrated under vacuum and the resulted crude was purified by silica gel column chromatography eluted with ethyl acetate/petroleum ether (3:1 to yield 3.1 g (74%) of the title compound as a light yellow solid. MS $(M+H)^+$= 463.2.

[00267] Step 12-5, preparation of benzyl N-[1-[2-amino-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl]carbamate : into a 100-mL 3-necked round-bottom flask, was placed benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate (2.0 g, 4.32 mmol, 1.00 equiv), 4,5-difluorobenzene-1,2-diamine (3.1 g, 21.51 mmol, 5.00 equiv), N,N-dimethylformamide

(50 mL), water (5 mL). The resulting solution was stirred for 48 h at 100 °C. The resulting solution was diluted with 200 mL of H_2O, extracted with 3x200 mL of ethyl acetate and ethyl acetate layer was washed with 3x100 mL of brine and dried over anhydrous sodium sulfate. The solids were filtered out and the resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography eluted with ethyl acetate/petroleum ether to produce 1.8 g (71%) of the title compound as a brown solid. MS $(M+H)^+$= 587.1.

[00268] Step 12-6, preparation of benzyl N-[1-[2-amino-3-(1-ethyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl]carbamate : into a 8-mL sealed tube, was placed benzyl N-[1-[2-amino-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl]carbamate (180 mg, 0.31 mmol, 1.00 equiv), sodium hydroxide (37 mg, 0.93 mmol, 3.00 equiv), N,N-dimethylformamide (2 mL), iodoethane (96 mg, 0.62 mmol, 2.00 equiv). The resulting solution was stirred for 1 h at 50 °C, then diluted with 100 mL of H_2O. The mixture was extracted with 3x100 mL of ethyl acetate and the ethyl acetate layer was washed with 3x100 mL of brine, then dried over anhydrous sodium sulfate. The resulting mixture after filtration to remove solids was concentrated under vacuum and purified by Pre-TLC (PE : EA = 1 : 1), to afford 120 mg (64%) of the title compound as a brown solid. MS $(M+H)^+$= 615.3.

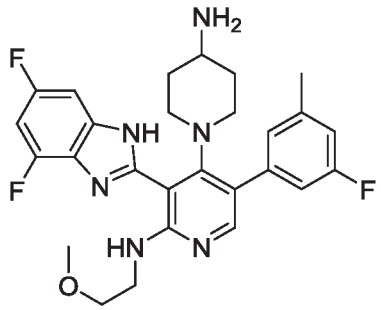
[00269] Step 12-7, preparation of 4-(4-aminopiperidin-1-yl)-3-(1-ethyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine dihydrochloride : into a 50-mL round-bottom flask, was placed benzyl N-[1-[2-amino-3-(1-ethyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl]carbamate (120 mg, 0.20 mmol, 1.00 equiv), trifluoroacetic acid (5 mL). The resulting solution was stirred for 2 h at 50 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC which produced 65 mg (60%) of the title compound as a off-white solid. MS $(M+H)^+$= 481.2. H-NMR (300 MHz, DMSO-d_6, ppm): δ 8.23 (m, 3H), 8.11 – 7.81 (m, 3H), 7.42 (m, 2H), 7.10 (m, 3H), 4.55 (m, 1H), 3.98 (m, 1H), 3.24 (m, 1H), 3.00 (m, 1H), 2.84 (m, 1H), 2.57 (m, 1H), 2.40 (s, 3H), 2.21 (t, J = 12.1 Hz, 1H), 1.52 (m, 1H), 1.41 – 0.98 (m, 6H), 0.59 (m, J = 12.9 Hz, 1H).

[00270] The position of ethyl was confirmed by a NMR NOE experiment.

[00271] The following compounds were prepared similarly to **Example 12** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
1-29	465.2
1-57	467.2

Example 13: 3-(4,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-(2-methoxyethyl)-4-(4-methylpiperidin-1-yl)pyridin-2-amine (compound 1-56)



[00272] Step 13-1, preparation of tert-butyl N-[1-(2-chloro-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: into a 40-mL round-bottom flask, was placed 2,4-dichloropyridine-3-carbaldehyde (2.0 g, 11.36 mmol, 1.00 equiv), tert-butyl N-(piperidin-4-yl)carbamate (2.3 g, 11.48 mmol, 1.00 equiv), TEA (3.5 g, 34.59 mmol, 3.00 equiv), N,N-dimethylformamide (10 mL). The resulting solution was stirred for 1 h at 40°C and then quenched with 50 mL water. The crude product was extracted out by 3x20 mL of ethyl acetate and ethyl acetate layer was washed with 4x20 mL of brine, then dried over anhydrous sodium sulfate. The solids were filtered out. The resulting mixture was concentrated and purified by silica gel column chromatography eluted with ethyl acetate/petroleum ether (1:3) to afford 3.2 g (83%) of the title compound as a yellow solid. MS $(M+H)^+$= 340.1/342.1.

[00273] Step 13-2, preparation of tert-butyl N-[1-[3-formyl-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate: into a 40-mL round-bottom flask, was placed tert-butyl N-[1-(2-chloro-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (2.0 g, 5.89 mmol, 1.00 equiv), tetrahydrofuran (20 mL), (methylsulfanyl)sodium (500 mg, 7.13 mmol, 1.20 equiv). The resulting solution was stirred for 4 hrs at 70 °C, then cooled to room temperature, quenched with 20 mL of water. The crude was extracted with 3x20 mL of ethyl acetate and ethyl acetate was washed with 3x20 mL of brine, then dried over anhydrous sodium sulfate and concentrated under vacuum, which resulted in 1.6 g (77%) of the title compound as a yellow solid. MS $(M+H)^+$= 352.2.

[00274] Step 13-3, preparation of tert-butyl N-[1-[5-bromo-3-formyl-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate: into a 40-mL round-bottom flask, was placed tert-butyl N-[1-[3-formyl-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate (1.5 g, 4.27 mmol, 1.00 equiv), DCE (20 mL), NBS (1.2 g, 6.74 mmol, 1.50 equiv). The resulting solution was stirred for 1 h at 80°C, then cooled to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column

chromatography eluted with ethyl acetate/petroleum ether to afford 1.2 g (65%) of the title compound as a yellow solid. MS $(M+H)^+$= 429.9/431.9.

[00275] Step 13-4, preparation of tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate: into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl N-[1-[5-bromo-3-formyl-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate (1.0 g, 2.32 mmol, 1.00 equiv), (3-fluoro-5-methylphenyl)boronic acid (546 mg, 3.55 mmol, 1.50 equiv), K_3PO_4 (1.5 g, 7.07 mmol, 3.00 equiv), $Pd_2(dba)_3.CHCl_3$ (240 mg, 0.10 equiv), $P(t\text{-}Bu)_3.BHF_4$ (135 mg, 0.20 equiv), toluene (15 mL), water (1.5 mL). The resulting solution was stirred for 2 hrs at 80 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether which resulted in 700 mg (66%) of the title compound as a yellow solid. MS $(M+H)^+$= 460.2.

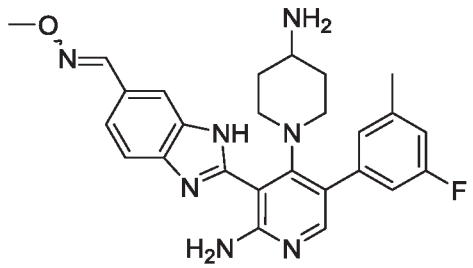
[00276] Step 13-5, preparation of tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate: into a 8-mL round-bottom flask, was placed tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate (200 mg, 0.44 mmol, 1.00 equiv), 3,5-difluorobenzene-1,2-diamine (184 mg, 1.28 mmol, 3.00 equiv), $Na_2S_2O_5$ (166 mg, 2.00 equiv), NMP (3 mL). The resulting solution was stirred for 48 h at 120 °C. The reaction was then quenched with 10 mL of water and extracted with 3x10 mL of ethyl acetate. Combined organics were washed with 3x10 mL of water and dried over anhydrous sodium sulfate. The solids were filtered out and resulting solutuon was concentrated under vacuum. The residue was purified by silica gel column chromatography eluted with ethyl acetate/petroleum ether (1:4) to yield 200 mg (79%) of the title compound as a yellow solid. MS $(M+H)^+$= 584.3.

[00277] Step 13-6, preparation of tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methanesulfinylpyridin-4-yl]piperidin-4-yl]carbamate: into a 50-mL round-bottom flask, was placed tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylsulfanyl)pyridin-4-yl]piperidin-4-yl]carbamate (200 mg, 0.34 mmol, 1.00 equiv), dichloromethane (10 mL), m-CPBA (73.3 mg, 0.42 mmol, 1.20 equiv). The resulting solution was stirred for 1 h at rt and then diluted with 10 mL of water. The crude was extracted out with 3x10 mL of ethyl acetate and ethyl acetate was washed with 3x10 mL of brine and dried over anhydrous sodium sulfate. The solids were filtered out and the resulting mixture was concentrated under vacuum resulted in 200 mg (97%) of the title compound as a gray solid. MS $(M+H)^+$= 600.3.

[00278] Step 13-7, preparation of tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-[(2-methoxyethyl)amino]pyridin-4-yl]piperidin-4-yl]carbamate: into a 8-mL round-bottom flask, was placed tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methanesulfinylpyridin-4-yl]piperidin-4-yl]carbamate (80 mg, 0.13 mmol, 1.00 equiv), 2-methoxyethan-1-amine (1 mL). The resulting solution was stirred for 12 hrs at 100 °C. After concentration, the crude was purified by Prep-TLC with ethyl acetate/petroleum ether (1:20) to afford 50 mg (61%) of the title compound as a light yellow solid. MS $(M+H)^+$= 611.4.

[00279] Step 13-8, preparation of 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-(2-methoxyethyl)pyridin-2-amine: into a 50-mL round-bottom flask, was placed tert-butyl N-[1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-[(2-methoxyethyl)amino]pyridin-4-yl]piperidin-4-yl]carbamate (50 mg, 0.08 mmol, 1.00 equiv), dichloromethane (5 mL), trifluoroacetic acid (1 mL). The resulting solution was stirred for 1 h at rt. The mixture was then concentrated under vacuum. The crude was purified by Prep-HPLC with the following conditions (Prep-HPLC-013): Column, SunFire Prep C18 OBD Column, 19x150mm 5um 10nm; mobile phase, Water (0.05% TFA) and ACN (11.0% ACN up to 23.0% in 6 min, hold 95.0% in 1 min, hold 11.0% in 1 min); Detector, 220 nm to produce 33.8 mg (66%) of the title compound as a off-white solid of trifluoroacetic acid salt. MS $(M+H)^+$= 511.3. ^{1}H NMR (300MHz, DMSO-d_6, ppm): δ ,7.77 (s, 1H), 7.72 (s, 3H), 7.32-7.29 (m, 1H), 7.23–7.00(m, 4H), 3.50 (s, 2H), 3.45-3.43 (m 2H), 3.23 (s, 3H), 3.03-2.99 (m, 2H), 2.90-2.88 (s, 1H), 2.41 (s, 3H), 2.36-2.28 (m, 2H), 1.47-1.43 (m, 2H), 1.03-1.06 (m, 2H).

Example 14: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{6-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine (1-40)



[00280] Step 14-1, preparation of methyl 2-[2-amino-4-(4-[[(benzyloxy)carbonyl]amino]piperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-6-carboxylate: into a 40-mL round-bottom flask, was placed benzyl N-[1-

[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate (400 mg, 0.86 mmol, 1.00 equiv), methyl 3,4-diaminobenzoate (575 mg, 3.46 mmol, 4.00 equiv), $Na_2S_2O_5$ (329 mg, 2.00 equiv), NMP (10 mL). The resulting solution was stirred for 48 h at 120 °C. The resulting solution was diluted with 20 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 3x20 mL of water. The resulting mixture was washed with 3x20 mL of brine, dried over anhydrous sodium sulfate. Then solids were filtered out and the solution was concentrated under vacuum and the crude was chromatagraphied via a silica gel column eluted with ethyl acetate/petroleum ether (4:1) to afford 240 mg (46%) of the title compound as a brown solid. MS $[M+H]^+$=609.0.

[00281] Step 14-2, preparation of benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-[6-(hydroxymethyl)-1H-1,3-benzodiazol-2-yl]pyridin-4-yl]piperidin-4-yl]carbamate: into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl 2-[2-amino-4-(4-[[(benzyloxy)carbonyl]amino]piperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-6-carboxylate (120 mg, 0.20 mmol, 1.00 equiv), tetrahydrofuran (20 mL). This was followed by the addition of $LiAlH_4$ (27 mg, 0.71 mmol, 3.00 equiv), in portions at 0 °C. The resulting solution was stirred for 1 h at room temperature and then quenched with 10 mL of water. The mixture was extracted with 2x20 mL of ethyl acetate and combined organic layer was washed with 3x20 mL of water and then dried over anhydrous sodium sulfate. After filtration to remove the solid, resulted solution was concentrated and the residue was applied onto a silica gel column with dichloromethane/methanol resulted in 35.0 mg (31%) of the title compound as a light yellow solid. MS: $[M+H]^+$=581.3.

[00282] Step 14-3, preparation of benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-(6-formyl-1H-1,3-benzodiazol-2-yl)pyridin-4-yl]piperidin-4-yl]carbamate: into a 8-mL round-bottom flask, was placed benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-[6-(hydroxymethyl)-1H-1,3-benzodiazol-2-yl]pyridin-4-yl]piperidin-4-yl]carbamate (35 mg, 0.06 mmol, 1.00 equiv), CH_3CN (5 mL), IBX (34 mg, 0.12 mmol, 2.00 equiv). The resulting solution was stirred for 24 h at room temperature and then 10 mL of water was added and the mixture was extracted with 3x10 mL of ethyl acetate and the combined ethyl acetate was washed with 3x10 mL of water, then dried over anhydrous sodium sulfate. After filtration to remove solid, the resulting solution was concentrated under vacuum to yield 30 mg (86%) of the title compound as a yellow solid. MS: $[M+H]^+$=579.2.

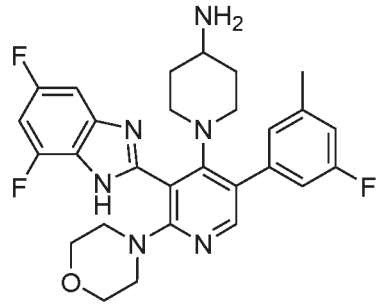
[00283] Step 14-4, preparation of benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-[6-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl]pyridin-4-yl]piperidin-4-yl]carbamate: into a 8-mL round-bottom flask, was placed benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-(6-formyl-5,6-dihydro-1H-1,3-benzodiazol-2-yl)pyridin-4-yl]piperidin-4-yl]carbamate (30 mg, 0.05 mmol, 1.00 equiv), O-methylhydroxylamine hydrochloride (13 mg, 0.16 mmol, 3.00 equiv), methanol (2 mL), pyridine (8.2 mg, 0.10 mmol, 2.00 equiv). The resulting solution was stirred for 5 h at room temperature and then concentrated under vacuum to yield 35 mg of the title compound as a crude yellow solid. MS: $[M+H]^+$=608.3.

[00284] Step 14-5, preparation of 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[6-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl]pyridin-2-amine: into a 8-mL round-bottom flask, was placed benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-[6-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl]pyridin-4-yl]piperidin-4-yl]carbamate (35 mg, 0.06 mmol, 1.00 equiv), trifluoroacetic acid (2 mL). The resulting solution was stirred for 1 h at 50 ^{0}C and then concentrated under vacuum. The crude product was purified by Prep HPLC which resulted in 2.5 mg (7%) of the title compound as a white solid of trifluoroacetic acid salt. MS: $[M+H]^+$= 474.2. H-NMR (300 MHz, CD_3OD, *ppm*): δ 8.27 (s, 1H), 7.94 (s, 1H), 7.84-7.81 (m, 2H), 7.69 (s, 1H), 7.19–7.00 (m, 3H), 3.98 (s, 3H), 3.05-2.95 (m, 1H), 2.61-2.53 (m, 3H), 2.47 (s, 3H), 1.60-1.56 (m, 2H), 1.35-1.31 (m, 2H), 1.27–1.11 (m, 2H).

[00285] The following compounds were prepared similarly to **Example 14** with appropriate substituting reagents and substrates at different steps:

Compound no.	MS $(M+H)^+$
1-22	460.2
1-44	474.3
1-47	459.2

Example 15: 1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-amine (Compound 4-8)



[00286] Step 15-1, preparation of tert-butyl N-[1-[3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate: a mixture of tert-butyl N-[1-(2-chloro-3-formylpyridin-4-

yl)piperidin-4-yl]carbamate made from Step 13-1 (500 mg, 1.47 mmol) and morpholine (5 ml) were heated at 100°C in a sealed tube for 5 h and then cooled to rt. It was then diluted with water and the crude was extracted with ethyl acetate (3x 100ml). The combined extracts were dried over Na_2SO_4, then concentrated after the solid was filtered off to afford the desired product, tert-butyl N-[1-[3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate, as a yellow solid (530 mg). MS: $[M+H]^+$=391.2.

[00287] Step 15-2, preparation of tert-butyl N-[1-[5-bromo-3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate: to a stirring solution of DCM (5 ml) containing tert-butyl N-[1-[3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate (300 mg, 0.77 mmol, 1.00 equiv), NBS (138 mg, 0.78 mmol, 1.00 equiv) was added. The resulting solution was stirred for 30 min at rt and concentrated. The residue was purified via a silica gel column chromatography eluted with ethyl acetate/petroleum ether, which yielded the title compound as a yellow solid (290 mg). MS: $[M+H]^+$=469.2, 471.2.

[00288] Step 15-3, preparation of tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate: under N_2, in toluene (10 ml), tert-butyl N-[1-[5-bromo-3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate (280 mg, 0.60 mmol, 1.00 equiv), (3-fluoro-5-methylphenyl)boronic acid (275 mg, 1.79 mmol, 3.00 equiv), $Pd_2(dba)_3$ (30 mg, 0.03 mmol, 0.05 equiv), $P(t\text{-}Bu)_3$ (60 mg), water (1 mL), and K_3PO_4 (379 mg, 3.00 equiv) were mixed and stirred for 2 h at 70 °C and then cooled to room temperature. The crude was extracted with ethyl acetate, dried and concentrated. The residual was purified via silica gel chromatography eluted with ethyl acetate/petroleum ether to afford the title compound as a light yellow solid (240 mg). MS: $[M+H]^+$= 449.3.

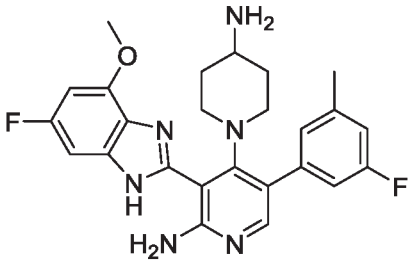
[00289] Step 15-4, preparation of 1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-amine: a mixture of tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-yl]carbamate (100 mg, 0.20 mmol, 1.00 equiv), 3,5-difluorobenzene-1,2-diamine (58 mg, 0.40 mmol, 2.00 equiv) and $Na_2S_2O_5$ (76 mg, 2.00 equiv) in DMSO (2 mL) was heated with stirring in a sealed tube for 16 h at 120 °C. The reaction mixture was then cooled to rt. The solids were filtered out. The crude product was purified by Prep-HPLC with the following conditions: Column, SunFire Prep C18 OBD Column, 19x150mm, 5um; mobile phases: A=Water (0.05%TFA), B=ACN (0.05%TFA), B from 10.0% to 33.0% in 6 min; Detector, UV 220nm. The fractions containing pure product were combined and freeze-dried to afford the title compound as an off-white solid (46.1 mg). MS: $[M+H]^+$= 523.3. ^{1}HNMR (300 MHz, CD_3OD): δ 8.04 (s, 2H), 7.28 (dd, J = 8.4, 1.8 Hz, 1H), 7.08 (s, 1H), 7.05-6.89 (m, 3H), 3.48-

3.46 (m, 4H), 3.40 (m, 2H), 3.27-3.22 (m, 4H), 2.93-2.85 (m, 1H), 2.56-2.52 (m, 2H), 2.47 (s, 3H), 1.62-1.58 (m, 2H), 1.07-0.95 (m, 2H).

[00290] The following compounds were prepared similarly to **Example 15** with appropriate substituting reagents and substrates at different steps:

Compound No.	MS (M+H)$^+$
4-4	475.3
4-5	481.3
4-6	493.2
4-7	523.3
4-9	509.5
4-11	520.3

Example 16: 4-(4-aminopiperidin-1-yl)-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine (1-58)



[00291] Step 16-1, preparation of 5-fluoro-3-methoxy-2-nitroaniline: into a 40-mL sealed tube, was placed 3,5-difluoro-2-nitroaniline (2 g, 11.5 mmol, 1.0 equiv), methanol (20 mL), potassium hydroxide (2 g, 35.6 mmol, 3.0 equiv). The resulting solution was stirred for 2 h at rt, diluted with 100 mL of H_2O, extracted with 3x100 mL of ethyl acetate. The organic layers combined and dried over anhydrous sodium sulfate. After the solids were filtered out, resulting solution was concentrated under vacuum and the residue was purified by a silica gel column eluted with ethyl acetate/petroleum ether to give the desired 5-fluoro-3-methoxy-2-nitroaniline (1.1g) as a yellow solid and a more polar minor isomer of 3-fluoro-5-methoxy-2-nitroaniline (300 mg) as a yellow solid. For the title compound: ^{1}HNMR (300 MHz, DMSO-d_6, ppm): δ, 6.50 (s, 2H), 6.27 (m, 1H), 6.23(m, 1H), 3.80(s, 3H).

[00292] Step 16-2, preparation of 5-fluoro-3-methoxybenzene-1,2-diamine: A mixture of 5-fluoro-3-methoxy-2-nitroaniline (1g, 5.4 mmol, 1.0 equiv), palladium carbon (50 mg) in propan-2-ol (50 mL) was stirred for 4 h at rt in the presence of hydrogen gas. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified

by a silica gel column chromatography, eluted with ethyl acetate/petroleum ether to afford the title compound (700 mg) as a brown solid. MS: $[M+H]^+$= 157.1.

[00293] Step 16-3, preparation of benzyl N-[1-(2-amino-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: A mixture of tert-butyl N-(4-chloro-3-formylpyridin-2-yl)carbamate (8.1 g, 31.6 mmol, 1.0 equiv), benzyl N-(piperidin-4-yl)carbamate (8.1 g, 34.6 mmol, 1.1 equiv), DIEA (12.2 g, 94.4 mmol, 3.0 equiv), ACN (100 mL was stirred for 16 hrs at 85 °C. The resulting mixture was then cooled and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with ethyl acetate/petroleum ether resulting in the title compound as a yellow solid (4.6 g). MS: $[M+H]^+$= 355.2.

[00294] Step 16-4, preparation of benzyl N-[1-(2-amino-5-bromo-3-formylpyridin-4-yl)piperidin-4-yl]carbamate: A mixture of benzyl N-[1-(2-amino-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (4.5 g, 12.7 mmol, 1.0 equiv), NBS (2.9 g, 16.3 mmol, 1.3 equiv), DCE (50 mL). The resulting solution was stirred for 40 min at 85 °C. The resulting mixture was concentrated under vacuum. The residue was purified by a silica gel column chromatography, eluted with ethyl acetate/petroleum ether, to afford the title compound as a yellow solid (3.9 g). $[M+H]^+$= 433.1, 435.1.

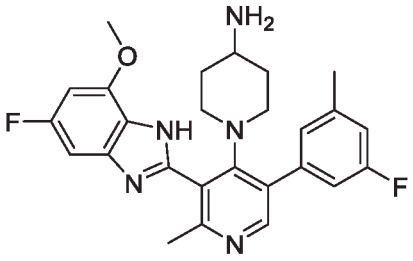
[00295] Step 16-4, preparation of benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate: Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed benzyl N-[1-(2-amino-5-bromo-3-formylpyridin-4-yl)piperidin-4-yl]carbamate (3.9 g, 9.0 mmol, 1.0 equiv), (3-fluoro-5-methylphenyl)boronic acid (2.8 g, 18.2 mmol, 2.0 equiv), $Pd_2(dba)_3$ (200 mg, 0.2 mmol, 0.02 equiv), *t*-Bu_3P (400 mg), K_3PO_4 (5.7 g, 3.0 equiv), THF (50 mL), water(10 mL). The resulting solution was stirred for 2 hrs at 30 °C. The resulting solution was diluted with 200 mL of H_2O, extracted with 3x200 mL of ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate. The solids were filtered out and the resulting solution was concentrated under vacuum. The remaining residue was purified by silica gel column chromatography, eluted with ethyl acetate/petroleum ether to produce the title compound as a light yellow solid (3.1g). $[M+H]^+$= 463.2.

[00296] Step 16-5, preparation of benzyl N-{1-[2-amino-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl}carbamate: a mixture of benzyl N-[1-[2-amino-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl]piperidin-4-yl]carbamate (250 mg, 0.54 mmol, 1.0 equiv), 5-fluoro-3-methoxybenzene-1,2-diamine (245 mg, 1.6 mmol, 3.0 equiv), $Na_2S_2O_5$ (207 mg, 2.0 equiv) in NMP (3 mL) and water (0.3 mL) was stirred for 16 hrs at 120 °C. The resulting solution was diluted with 100

mL of H_2O, extracted with 3x100 mL of ethyl acetate. The organic layers were combined and washed with 3x100 mL of brine, then dried over anhydrous sodium sulfate. After the solids were filtered out. The solution was concentrated under vacuum. The remaining was purified by Pre-TLC (petrolem ether:ethyl acetate =1:1) to afford the title compound as a light yellow solid (200 mg). $[M+H]^+$= 599.5.

[00297] Step 16-6, preparation of 4-(4-aminopiperidin-1-yl)-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine: benzyl N-{1-[2-amino-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-yl}carbamate (200 mg, 0.33 mmol, 1.0 equiv) in trifluoroacetic acid (5 mL) was stirred for 2 hrs at 50 °C and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Prep C18, 19 x150 mm; mobile phase A: water (0.05% TFA); mobile phase B: ACN; gradient: B from 15% to 38% in 6 min; Flow rate: 20 mL/min; Detector, 220 nm. The fractions contained pure product were combined and lyophilized to afford the title compound as trifluoroacetic acid salt (off-white solid, 188 mg). $[M+H]^+$= 465.2. ^{1}HNMR (300 MHz, DMSO-d_6, ppm): δ, 8.16 (s, 3H), 7.79 (s, 1H), 7.61 (s, 2H), 7.13-7.10 (m, 4H), 6.88 (d, J = 11.1 Hz, 1H), 3.99 (s, 3H), 3.05 (d, J = 12.6 Hz, 1H), 2.89 (s, 1H), 2.43 (s, 3H), 1.53-1.49 (m, 2H), 1.17-1.13 (m, 2H).

Example 17: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methylpyridin-4-yl]piperidin-4-amine (Compound 2-15)



[00298] Step 17-1, preparation of tert-butyl N-[1-(3-formyl-2-methylpyridin-4-yl)piperidin-4-yl]carbamate: a mixture of tert-butyl N-[1-(2-chloro-3-formylpyridin-4-yl)piperidin-4-yl]carbamate made from **Example 13**, Step 13-1 (340 mg, 1.0 mmol), methylboronic acid (300 mg, 5.0 mmol), Pd(DTBPF)Cl_2 (34 mg, 0.05 mmol), Cs_2CO_3 (650 mg, 2.0 mmol), dioxane (5 mL), H_2O (0.5 mL) was stirred for 1 h at 100 °C under inert atomsphere. The mixture was then concentrated under vacuum and the residue was directly loaded on a silica gel column , eluted with ethyl acetate/petroleum ether which produced tert-butyl N-[1-(3-formyl-2-methylpyridin-4-yl)piperidin-4-yl]carbamate as a brown solid (110mg). MS: $[M+H]^+$= 320.2.

[00299] Step 17-2, preparation of tert-butyl N-[1-(5-bromo-3-formyl-2-methylpyridin-4-yl)piperidin-4-yl]carbamate: into a 100-mL flask containing tert-butyl N-[1-(3-formyl-2-methylpyridin-4-yl)piperidin-4-yl]carbamate (130 mg, 0.41 mmol), NBS (73 mg, 0.41 mmol), DMF (5 mL) were added. The mixture was stirred for 16 h at rt and the resulting solution was diluted with 100 mL of water. The product was extracted by ethyl acetate (3x100 mL). The ethyl acetate solution was washed with brine (3x100 mL) and then dried over anhydrous sodium sulfate. After the solids were filtered out, the solution was concentrated and purified via a silica gel column, eluted with ethyl acetate/petroleum ether which afforded tert-butyl N-[1-(5-bromo-3-formyl-2-methylpyridin-4-yl)piperidin-4-yl]carbamate as a yellow solid (60 mg). MS: $[M+H]^+$= 398.2.

[00300] Step 17-3, preparation of tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-methylpyridin-4-yl]piperidin-4-yl]carbamate: a mixture of tert-butyl N-[1-(5-bromo-3-formyl-2-methylpyridin-4-yl)piperidin-4-yl]carbamate (50 mg, 0.13 mmol), (3-fluoro-5-methylphenyl)boronic acid (58 mg, 0.38 mmol), $Pd(dppf)Cl_2$ (10 mg, 0.01 mmol), K_2CO_3 (52 mg, 0.38 mmol, 3.00 equiv), toluene (1 mL), H_2O (0.1 mL) was stirred for 2 hrs at 80 ^oC under an inert atomsphere. The resulting mixture was concentrated and purified via a silica gel column, eluted with ethyl acetate/petroleum ether to afford tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-methylpyridin-4-yl]piperidin-4-yl]carbamate as a yellow solid (30 mg). MS: $[M+H]^+$= 428.6.

[00301] Step 17-4, preparation of 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methylpyridin-4-yl]piperidin-4-amine: tert-butyl N-{1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methylpyridin-4-yl]piperidin-4-yl}carbamate (18 mg), prepared according to Step 15-4 with tert-butyl N-[1-[5-(3-fluoro-5-methylphenyl)-3-formyl-2-methylpyridin-4-yl]piperidin-4-yl]carbamate (30 mg, 0.07 mmol) and 5-fluoro-3-methoxybenzene-1,2-diamine (Step 17-2, 22 mg, 0.14 mmol), was stirred with TFA (1 ml) in DCM (5 ml) for 1h at rt. The mixture was concentrated and rediluted with water (5 ml) and acetonitrile (1 ml) and then lyophilized to produce 1-[3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methylpyridin-4-yl]piperidin-4-amine as trifluoroacetic acid (off-white solid, 6. 9 mg). MS: $[M+H]^+$= 464.2. ^{1}HNMR (300 MHz, CD_3OD): δ 8.33 (s, 1H), 7.23 – 7.11 (m, 3H), 7.08-7.00 (m, 1H), 6.804-6.80 (m, 1H), 4.05 (s, 3H), 3.10-2.93 (m, 1H), 2.68-2.52 (m, 2H), 2.49 (s, 3H), 2.41 (s, 3H), 1.69-1.52 (m, 2H), 1.30-1.12 (m, 2H).

Example A-1: Parenteral Pharmaceutical Composition

[00302] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 1-100 mg of a water-soluble salt of a compound Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. A suitable buffer is optionally added as well as optional acid or base to adjust the pH. The mixture is incorporated into a dosage unit form suitable for administration by injection

Example A-2: Oral Solution

[00303] To prepare a pharmaceutical composition for oral delivery, a sufficient amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is added to water (with optional solubilizer(s),optional buffer(s) and taste masking excipients) to provide a 20 mg/mL solution.

Example A-3: Oral Tablet

[00304] A tablet is prepared by mixing 20-50% by weight of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, 20-50% by weight of microcrystalline cellulose, 1-10% by weight of low-substituted hydroxypropyl cellulose, and 1-10% by weight of magnesium stearate or other appropriate excipients. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 100 -500 mg.

Example A-4: Oral Capsule

[0001] To prepare a pharmaceutical composition for oral delivery, 10-500 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[00305] In another embodiment, 10-500 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

Example A-5: Topical Gel Composition

[00306] To prepare a pharmaceutical topical gel composition, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with hydroxypropyl celluose, propylene

glycol, isopropyl myristate and purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

Example B-1: SSTR assays

Membrane preparation:

[00307] Crude membrane fractions are prepared from Chinese hamster ovary (CHO) cells stably expressing one of the five human or rodent somatostatin receptor subtypes. The cells are grown to 85 - 100% confluence on standard tissue culture dishes in DM-MEM growth media (Gibco) with following additives: 10% fetal bovine serum (Gibco), 100 U/mL penicillin (Gibco), 100 ug/mL streptomycin (Gibco), 10 mM HEPES (Gibco), 0.5 mg/mL G-418 (Gibco). To prepare membranes, cells are washed once with 1X Dulbecco's phosphate buffered saline (Gibco) containing 10 mM HEPES (Gibco) then once with sodium free binding buffer (50 mM Tris Base, 5 mM $MgC1_2$-$6H_20$ and 1 mM EGTA adjusted to pH 7.8). The cells are then scraped into binding buffer containing a protease inhibitor cocktail (100 ug/mL pepstatin A (Sigma), 50 ug/mL leupeptin (Sigma), 25 ug/mL aprotinin (Sigma) and 10 mg/mL Bacitracin (USB Corporation)). The cells are centrifuged at 43,500 x g, homogenized, and the resulting membranes are collected by centrifugation at 67,000 x g. The membranes are then resuspended in binding buffer containing the protease inhibitor cocktail using a glass dounce homogenizer.

Functional assay for SSTR2 agonists

[00308] General overview: All five SSTR subtypes are Gi coupled G-protein coupled receptors (GPCRs) that lead to decreases in intracellular cyclic AMP (cAMP) when activated by an agonist. Therefore, measurement of intracellular cAMP levels can be used to assess whether compounds of the invention are agonists of SSTR subtypes (John Kelly, Troy Stevens,W. Joseph Thompson, and Roland Seifert, *Current Protocols in Pharmacology,* 2005,2.2.1-2.2). One example of an intracellular cAMP assay is described below.

cAMP assay protocol:

[00309] Four days prior to the assay, 5,000 Chinese hamster ovary cells (CHO-K1, ATCC #CCL-61) stably expressing the human somatostatin receptor subtype 2 are plated in each well of a 96-well tissue culture-treated plate in Ham's F12 growth media (ThermoFisher #10-080-CM) supplemented with 10% donor bovine serum (Gemini Bio-Products #100-506), 100 U/mL penicillin; 100 ug/mL streptomycin; 2 mM L-glutamine (Gemini Bio-Products #400-110) and 0.2 mg/mL hygromycin B (GoldBio #31282-04-9). The cells are cultured at 37 °C,

5% CO_2 and 95% humidity. On the day of the assay, the media is aspirated and the cells are treated with 50 µL of 1.6 µM NKH477 (Sigma #N3290) plus various dilutions of compounds of the invention in assay buffer [lx Hank's Balanced Salt Solution (ThermoFisher #SH3058802), 0.5 mM HEPES pH 7.4, 0.1% bovine serum albumin, 0.2 mM 3-Isobutyl-1-methylxanthine (IBMX, VWR #200002-790)]. The cells are incubated for 20 minutes at 37 °C (the final concentration of the compounds of the invention are typically 0 - 10,000 nM). The cells are treated with 50 µL of lysis buffer (HRTF cAMP kit, Cisbio). The lysate is transferred to 384-well plates and cAMP detection and visualization antibodies are added and incubated for 1-24 hours at room temperature. The time-resolved fluorescent signal is read with a Tecan M1000Pro multiplate reader. The intracellular cAMP concentrations are calculated by regression to a standard curve and are plotted vs. the concentration of the compounds of the invention and the EC_{50} of the compounds are calculated using standard methods. All data manipluations are in GraphPad Prism v6.

[00310] Illustrative biological activity of compounds is demonstrated in the following Table by evaluating the inhibition of cAMP activities via human SST2 receptor (SSTR2):

Table A.

Cpd No.	EC_{50}
1-1	A
1-2	A
1-3	A
1-4	A
1-5	A
1-6	A
1-7	A
1-8	A
1-9	A
1-10	A
1-11	A
1-12	A
1-13	A
1-14	A
1-15	A
1-16	A
1-17	B
1-18	B
1-19	A
1-20	A
1-21	A
1-22	A
1-23	B

Cpd No.	EC_{50}
1-24	A
1-25	A
1-26	A
1-27	A
1-28	A
1-29	A
1-30	A
1-31	A
1-32	A
1-33	A
1-34	A
1-35	A
1-36	B
1-37	A
1-38	A
1-39	C
1-40	A
1-41	A
1-42	A
1-44	A
1-45	A
1-46	A
1-47	A
1-48	A
1-49	A
1-50	A
1-51	A
1-52	A
1-53	A
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1-55	A
1-56	A
1-57	A
1-58	A
1-59	A
1-60	A
1-61	A
1-65	A
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1-74	A
1-75	A

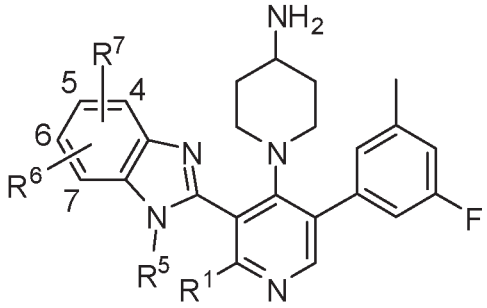
Cpd No.	EC_{50}
1-76	A
1-77	A
1-78	A
1-79	A
1-80	A
1-81	A
1-82	A
1-83	A
1-84	A
1-85	A
1-86	A
1-87	A
1-88	A
1-89	A
1-90	A
1-91	A
1-92	A
1-93	A
1-94	A
2-1	A
2-2	A
2-3	A
2-4	A
2-5	A
2-6	B
2-7	B
2-8	A
2-9	A
2-10	B
2-11	A
2-12	C
2-13	A
2-14	B
2-15	A
3-1	A
3-2	A
3-3	A
3-4	A
3-5	A
3-6	A
3-7	A
3-8	A
3-9	A
3-10	A
3-11	A
3-12	A
3-13	A

Cpd No.	EC_{50}
3-14	A
3-15	C
3-16	A
3-17	A
3-18	A
3-19	A
3-20	B
3-21	A
3-22	A
3-23	A
3-24	A
3-25	A
3-26	A
4-1	A
4-2	A
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4-11	A

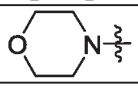
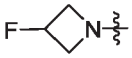
A = EC_{50} below 10 nM; B = EC_{50} between 10 nM and 100 nM; C=EC_{50} above 100 nM

[00311] The following Table demonstrates improved selectivity of exemplary compounds for inhibition of cAMP via hSSTR2 vs. hSSTR4.

Table B:



R^1	R^5	R^6	R^7	hSST4/hSST2 (ratio)
H	H	5-Cl	H	e
NH_2	H	5-Cl	H	b
CH_3NH-	H	5-Cl	H	a
CH_3CH_2NH-	H	5-Cl	H	a
-OCH_3	H	5-Cl	H	a
H	H	5-F	7-F	d
NH_2	H	5-F	7-F	b

R^1	R^5	R^6	R^7	hSST4/hSST2 (ratio)
CH_3NH-	H	5-F	7-F	a
CH_3CH_2NH-	H	5-F	7-F	a
CH_3O-CH_2CH_2NH-	H	5-F	7-F	a
	H	5-F	7-F	a
-OCH_3	H	5-F	7-F	a
H	H	5-F	6-F	e
NH_2	H	5-F	6-F	b
CH_3NH-	H	5-F	6-F	a
CH_3CH_2NH-	H	5-F	6-F	a
H	-CH_3	5-F	6-F	c
NH_2	-CH_3	5-F	6-F	a
H	-CH_2CH_3	5-F	6-F	c
NH_2	-CH_2CH_3	5-F	6-F	b
H	H	5-F	H	e
NH_2	H	5-F	H	b
-OCH_3	H	5-F	H	a
H	H	5-OCH_3	H	d
NH_2	H	5-OCH_3	H	b
-OCH_3	H	5-OCH_3	H	a
H	H	H	7-CH_3	e
NH_2	H	H	7-CH_3	c
H	H	H	7-F	e
NH_2	H	H	7-F	c
H	H	5-CN	H	c
NH_2	H	5-CN	H	a
H	H	H	7-OCH_3	e
NH_2	H	H	7-OCH_3	d
CH_3NH-	H	H	7-OCH_3	c
H	H	5-OCF_3	H	c
NH_2	H	5-OCF_3	H	a
H	H	6-F	7-F	e
NH_2	H	6-F	7-F	c
H	H	6-F	4-OCH_3	e
NH_2	H	6-F	4-OCH_3	c
$(CH_3)_2N$-	H	6-F	4-OCH_3	b
	H	6-F	4-OCH_3	a
CH_3	H	6-F	4-OCH_3	c
H	H	5-Cl	7-F	d
NH_2	H	5-Cl	7-F	a
CH_3NH-	H	5-Cl	7-F	a
H	H	5-F	7-OCH_2CN	e
NH_2	H	5-F	7-OCH_2CN	c
H	H	4-F	6-OMe	d

R^1	R^5	R^6	R^7	hSST4/hSST2 (ratio)
NH_2	H	4-F	6-OMe	b

a=above 50, b= between 15 and 50; c= between 2.5 and 15; d= between 1 and 2.5; e= below 1

Example B-2: CYP2D6 assay protocol:

[00312] On the day of the assay, various dilutions of test articles of the invention are prepared in assay buffer (Vivid® CYP2D6 Blue Screening Kit, ThermoFisher Scientific #P2972) and dilutions are added to a preparation of CYP450 microsomes expressing the functional human CYP2D6 isozyme (supplied by the kit) and incubated for 15 minutes at 37°C to allow interactions between the test article of invention and the enzyme in the absence of enzyme turnover. The enzymatic reaction is initiated by addition of the NADPH co-factor in the precense of the fluorogenic substrate. Under normal conditions, this substrate (which is not fluorescent) is cleaved by active CYP2D6 to produce a a fluorescent product. When in the presence of test article, the lack of appearance of the fluorescent product is evidence of inhibition of the CYP2D6 enzyme by the test article. The enzymatic reaction is allowed to proceed for 30 minutes at 37°C and then terminated by the addition of 0.5 M Tris pH 10.8. The concentration of fluorescent cleavage product is measured using spectroscopic parameters prescribed in the kit with a Tecan M1000Pro multiplate reader. The percent inhibition is calculated based on the fluorescence intensity observed in the presence of the positive control inhibitor, quinidine (Sigma #Q3625), included in each assay. The percent inhibition is plotted versus test article concentration and an IC_{50} for CYP2D6 inhibition is calcuated using standard methods. All data manipluations are in GraphPad Prism v6.

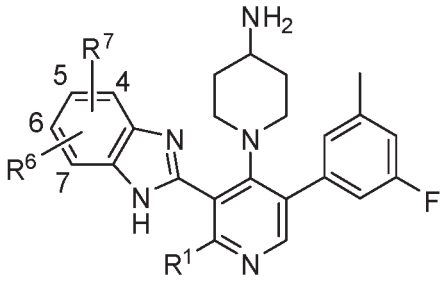
Example B-3: hERG assay protocol:

[00313] On the day of the assay, various dilutions of test articles of the invention are prepared in assay buffer (Predictor™ hERG Fluorescence Polarization Assay Kit, ThermoFisher Scientific #PV5365) and dilutions are added to membranes fractions that contain the functional hERG ion channel (supplied by the kit). A high-affinity fluorescent hERG ion channel ligand or tracer is added and incubated for 2 hours at room temperature. Under normal conditions, the tracer binds to the hERG channel and the fluorecence polarization measured is high. Tracer displacement by a test article of invention results in lower fluorecent polarization and is indicative of the test article's affinity to the hERG channel. The concentration of free tracer is measured via fluorescence polarization using

parameters prescribed in the kit with a Tecan M1000Pro multiplate reader. A potent hERG channel ligand, E-4031 supplied with the kit, displaces 100% of the tracer is included in all the assays and is used to establish the assay window for data analysis. The fluorescence polarization is plotted versus test article concentration and an IC_{50} for hERG inhibition is calculated using standard methods. All data manipluations are in GraphPad Prism v6.

[00314] CYP2D6 and hERG inhibitions for exemplary compounds are shown in Table C.

Table C.



R^6	R^7	R^1	hSST2 (EC_{50}, nM)	hSST4 (EC_{50}, nM)	CYP2D6 inh.	hERG inh.
5-Cl	H	H	0.06	0.06	+	+
5-Cl	H	NH_2	0.03	0.70	++	++
5-F	7-F	H	0.08	0.15	+	+
5-F	7-F	NH_2	0.05	1.3	++	++
5-F	7-F	CH_3NH-	0.18	15	++	++
5-F	H	H	0.18	0.12	+	+
5-F	H	NH_2	0.06	0.92	++	++
7-F	H	H	0.43	0.09	+	++
7-F	H	NH_2	0.27	0.71	++	++
5-CN	H	H	0.13	1.2	++	+
5-CN	H	NH_2	0.06	14	++	++

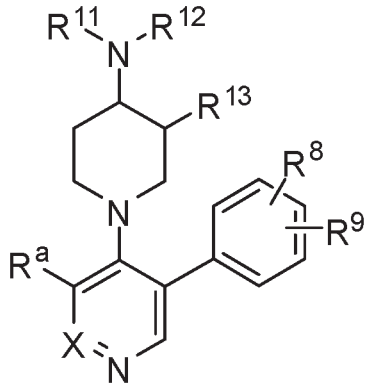
+ = IC_{50} below 5 μM ; ++ = IC_{50} above 5 μM.

[00315] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, enantiomer or prodrug thereof:



Formula (I)

wherein:

X is C-R^1 or N;

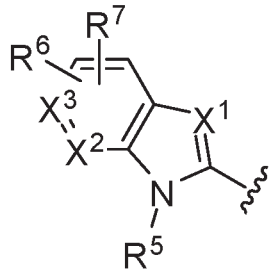
R^1 is -NR^2R^3, -OR^2, or R^4;

R^2 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

R^3 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring;

R^4 is F, Cl, Br, -CN, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4alkoxy, -SC_1-C_4alkyl, -S(=O)C_1-C_4alkyl , -$S(=O)_2$-C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, -CO_2R^{15}, -C(=O)$N(R^{15})_2$;

R^a is  or R^b-O-N=CH-;

R^b is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle,

R^5 is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, or substituted or unsubstituted C_3-C_6cycloalkyl;

each R^6 and R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, substituted or unsubstituted monocyclic heterocycle, -CN, -OR^{15}, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, -$C(=O)N(R^{15})OR^{15}$, -$N(R^{15})_2$, -$NR^{15}C(=O)R^{15}$, -$NR^{15}C(=O)OR^{15}$, -$OC(=O)N(R^{15})_2$, -$NR^{15}C(=O)N(R^{15})_2$, -$NR^{15}C(=O)NR^{15}OR^{15}$, -$C(R^{15})$=N-$OR^{15}$, -$SR^{15}$, -$S(=O)R^{14}$, -$SO_2R^{14}$, or -$SO_2N(R^{15})_2$;

or R^6 and an adjacent R^7 are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 5-membered or 6-membered ring;

R^8 and R^9 are independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, substituted or unsubstituted monocyclic heterocycle, -CN, -OR^{15}, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, -$C(=O)N(R^{15})OR^{15}$, -$N(R^{15})_2$, -$CH_2N(R^{15})_2$, -$NR^{15}C(=O)R^{15}$, -$NR^{15}C(=O)OR^{15}$, -$OC(=O)N(R^{15})_2$, -$NR^{15}C(=O)N(R^{15})_2$, -$NR^{15}C(=O)NR^{15}OR^{15}$, -$C(R^{15})$=N-$OR^{15}$, -$SR^{15}$, -$S(=O)R^{14}$, -$SO_2R^{14}$, or -$SO_2N(R^{15})_2$;

X^1 is N or C-R^{10};

R^{10} is hydrogen, F, Cl, Br, -CN, -$N(R^{15})_2$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4alkoxy, substituted or unsubstituted C_1-

C_4fluoroalkyl, substituted or unsubstituted C_1-C_4fluoroalkoxy, substituted or unsubstituted C_1-C_4heteroalkyl, or substituted C_3-C_6cycloalkyl;

X^2 is C-R^7 or N;

X^3 is C-R^7 or N;

R^{11} and R^{12} are independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted N-containing heterocyclic ring;

R^{13} is hydrogen, -OR^{15}, -$N(R^{15})_2$, -CN, -CO_2R^{14}, -$C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6 alkyl, and substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic carbocycle, or substituted or unsubstituted monocyclic heterocycle;

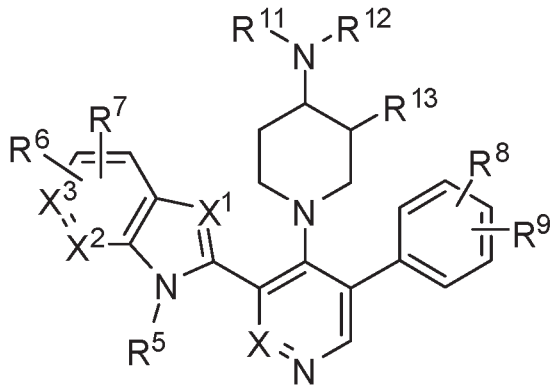
or R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted N-containing heterocyclic ring;

each R^{14} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^{15} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

or two R^{15} on the same N atom are taken together with the N atom to which they are attached to form an substituted or unsubstituted N-containing heterocycle.

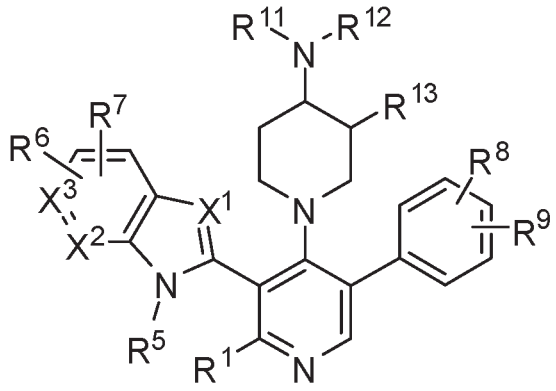
2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (II), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (II).

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
X is C-R^1.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (III), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (III)

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^1 is -NR^2R^3.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^2 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl;
R^3 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, or $-CH_2CN$;

R^3 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, or $-CH_2CF_3$;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, or substituted or unsubstituted piperazinyl.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^3 is hydrogen.

9. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^1 is $-OR^2$.

10. The compound of claim 9, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

11. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^1 is R^4;

R^4 is F, Cl, Br, -CN, C_1-C_4alkyl, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl , $-S(=O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, $-CO_2C_1$-C_4alkyl, or $-C(=O)N(R^{15})_2$.

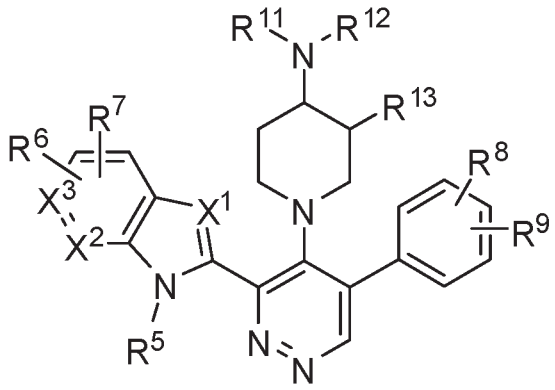
12. The compound of claim 11, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^4 is F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$;

13. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^1 is $-NR^2R^3$, $-OR^2$, F, Cl, Br, -CN, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

14. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (IV), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (IV).

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^{11} hydrogen;

R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted *N*-containing heterocycloalkyl;

R^{13} is hydrogen, $-OR^{15}$, $-N(R^{15})_2$, -CN, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl;

or R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 4- to 7-membered saturated *N*-containing heterocyclic ring.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^{11} hydrogen;

R^{12} is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, cyclopropyl, $CH_2CH_2CH_2OCH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl;

R^{13} is hydrogen, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CN$, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

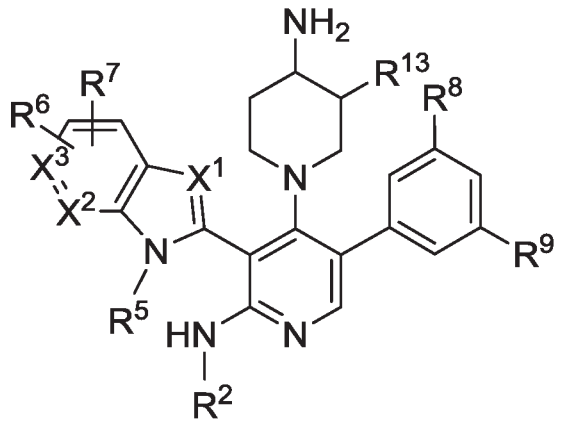
or R^{12} and R^{13} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted monocyclic 4- to 7-membered heterocyclic ring selected from substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^{11} hydrogen;

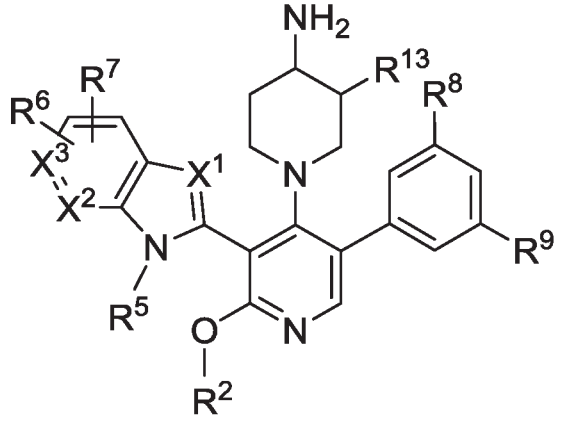
R^{12} is hydrogen or $-CH_3$.

18. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (V), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (V)

19. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (VI), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:

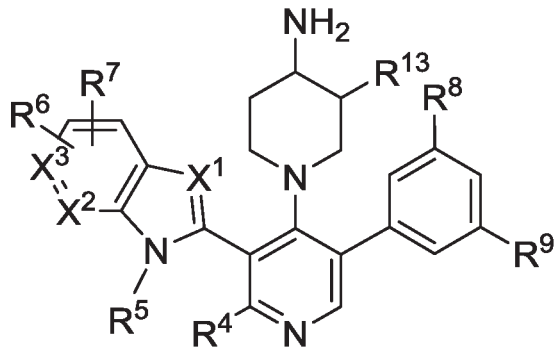


Formula (VI)

20. The compound of claim 18 or claim 19, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, or $-CH_2CF_3$.

21. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (VII), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:

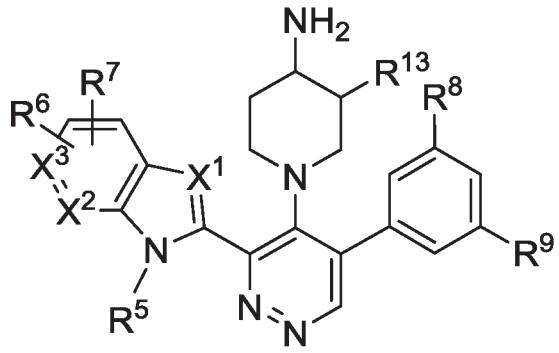


Formula (VII)

22. The compound of claim 21, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^4 is F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-S(=O)_2CH_3$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, or $-C(=O)N(CH_3)_2$.

23. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (VIII), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (VIII)

24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^5 is hydrogen, or C_1-C_4alkyl;

X^1 is N or C-R^{10};

R^{10} is hydrogen, F, Cl, Br, -CN, $-N(R^{15})_2$, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy.

25. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
X^1 is N.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
X^2 is C-R^7; and
X^3 is C-R^7.

27. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
X^2 is N, and X^3 is C-R^7;
or X^2 is C-R^7, and X^3 is N.

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
each R^6 and R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, substituted or unsubstituted monocyclic C_1-C_5heteroaryl, -CN, -OR^{15}, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, -$C(=O)N(R^{15})OR^{15}$, -$N(R^{15})_2$, -$NR^{15}C(=O)R^{15}$, -$NR^{15}C(=O)OR^{15}$, -$OC(=O)N(R^{15})_2$, -$NR^{15}C(=O)N(R^{15})_2$, -$NR^{15}C(=O)NR^{15}OR^{15}$, -$C(R^{15})$=N-$OR^{15}$, -$SR^{15}$, -$S(=O)R^{14}$, -$SO_2R^{14}$, or -$SO_2N(R^{15})_2$.

29. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^6 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, substituted or unsubstituted monocyclic C_1-C_5heteroaryl, -CN, -OR^{15}, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, -$C(=O)N(R^{15})OR^{15}$, -$N(R^{15})_2$, -$NR^{15}C(=O)R^{15}$, -$NR^{15}C(=O)OR^{15}$, -$OC(=O)N(R^{15})_2$, -$NR^{15}C(=O)N(R^{15})_2$, -$NR^{15}C(=O)NR^{15}OR^{15}$, -$C(R^{15})$=N-$OR^{15}$, -$SR^{15}$, -$S(=O)R^{14}$, -$SO_2R^{14}$, or -$SO_2N(R^{15})_2$;

each R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -O-(substituted or unsubstituted C_1-C_4alkyl), or -O-(substituted or unsubstituted C_1-C_4fluoroalkyl).

30. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^6 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, oxetanyloxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, azetidinyl, pyrrolidinyl, tetrazolyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, or $-SO_2N(CH_3)_2$;

each R^7 is independently hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, or $-OCF_3$.

31. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^6 is hydrogen, F, Cl, $-CH_3$, $-CF_3$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCF_3$, azetidinyl, pyrrolidinyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, or $-SO_2NH_2$;

each R^7 is independently hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$.

32. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^6 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -O-(substituted or unsubstituted C_1-C_4alkyl), or -O-(substituted or unsubstituted C_1-C_4fluoroalkyl);

each R^7 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, substituted or unsubstituted monocyclic C_1-C_5heteroaryl, -CN, $-OR^{15}$, $-CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-C(=O)N(R^{15})OR^{15}$, $-N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-NR^{15}C(=O)OR^{15}$, $-OC(=O)N(R^{15})_2$, $-NR^{15}C(=O)N(R^{15})_2$, $-NR^{15}C(=O)NR^{15}OR^{15}$, $-C(R^{15})=N-OR^{15}$, $-SR^{15}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$.

33. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^6 is hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, or $-OCF_3$;

each R^7 is independently hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, oxetanyloxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, azetidinyl, pyrrolidinyl, tetrazolyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, -

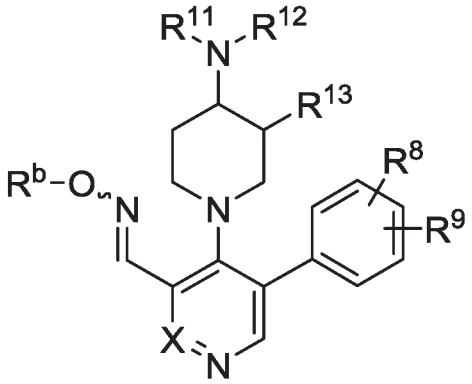
$NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, or $-SO_2N(CH_3)_2$.

34. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^6 is hydrogen, F, Cl, Br, -CN, $-CH_3$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$;

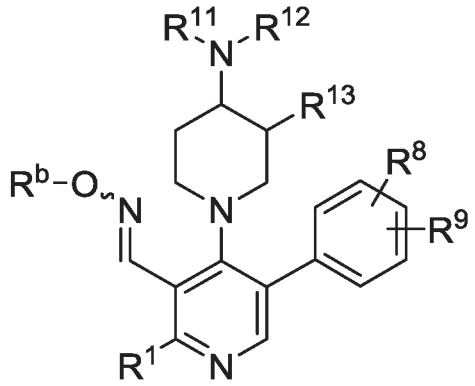
each R^7 is independently hydrogen, F, Cl, $-CH_3$, $-CF_3$, $-C\equiv CH$, -CN, -OH, $-OCH_3$, $-OCF_3$, azetidinyl, pyrrolidinyl, tetrazolyl, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHOCH_3$, $-C(=O)N(CH_3)OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-NHC(=O)OCH_3$, $-NCH_3C(=O)OCH_3$, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-NHC(=O)NH_2$, $-NHC(=O)NHCH_3$, $-NCH_3C(=O)N(CH_3)_2$, $-NHC(=O)NHOCH_3$, $-NHC(=O)NCH_3OCH_3$, $-NCH_3C(=O)NCH_3OCH_3$, -CH=N-OH, $-CH=N-OCH_3$, $-SO_2CH_3$, or $-SO_2NH_2$.

35. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (IX), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (IX).

36. The compound of claim 35, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (X), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (X)

37. The compound of claim 36, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^1 is $-NR^2R^3$;

R^2 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl;

R^3 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-membered, substituted or unsubstituted 5-membered or substituted or unsubstituted 6-membered N-containing heterocyclic ring.

38. The compound of claim 37, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$ or $-CH_2CF_3$;

R^3 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, or $-CH_2CF_3$;

or R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, or substituted or unsubstituted piperazinyl.

39. The compound of any one of claims 37-38, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^3 is hydrogen.

40. The compound of claim 36, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^1 is $-OR^2$;
R^2 is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, or C_3-C_6cycloalkyl.

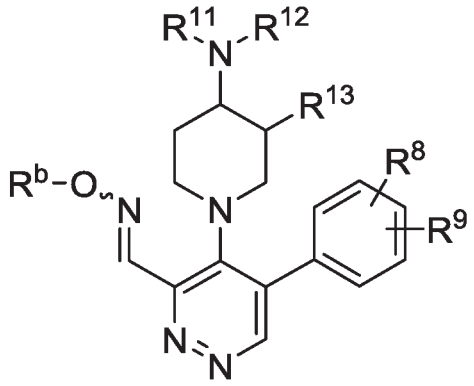
41. The compound of claim 40, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^2 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

42. The compound of claim 36, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^1 is R^4;
R^4 is F, Cl, Br, -CN, C_1-C_4alkyl, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl , $-S(=O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, $-CO_2C_1$-C_4alkyl, or $-C(=O)N(R^{15})_2$.

43. The compound of claim 42, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^4 is F, Cl, Br, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-S(=O)_2CH_3$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, or $-C(=O)N(CH_3)_2$.

44. The compound of claim 36, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:
R^1 is $-NR^2R^3$, $-OR^2$, F, Cl, Br, -CN, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

45. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein the compound has the structure of Formula (XI), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof:



Formula (XI).

46. The compound of any one of claims 35-45, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^{11} hydrogen;

R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl or substituted or unsubstituted C_3-C_5heterocycloalkyl that has 1 O atom;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted *N*-containing heterocycloalkyl;

R^{13} is hydrogen, -OR^{15}, -$N(R^{15})_2$, -CN, -CO_2R^{15}, -$C(=O)N(R^{15})_2$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl;

or R^{12} and R^{13} are taken together with the intervening atoms to which they are attached to form a substituted or unsubstituted 4- to 7-membered saturated *N*-containing heterocyclic ring.

47. The compound of any one of claims 35-45, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^{11} hydrogen;

R^{12} is hydrogen, -CH_3, -CH_2CH_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -$CH_2CH_2OCH_3$, -$CH_2CH_2NH_2$, -$CH_2CH_2NHCH_3$, -$CH_2CH_2N(CH_3)_2$, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, cyclopropyl, $CH_2CH_2CH_2OCH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$C(CH_3)_3$, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl;

or R^{11} and R^{12} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted

morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl;

R^{13} is hydrogen, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -CN, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

or R^{12} and R^{13} are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted monocyclic 4- to 7-membered heterocyclic ring selected from substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted piperazinyl, or substituted or unsubstituted azepanyl.

48. The compound of any one of claims 35-45, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^{11} hydrogen;

R^{12} is hydrogen or $-CH_3$.

49. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^8 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, -CN, -OH, $-OR^{14}$, $-CO_2R^{15}$, $-CH_2CO_2R^{15}$, $-C(=O)N(R^{15})_2$, $-CH_2C(=O)N(R^{15})_2$, $-N(R^{15})_2$, $-CH_2N(R^{15})_2$, $-NR^{15}C(=O)R^{15}$, $-CH_2NR^{15}C(=O)R^{14}$,$-SR^{14}$, $-S(=O)R^{14}$, $-SO_2R^{14}$, or $-SO_2N(R^{15})_2$; and

R^9 is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_3-C_5heterocycloalkyl, -CN, -OH, -O-(substituted or unsubstituted C_1-C_4alkyl), or -O-(substituted or unsubstituted C_1-C_4fluoroalkyl).

50. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^8 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CN$, $-OCF_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, -

$C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, or pyrrolidinyl;

R^9 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CN$, or $-OCF_3$.

51. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, wherein:

R^8 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, azetidinyl, or pyrrolidinyl;

R^9 is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, or $-OCF_3$.

52. The compound of claim 1, wherein the compound is:

1-1: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-2: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-3: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-4: 4-(4-aminopiperidin-1-yl)-3-(1-ethenyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-5: 4-(4-aminopiperidin-1-yl)-3-(1-ethyl-5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-6: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-7: 4-[*trans*-4-amino-3-methoxypiperidin-1-yl]-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-8: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(5-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-9: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-5-sulfonamide;

1-10: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methyl-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-11: 4-(4-aminopiperidin-1-yl)-3-(7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-12: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-5-carbonitrile;

1-13: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-14: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[5-(trifluoromethoxy)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-15: 4-(4-aminopiperidin-1-yl)-3-(6,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amineine;

1-16: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[5-(oxetan-3-yloxy)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-17: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-1H-1,3-benzodiazole-7-carboxamide;

1-18: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-N-methyl-1H-1,3-benzodiazole-7-carboxamide;

1-19: 4-(4-aminopiperidin-1-yl)-3-(5-cyclobutoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-20: 4-(4-aminopiperidin-1-yl)-3-(5-cyclopropoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-21: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazole-7-carbonitrile;

1-22: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-[(hydroxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-23: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-1H-1,3-benzodiazole-5-carboxamide;

1-24: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-N-methoxy-N-methyl-1H-1,3-benzodiazole-5-carboxamide;

1-25: 3-[6-amino-4-(4-aminopiperidin-1-yl)-5-(5-chloro-1H-1,3-benzodiazol-2-yl)pyridin-3-yl]-5-methylbenzonitrile;

1-26: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[5-(3-fluoroazetidin-1-yl)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-27: methyl N-{2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazol-7-yl}carbamate;

1-28: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-29: 4-(4-aminopiperidin-1-yl)-3-(6-chloro-1-methyl-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-30: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-N-ethyl-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-31: 4-(4-aminopiperidin-1-yl)-3-{5,5-difluoro-4,6-dioxa-10,12-diazatricyclo[7.3.0.0^{3},^{7}]dodeca-1,3(7),8,10-tetraen-11-yl}-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-32: 3-[6-amino-4-(4-aminopiperidin-1-yl)-5-(5-chloro-1H-1,3-benzodiazol-2-yl)pyridin-3-yl]-5-fluorobenzonitrile;

1-33: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-indole-6-carbonitrile;

1-34: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-2-amine;

1-35: 4-(4-aminopiperidin-1-yl)-3-[(tert-butoxy)imino]methyl]-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-36: 4-(4-aminopiperidin-1-yl)-3-[(tert-butoxy)imino]methyl]-5-(3,5-dimethylphenyl)pyridin-2-amine;

1-37: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-[(propan-2-yloxy)imino]methyl]pyridin-2-amine;

1-38: 4-(4-aminopiperidin-1-yl)-3-[(tert-butoxy)imino]methyl]-5-(3-chloro-5-methylphenyl)pyridin-2-amine;

1-39: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-[(hydroxyimino)methyl]pyridin-2-amine;

1-40: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{5-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-41: *trans*-4-amino-1-[2-amino-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3,5-dimethylphenyl)pyridin-4-yl]piperidine-3-carbonitrile;

1-42: *trans*-4-amino-1-[2-amino-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidine-3-carbonitrile;

1-43: 4-(4-aminopiperidin-1-yl)-3-[5-(azetidin-1-yl)-1H-imidazo[4,5-b]pyridin-2-yl]-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-44: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{4-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-45: methyl N-{2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazol-5-yl}carbamate;

1-46: 1-{2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-1H-1,3-benzodiazol-5-yl}-3-methoxyurea;

1-47: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{5-[(hydroxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-48: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-49: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-N-ethyl-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-50: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-N-ethyl-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-51: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{1H-imidazo[4,5-c]pyridin-2-yl}pyridin-2-amine;

1-52: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{1H-imidazo[4,5-b]pyridin-2-yl}pyridin-2-amine;

1-53: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(5-methanesulfonyl-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-54: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-55: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-56: 3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-(2-methoxyethyl)-4-(4-methylpiperidin-1-yl)pyridin-2-amine;

1-57: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1-methyl-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-58: 4-(4-aminopiperidin-1-yl)-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-59: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(4-fluoro-6-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine.

1-60: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-4-fluoro-1H-1,3-benzodiazol-6-yl}oxy)acetonitrile;

1-61: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-fluoro-5-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-62: 4-(4-aminopiperidin-1-yl)-3-{6-fluoro-4-[(hydroxyimino)methyl]-1H-1,3-benzodiazol-2-yl}-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-63：4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{4-[(hydroxyimino)methyl]-1H-imidazo[4,5-c]pyridin-2-yl}pyridin-2-amine；

1-64：4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-[(hydroxyimino)methyl]-3H-imidazo[4,5-b]pyridin-2-yl}pyridin-2-amine；

1-65: 4-(4-aminopiperidin-1-yl)-3-(5-ethynyl-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-66: 4-(4-aminopiperidin-1-yl)-3-(5-ethynyl-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-67: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methoxyphenyl)pyridin-2-amine;

1-68: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methoxyphenyl)pyridin-2-amine;

1-69: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

1-70: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylamino)pyridin-3-yl]-1H-1,3-benzodiazole-6-carbonitrile;

1-71: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methoxy-1H-1,3-benzodiazol-2-yl)-N-methylpyridin-2-amine;

1-72: 4-(4-aminopiperidin-1-yl)-3-(7-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-73: 4-(4-aminopiperidin-1-yl)-3-(7-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

1-74: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-3-yl]-5-fluoro-1H-1,3-benzodiazol-7-yl}oxy)acetonitrile;

1-75: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methylpyridin-2-amine;

1-76: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-{7-methoxy-5-[(methoxyimino)methyl]-1H-1,3-benzodiazol-2-yl}pyridin-2-amine;

1-77: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-78: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3,5-dimethylphenyl)pyridin-2-amine;

1-79: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-methylphenyl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-80: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-methoxy-5-methylphenyl)pyridin-2-amine;

1-81: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3,5-difluorophenyl)pyridin-2-amine;

1-82: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3,5-difluorophenyl)pyridin-2-amine;

1-83: 4-(4-aminopiperidin-1-yl)-5-(3,5-dimethylphenyl)-3-(6-fluoro-4-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-84: 4-(4-aminopiperidin-1-yl)-5-(3,5-dimethylphenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-85: 2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

1-86: 4-(4-aminopiperidin-1-yl)-5-(3,5-difluorophenyl)-3-[5-(trifluoromethoxy)-1H-1,3-benzodiazol-2-yl]pyridin-2-amine;

1-87: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)pyridin-3-yl]-5-fluoro-1H-1,3-benzodiazol-7-yl}oxy)acetonitrile;

1-88: 2-({2-[2-amino-4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazol-5-yl}oxy)acetonitrile;

1-89: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-2-(methylamino)pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

1-90: 4-(4-aminopiperidin-1-yl)-5-(3-chloro-5-fluorophenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-91: 4-(4-aminopiperidin-1-yl)-5-(4-fluoro-3-methylphenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-92: 4-(4-aminopiperidin-1-yl)-5-(3-chlorophenyl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-2-amine;

1-93: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-methylphenyl)pyridin-2-amine;

1-94: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-amine;

2-1: 1-[3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-2: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-3: 1-[5-(3-fluoro-5-methylphenyl)-2-methoxy-3-(5-methoxy-1H-1,3-benzodiazol-2-yl)pyridin-4-yl]piperidin-4-amine;

2-4: 4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol;

2-5: 1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-6: 3-[4-(4-aminopiperidin-1-yl)-5-(5-chloro-1H-1,3-benzodiazol-2-yl)-6-methoxypyridin-3-yl]-5-methylbenzonitrile;

2-7: 4-(4-aminopiperidin-1-yl)-3-(5,6-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol;

2-8: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-3-yl]-1H-1,3-benzodiazole-5-carbonitrile;

2-9: 1-(3-{6-chloro-3H-imidazo[4,5-c]pyridin-2-yl}-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl)piperidin-4-amine;

2-10: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-ol;

2-11: 1-[2-chloro-3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl]piperidin-4-amine;

2-12: 1-{3-[(1E)-[(tert-butoxy)imino]methyl]-5-(3-chloro-5-methylphenyl)-2-methoxypyridin-4-yl}piperidin-4-amine;

2-13: 1-(3-{5-chloro-1H-imidazo[4,5-b]pyridin-2-yl}-5-(3-fluoro-5-methylphenyl)-2-methoxypyridin-4-yl)piperidin-4-amine;

2-14: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3,5-difluorophenyl)-2-methoxypyridin-4-yl]piperidin-4-amine;

2-15: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-methylpyridin-4-yl]piperidin-4-amine;

3-1: 1-[3-(5-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-2: 1-[3-(6-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-3: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-4: 1-[3-(6-fluoro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-5: 1-[5-(3-fluoro-5-methylphenyl)-3-(6-methoxy-1H-indol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-6: 1-[3-(4-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-7: 1-[3-(7-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-8: 1-[3-(5-fluoro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-9: 1-[5-(3-fluoro-5-methylphenyl)-3-(5-methoxy-1H-indol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-10: 1-[5-(3-fluoro-5-methylphenyl)-3-(5-methoxy-1H-1,3-benzodiazol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-11: *trans*-1-[3-(6-chloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]-3-methoxypiperidin-4-amine;

3-12: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-6-carbonitrile;

3-13: 1-[3-(5-fluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-14: 1-[3-(3,6-dichloro-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-15: 1-[5-(3-fluoro-5-methylphenyl)-3-[6-(2H-1,2,3,4-tetrazol-5-yl)-1H-indol-2-yl]pyridazin-4-yl]piperidin-4-amine;

3-16: 1-[5-(3-fluoro-5-methylphenyl)-3-(6-methyl-1H-indol-2-yl)pyridazin-4-yl]piperidin-4-amine;

3-17: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-5-carbonitrile;

3-18: methyl 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-6-carboxylate;

3-19: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-6-carboxamide;

3-20: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-N-methoxy-1H-indole-6-carboxamide;

3-21: 1-[3-(3-chloro-6-methoxy-1H-indol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-4-yl]piperidin-4-amine;

3-22: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-1,3-benzodiazole-5-carbonitrile;

3-23: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-7-carbonitrile;

3-24: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-3-chloro-1H-indole-6-carbonitrile;

3-25: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-6-methoxy-1H-indole-3-carbonitrile;

3-26: 2-[4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridazin-3-yl]-1H-indole-3,6-dicarbonitrile;

4-1: 3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N-methyl-4-[4-(methylamino)piperidin-1-yl]pyridin-2-amine;

4-2: 2-[2-amino-5-(3-fluoro-5-methylphenyl)-4-[4-(methylamino)piperidin-1-yl]pyridin-3-yl]-1H-1,3-benzodiazole-6-carbonitrile;

4-3: 2-[2-amino-5-(3-fluoro-5-methylphenyl)-4-[4-(methylamino)piperidin-1-yl]pyridin-3-yl]-7-fluoro-1H-1,3-benzodiazole-5-carbonitrile;

4-4: 4-(4-aminopiperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-(7-methoxy-1H-1,3-benzodiazol-2-yl)-N,N-dimethylpyridin-2-amine;

4-5: 4-(4-aminopiperidin-1-yl)-3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N,N-dimethylpyridin-2-amine;

4-6: 4-(4-aminopiperidin-1-yl)-3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-N,N-dimethylpyridin-2-amine;

4-7: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(3-fluoroazetidin-1-yl)pyridin-4-yl]piperidin-4-amine;

4-8: 1-[3-(5,7-difluoro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(morpholin-4-yl)pyridin-4-yl]piperidin-4-amine;

4-9: 1-[3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-2-(3-fluoroazetidin-1-yl)-5-(3-fluorophenyl)pyridin-4-yl]piperidin-4-amine;

4-10: 3-(5-fluoro-7-methoxy-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-4-[4-(methylamino)piperidin-1-yl]pyridin-2-amine;

4-11: 1-[3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl]piperidin-4-amine;
or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or individual enantiomers thereof.

53. A pharmaceutical composition comprising a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomersthereof, and at least one pharmaceutically acceptable excipient.

54. The pharmaceutical composition of claim 53, wherein the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration.

55. The pharmaceutical composition of claim 53, wherein the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

56. A method of treating a disease or condition in a mammal that would benefit from the modulation of somatostatin receptor subtype 2 (SSTR2) activity comprising administering a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, diastereomeric mixture, or individual enantiomers thereof, to the mammal in need thereof.

57. The method of claim 56, wherein the disease or condition is acromegaly, a neuroendocrine tumor, an ophthalmic disease or condition, neuropathy, nephropathy, a respiratory disease or condition, cancer, pain, a neurodegenerative disease or condition, an inflammatory disease or condition, a psychiatric disease or condition, or combinations thereof.