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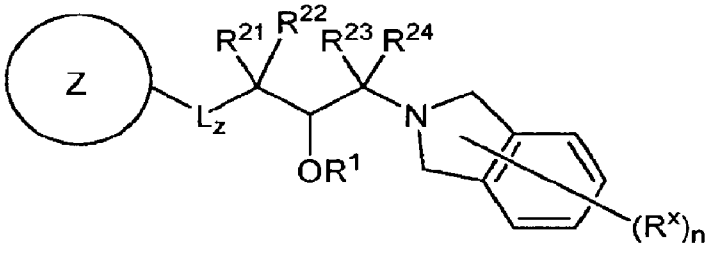
(54) Title: PRMT5 INHIBITORS AND USES THEREOF



(A)

(57) Abstract: Described herein are compounds of formula (A), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. Compounds of the present invention are useful for inhibiting PRMT5 activity. Methods of using the compounds for treating PRMT5-mediated disorders are also described.

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PRMT5 Inhibitors and Uses Thereof

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent applications, U.S.S.N. 61/745,494, filed December 21, 2012, and U.S.S.N. 61/785,095, filed March 14, 2013, the entire contents of each of which are incorporated herein by reference.

Background of the Invention

[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases.

[0003] Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.*, PRMT5), many of which are associated with specific genetic alterations that can cause human disease.

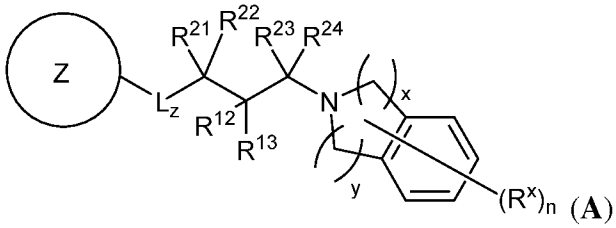
[0004] Disease-associated chromatin-modifying enzymes (*e.g.*, PRMT5) play a role in diseases such as proliferative disorders, metabolic disorders, and blood disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of PRMT5.

Detailed Description of Certain Embodiments

[0005] Protein arginine methyltransferase 5 (PRMT5) catalyzes the addition of two methyl groups to the two ω-guanidino nitrogen atoms of arginine, resulting in ω-NG, N′G symmetric dimethylation of arginine (sDMA) of the target protein. PRMT5 functions in the nucleus as well as in the cytoplasm, and its substrates include histones, spliceosomal proteins, transcription factors (See *e.g.,* Sun *et al.*, *PNAS* (2011) 108: 20538-20543). PRMT5 generally functions as part of a molecule weight protein complex. While the protein complexes of PRMT5 can have a variety of components, they generally include the protein MEP50 (methylosome protein 50). In addition, PRMT5 acts in conjunction with cofactor

SAM (S-adenosyl methionine).

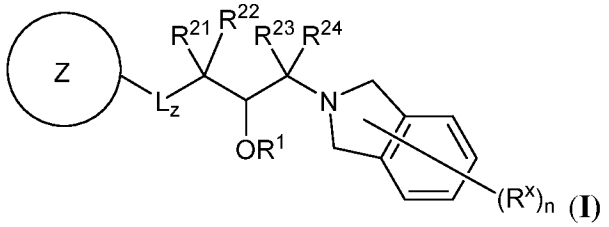
[0006] PRMT5 is an attractive target for modulation given its role in the regulation of diverse biological processes. It has now been found that compounds described herein, and pharmaceutically acceptable salts and compositions thereof, are effective as inhibitors of PRMT5. Such compounds have the general Formula (**A**):



(**A**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{12}, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, x, y, and n are as defined herein.

[0007] In some embodiments, the inhibitors of PRMT5 have the general Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as defined herein.

[0008] In some embodiments, pharmaceutical compositions are provided which comprise a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0009] In certain embodiments, compounds described herein inhibit activity of PRMT5. In certain embodiments, methods of inhibiting PRMT5 are provided which comprise contacting PRMT5 with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or a subject. Thus, such methods encompass inhibition of PRMT5 activity both *in vitro* and *in vivo*. In certain embodiments, the PRMT5 is wild-type PRMT5. In certain embodiments, the PRMT5 is overexpressed. In certain embodiments, the PRMT5 is a mutant. In certain embodiments, the PRMT5 is in a cell. In certain embodiments, the PRMT5 is in an animal, *e.g.*, a human. In some embodiments, the PRMT5 is in a subject that is susceptible to normal levels of PRMT5 activity due to one or more

mutations associated with a PRMT5 substrate. In some embodiments, the PRMT5 is in a subject known or identified as having abnormal PRMT5 activity (*e.g.*, overexpression). In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective relative to one or more other methyltransferases.

[0010] In certain embodiments, methods of altering gene expression in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, cell is in an animal, *e.g.*, a human.

[0011] In certain embodiments, methods of altering transcription in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human.

[0012] In some embodiments, methods of treating a PRMT5-mediated disorder are provided which comprise administering to a subject suffering from a PRMT5-mediated disorder an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the PRMT5-mediated disorder is a proliferative disorder, a metabolic disorder, or a blood disorder. In certain embodiments, compounds described herein are useful for treating cancer. In certain embodiments, compounds described herein are useful for treating hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer. In certain embodiments, compounds described herein are useful for treating a hemoglobinopathy. In certain embodiments, compounds described herein are useful for treating sickle cell anemia. In certain embodiments, compounds described herein are useful for treating diabetes or obesity. In certain embodiments, a provided compound is useful in treating inflammatory and autoimmune disease.

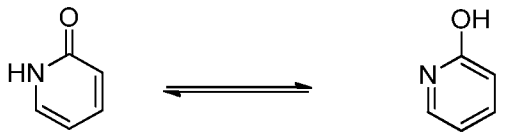
[0013] Compounds described herein are also useful for the study of PRMT5 in biological and pathological phenomena, the study of intracellular signal transduction pathways mediated by PRMT5, and the comparative evaluation of new PRMT5 inhibitors.

[0014] This application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

[0015] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0016] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0017] It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of any compound described herein does not exclude any tautomer form.



pyridin-2(1*H*)-one pyridin-2-ol

[0018] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0019] The term "aliphatic," as used herein, includes both saturated and unsaturated, nonaromatic, straight chain (*i.e.*, unbranched), branched, acyclic, and cyclic (*i.e.*, carbocyclic) hydrocarbons. In some embodiments, an aliphatic group is optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl moieties.

[0020] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0021] "Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the

like. In certain embodiments, each instance of an alkyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (*e.g.*, $-CH_3$). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl.

[0022] In some embodiments, an alkyl group is substituted with one or more halogens. "Perhaloalkyl" is a substituted alkyl group as defined herein wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the alkyl moiety has 1 to 8 carbon atoms ("C_{1-8} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 6 carbon atoms ("C_{1-6} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 4 carbon atoms ("C_{1-4} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 3 carbon atoms ("C_{1-3} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 2 carbon atoms ("C_{1-2} perhaloalkyl"). In some embodiments, all of the hydrogen atoms are replaced with fluoro. In some embodiments, all of the hydrogen atoms are replaced with chloro. Examples of perhaloalkyl groups include $-CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

[0023] "Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. In certain embodiments, each instance of an alkenyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain

embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

[0024] "Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds, and optionally one or more double bonds ("C_{2-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. In certain embodiments, each instance of an alkynyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[0025] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups

include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. In certain embodiments, each instance of a carbocyclyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

[0026] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). In certain embodiments, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

[0027] "Heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 14–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In certain embodiments, heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. In certain embodiments, each instance of heterocyclyl is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[0028] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms independently selected from nitrogen, oxygen, and

sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0029] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0030] "Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl

groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. In certain embodiments, each instance of an aryl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

[0031] "Heteroaryl" refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–14 membered heteroaryl"). In certain embodiments, heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *e.g.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

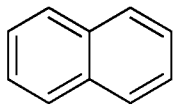
[0032] In some embodiments, a heteroaryl group is a 5–14 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–14 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided

in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, each instance of a heteroaryl group is independently optionally substituted, *e.g.*, unsubstituted ("unsubstituted heteroaryl") or substituted ("substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[0033] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–

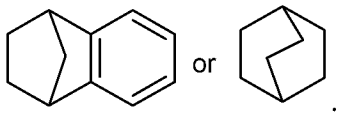
bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0034] "Fused" or "ortho-fused" are used interchangeably herein, and refer to two rings that have two atoms and one bond in common, *e.g.*.,



napthalene .

[0035] "Bridged" refers to a ring system containing (1) a bridgehead atom or group of atoms which connect two or more non-adjacent positions of the same ring; or (2) a bridgehead atom or group of atoms which connect two or more positions of different rings of a ring system and does not thereby form an ortho-fused ring, *e.g.*,



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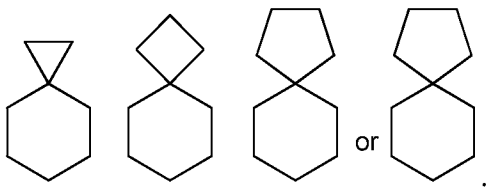
[0036] "Spiro" or "Spiro-fused" refers to a group of atoms which connect to the same atom of a carbocyclic or heterocyclic ring system (geminal attachment), thereby forming a ring, *e.g.*,



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Spiro-fusion at a bridgehead atom is also contemplated.

[0037] "Partially unsaturated" refers to a group that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.*, aryl or heteroaryl groups) as herein defined. Likewise, "saturated" refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

[0038] In some embodiments, aliphatic, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, "substituted" or "unsubstituted" aliphatic, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one

hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, including any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0039] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group $=O$, $=S$, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl,

carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3{}^+X^–$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1-6}$ alkyl, $–ON(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_2$, $–N(C_{1-6}$ alkyl$)_3^+X^-$, $–NH(C_{1-6}$ alkyl$)_2^+X^-$, $–NH_2(C_{1-6}$ alkyl$)^+X^-$, $–NH_3^+X^-$, $–N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl), –N(OH)(C_{1-6} alkyl), –NH(OH), –SH, $–SC_{1-6}$ alkyl, $–SS(C_{1-6}$ alkyl), $–C(=O)(C_{1-6}$ alkyl), $–CO_2H$, $–CO_2(C_{1-6}$ alkyl), $–OC(=O)(C_{1-6}$ alkyl), $–OCO_2(C_{1-6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1-6}$ alkyl$)_2$, –OC(=O)NH(C_{1-6} alkyl), –NHC(=O)(C_{1-6} alkyl), $–N(C_{1-6}$ alkyl$)C(=O)($ C_{1-6} alkyl), $–NHCO_2(C_{1-6}$ alkyl), $–NHC(=O)N(C_{1-6}$ alkyl$)_2$, –NHC(=O)NH(C_{1-6} alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1-6}$ alkyl),$–OC(=NH)(C_{1-6}$ alkyl), $–OC(=NH)OC_{1-6}$ alkyl, $–C(=NH)N(C_{1-6}$ alkyl$)_2$, $–C(=NH)NH(C_{1-6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1-6}$ alkyl$)_2$, –OC(NH)NH(C_{1-6} alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1-6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1-6}$ alkyl), $–SO_2N(C_{1-6}$ alkyl$)_2$, $–SO_2NH(C_{1-6}$ alkyl), $–SO_2NH_2$,$–SO_2C_{1-6}$ alkyl, $–SO_2OC_{1-6}$ alkyl, $–OSO_2C_{1-6}$ alkyl, $–SOC_{1-6}$ alkyl, $–Si(C_{1-6}$ alkyl$)_3$, $–OSi(C_{1-6}$ alkyl$)_3$ –C(=S)N(C_{1-6} alkyl$)_2$, C(=S)NH(C_{1-6} alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1-6}$ alkyl), $–C(=S)SC_{1-6}$ alkyl, $–SC(=S)SC_{1-6}$ alkyl, $–P(=O)_2(C_{1-6}$ alkyl), $–P(=O)(C_{1-6}$ alkyl$)_2$, $–OP(=O)(C_{1-6}$ alkyl$)_2$, –OP(=O)(OC_{1-6} alkyl$)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

[0040] A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.,* acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0041] "Halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0042] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0043] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $C_{1–10}$ alkyl (*e.g.,* aralkyl, heteroaralkyl), $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0044] Amide nitrogen protecting groups *(e.g.,* $–C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine, *o*–nitrobenzamide, and *o*–(benzoyloxymethyl)benzamide.

[0045] Carbamate nitrogen protecting groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxyacylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl

carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, and 2,4,6–trimethylbenzyl carbamate.

[0046] Sulfonamide nitrogen protecting groups (*e.g.*, $–S(=O)_2R^{aa}$) include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0047] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl–(10)–acyl derivative, *N'*–*p*–toluenesulfonylaminoacyl derivative, *N'*–phenylaminothioacyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– or tungsten)acyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp),

dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

[0048] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

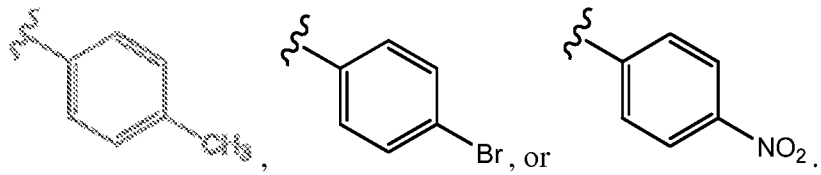
[0049] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4′–

bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4′,4″–tris(levulinoyloxyphenyl)methyl, 4,4′,4″–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4′,4″–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1′–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodisulfuran–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), *t*–butyl carbonate (BOC), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl *o*–nitrobenzyl carbonate, alkyl *p*–nitrobenzyl carbonate, alkyl *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0050] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $–R^{aa}$, $–N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, –

$Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0051] As used herein, a "leaving group", or "LG", is a term understood in the art to refere to a molecular fragment that departs with a pair of electrons upon heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. See, for example, Smith, March *Advanced Organic Chemistry* 6th ed. (501–502). Examples of suitable leaving groups include, but are not limited to, halides (such as chloride, bromide, or iodide), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, N,O-dimethylhydroxylamino, pixyl, haloformates, $-NO_2$, trialkylammonium, and aryliodonium salts. In some embodiments, the leaving group is a sulfonic acid ester. In some embodiments, the sulfonic acid ester comprises the formula $-OSO_2R^{LG1}$ wherein R^{LG1} is selected from the group consisting alkyl optionally, alkenyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, arylalkyl optionally substituted, and heterarylalkyl optionally substituted. In some embodiments, R^{LG1} is substituted or unsubstituted C_1-C_6 alkyl. In some embodiments, R^{LG1} is methyl. In some embodiments, R^{LG1} is $-CF_3$. In some embodiments, R^{LG1} is substituted or unsubstituted aryl. In some embodiments, R^{LG1} is substituted or unsubstituted phenyl. In some embodiments R^{LG1} is:



[0052] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The present disclosure is not intended to be limited in any manner by the above exemplary listing of substituents.

[0053] "Pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in

detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds describe herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, quaternary salts.

[0054] A "subject" to which administration is contemplated includes, but is not limited to, humans (*e.g.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or other non–human animals, for example, non-human mammals (*e.g.*, primates (*e.g.,* cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), rodents (*e.g.*, rats and/or mice), reptiles, amphibians, and fish. In certain embodiments, the non–human animal is a mammal. The non–human animal may be a male or female at any stage of development. A non–human animal may be a transgenic animal.

[0055] "Condition," "disease," and "disorder" are used interchangeably herein.

[0056] "Treat," "treating" and "treatment" encompasses an action that occurs while a subject is suffering from a condition which reduces the severity of the condition or retards or slows the progression of the condition ("therapeutic treatment"). "Treat," "treating" and "treatment" also encompasses an action that occurs before a subject begins to suffer from the

condition and which inhibits or reduces the severity of the condition ("prophylactic treatment").

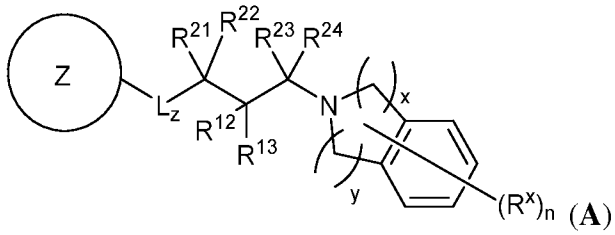
[0057] An "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, treat the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0058] A "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0059] A "prophylactically effective amount" of a compound is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0060] As used herein, the term "methyltransferase" represents transferase class enzymes that are able to transfer a methyl group from a donor molecule to an acceptor molecule, *e.g.*, an amino acid residue of a protein or a nucleic base of a DNA molecule. Methytransferases typically use a reactive methyl group bound to sulfur in S-adenosyl methionine (SAM) as the methyl donor. In some embodiments, a methyltransferase described herein is a protein methyltransferase. In some embodiments, a methyltransferase described herein is a histone methyltransferase. Histone methyltransferases (HMT) are histone-modifying enzymes, (including histone-lysine N-methyltransferase and histone-arginine N-methyltransferase), that catalyze the transfer of one or more methyl groups to lysine and arginine residues of histone proteins. In certain embodiments, a methyltransferase described herein is a histone-arginine N-methyltransferase.

[0061] As generally described above, provided herein are compounds useful as PRMT5 inhibitors. In some embodiments, provided is a compound of Formula (**A**):



(**A**)

or a pharmaceutically acceptable salt thereof,

wherein:

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^1$;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L_z is absent or a linker;

Ring Z is an optionally substituted, monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{21}, R^{22}, R^{23}, and R^{24} are each independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic;

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

and

x is 0 and y is 2, 3, or 4; or

x is 1 and y is 1; or

x is 1 and y is 3.

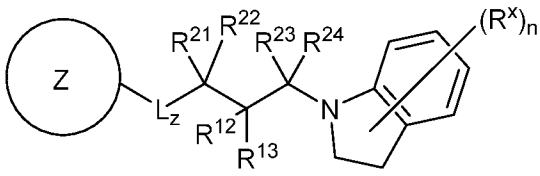
[0062] In some embodiments, the carbon attached to R^{12} has (*S*)-stereochemistry. In some embodiments, the carbon attached to R^{12} has (*R*)-stereochemistry. In some embodiments, the carbon attached to R^{13} has (*S*)-stereochemistry. In some embodiments, the carbon attached to R^{13} has (*R*) stereochemistry. In some embodiments, R^{12} is hydrogen. In some embodiments, R^{13} is hydrogen. In some embodiments, both R^{12} and R^{13} are hydrogen. In some

embodiments, R^{12} is optionally substituted C_{1-3}alkyl. In some embodiments, R^{13} is optionally substituted C_{1-3}alkyl. In some embodiments, both R^{12} and R^{13} are optionally substituted C_{1-3}alkyl. In some embodiments, R^{12} is halogen *e.g.,* fluoro, bromo, chloro, or iodo, provided that R^{13} is not $-OR^1$. In some embodiments, R^{13} is halogen *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, both R^{12} and R^{13} are halogen *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, R^{12} is halogen *e.g.,* fluoro, bromo, chloro, or iodo and R^{13} is optionally substituted C_{1-3}alkyl. In some embodiments, R^{12} is optionally substituted C_{1-3}alkyl and R^{13} is halogen *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, R^{13} is $-OR^1$. In some embodiments, R^{12} is optionally substituted C_{1-3}alkyl and R^{13} is $-OR^1$. In some embodiments, R^{12} is hydrogen and R^{13} is $-OR^1$. In some embodiments, R^{12} is hydrogen and R^{13} optionally substituted C_{1-3}alkyl. In some embodiments, R^{12} is optionally substituted C_{1-3}alkyl and R^{13} is hydrogen. In some embodiments, R^{12} is halogen *e.g.,* fluoro, bromo, chloro, or iodo and R^{13} is hydrogen. In some embodiments, R^{12} is hydrogen and R^{13} is halogen *e.g.,* fluoro, bromo, chloro, or iodo.

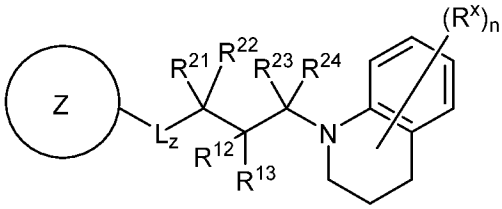
[0063] As generally defined above, R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl. In certain embodiments, R^{12} is hydrogen. In certain embodiments, R^{12} is optionally substituted C_{1-3}alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{12} is optionally substituted C_1alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{12} is optionally substituted C_2 alkyl, *e.g.,* ethyl. In certain embodiments, R^{12} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{12} is fluoro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is chloro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is bromo, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is iodo, provided that R^{13} is not $-OR^1$.

[0064] As generally defined above, R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$ or $-OR^1$. In certain embodiments, R^{13} is hydrogen. In certain embodiments, R^{13} is optionally substituted C_{1-3}alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{13} is optionally substituted C_1alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{13} is optionally substituted C_2 alkyl, *e.g.,* ethyl. In certain embodiments, R^{13} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{13} is fluoro. In certain embodiments, R^{13} is chloro. In certain embodiments, R^{13} is bromo. In certain embodiments, R^{13} is iodo.

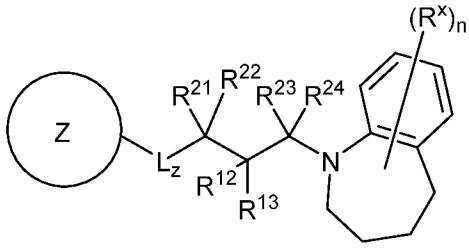
[0065] For example, in some embodiments of Formula (**A**), wherein x is 0 and y is 2, 3, or 4, provided is a compound of Formula (**A-i**), (**A-ii**), or (**A-iii**):



(**A-i**),



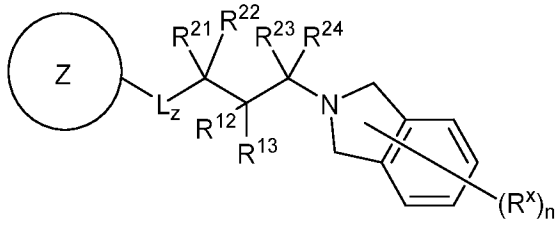
(**A-ii**), or



(**A-iii**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

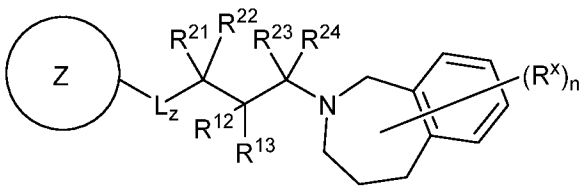
[0066] In some embodiments of Formula (**A**), wherein x is 1 and y is 1, provided is a compound of Formula (**A-iv**):



(**A-iv**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

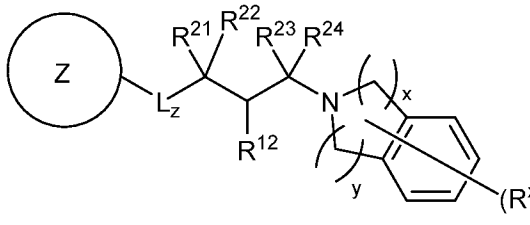
[0067] In some embodiments of Formula (**A**), wherein x is 1 and y is 3, provided is a compound of Formula (**A-v**):



(**A-v**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

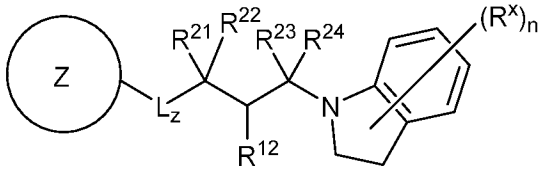
[0068] In some embodiments of Formula (**A**), wherein R^{13} is hydrogen, provided is a compound of Formula (**A-1**):



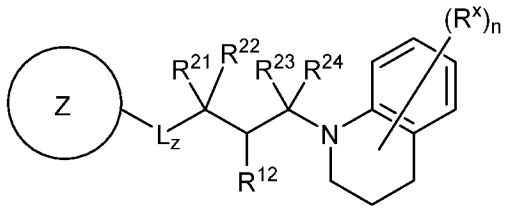
(**A-1**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, x, y, and n are as described herein.

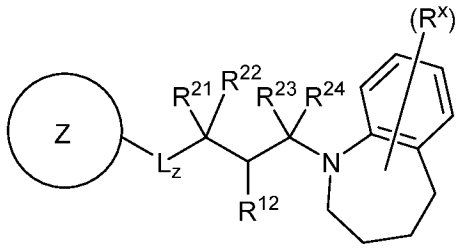
[0069] For example, in some embodiments of Formula (**A-1**), wherein x is 0 and y is 2, 3, or 4, provided is a compound of Formula (**A-1-i**), (**A-1-ii**), or (**A-1-iii**):



(**A-1-i**),



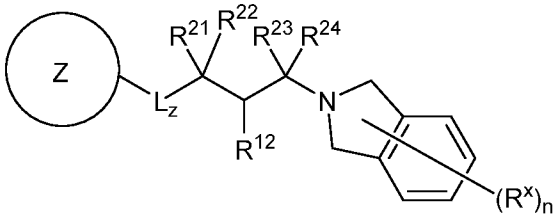
(**A-1-ii**), or



(**A-1-iii**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

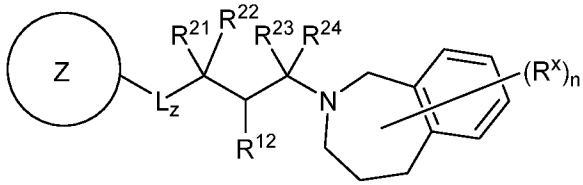
[0070] In some embodiments of Formula (**A-1**), wherein x is 1 and y is 1, provided is a compound of Formula (**A-1-iv**):



(**A-1-iv**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

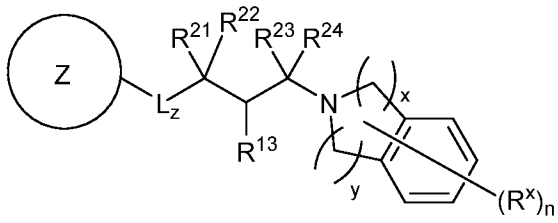
[0071] In some embodiments of Formula (**A-1**), wherein x is 1 and y is 3, provided is a compound of Formula (**A-1-v**):



(**A-1-v**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

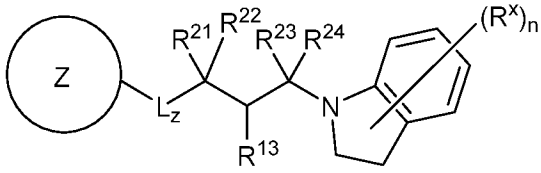
[0072] In some embodiments of Formula (**A**), wherein R^{12} is hydrogen, provided is a compound of Formula (**A-1***):



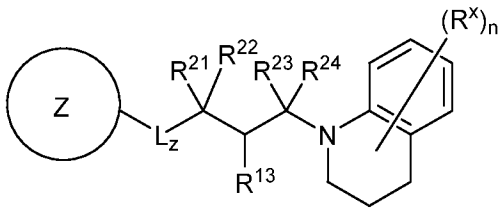
(**A-1***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, x, y, and n are as described herein.

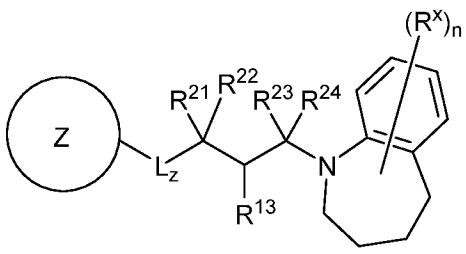
[0073] For example, in some embodiments of Formula (**A-1***), wherein x is 0 and y is 2, 3, or 4, provided is a compound of Formula (**A-1-i***), (**A-1-ii***), or (**A-1-iii***):



(**A-1-i***),



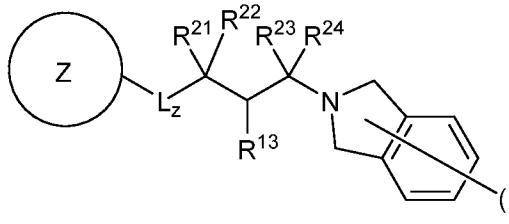
(**A-1-ii***), or



(**A-1-iii***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

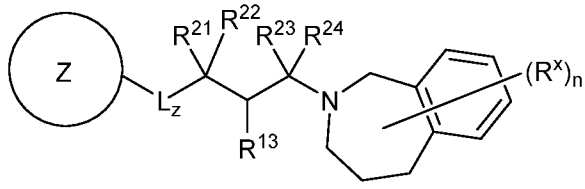
[0074] In some embodiments of Formula (**A-1***), wherein x is 1 and y is 1, provided is a compound of Formula (**A-1-iv***):



(**A-1-iv***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

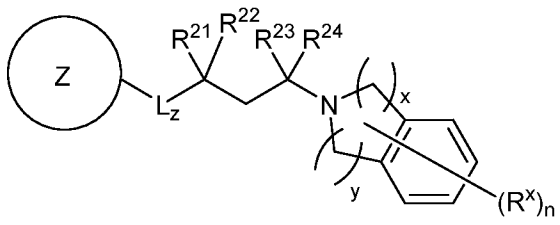
[0075] In some embodiments of Formula (**A-1***), wherein x is 1 and y is 3, provided is a compound of Formula (**A-1-v***):



(**A-1-v***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{13}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

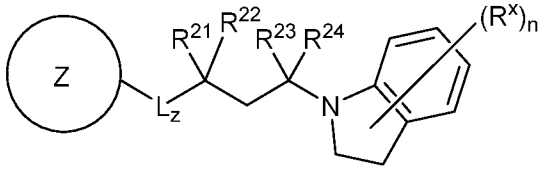
[0076] In some embodiments of Formula (**A**), wherein both R^{12} and R^{13} are hydrogen, provided is a compound of Formula (**A-2**):



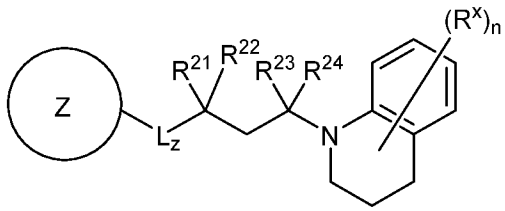
(**A-2**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{21}, R^{22}, R^{23}, R^{24}, R^x, x, y, and n are as described herein.

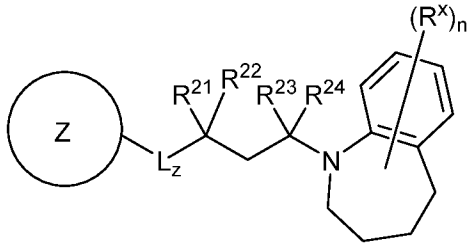
[0077] For example, in some embodiments of Formula (**A-2**), wherein x is 0 and y is 2, 3, or 4, provided is a compound of Formula (**A-2-i**), (**A-2-ii**), or (**A-2-iii**):



(**A-2-i**),



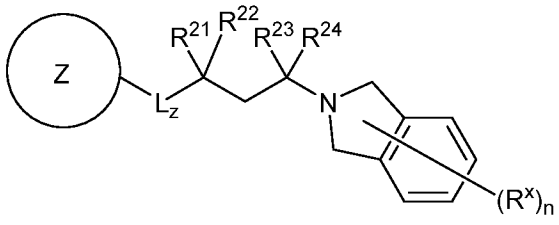
(**A-2-ii**), or



(**A-2-iii**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

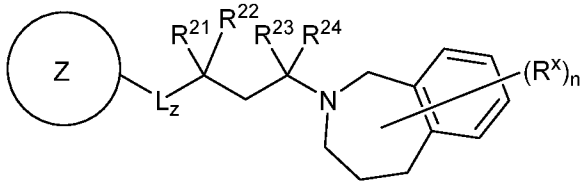
[0078] In some embodiments of Formula (**A-2**), wherein x is 1 and y is 1, provided is a compound of Formula (**A-2-iv**):



(**A-2-iv**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

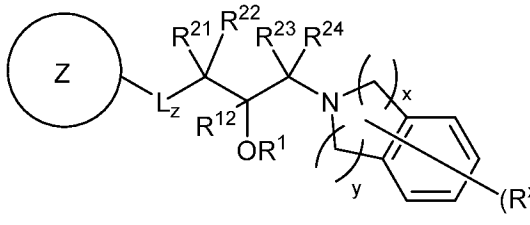
[0079] In some embodiments of Formula (**A-2**), wherein x is 1 and y is 3, provided is a compound of Formula (**A-2-v**):



(**A-2-v**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

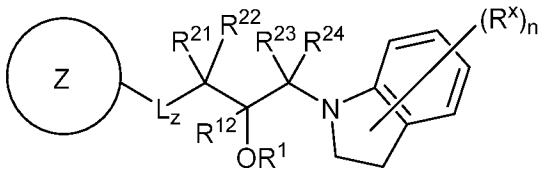
[0080] In some embodiments of Formula (**A**), wherein R^{13} is $-OR^1$, provided is a compound of Formula (**A-3**):



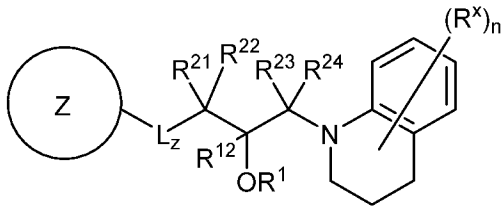
(**A-3**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, x, y, and n are as described herein.

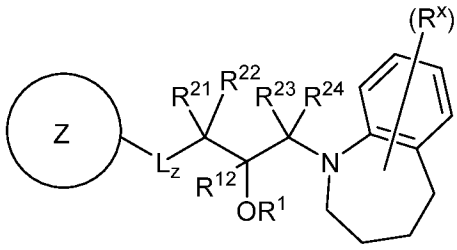
[0081] For example, in some embodiments of Formula (**A-3**), wherein x is 0 and y is 2, 3, or 4, provided is a compound of Formula (**A-3-i**), (**A-3-ii**), or (**A-3-iii**):



(**A-3-i**),



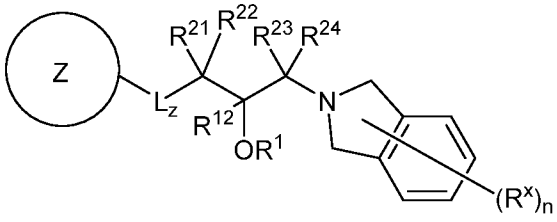
(**A-3-ii**), or



(**A-3-iii**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

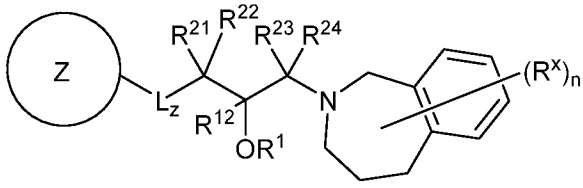
[0082] In some embodiments of Formula (**A-3**), wherein x is 1 and y is 1, provided is a compound of Formula (**A-3-iv**):



(**A-3-iv**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

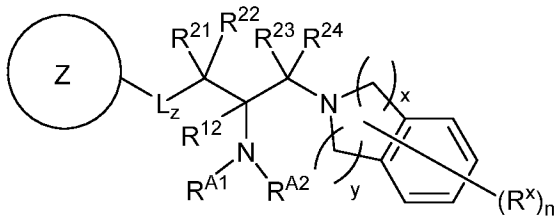
[0083] In some embodiments of Formula (**A**), wherein x is 1 and y is 3, provided is a compound of Formula (**A-v**):



(**A-3-v**)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

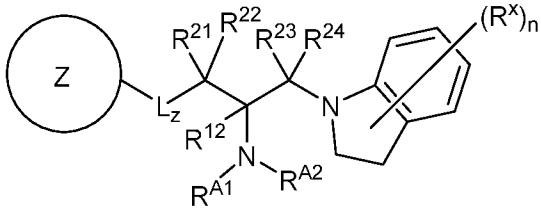
[0084] In some embodiments of Formula (**A**), wherein R^{13} is $-NR^{A1}R^{A2}$, provided is a compound of Formula (**A-3***):



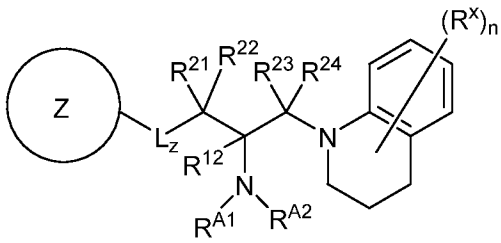
(**A-3***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, R^{A1}, R^{A2}, x, y, and n are as described herein.

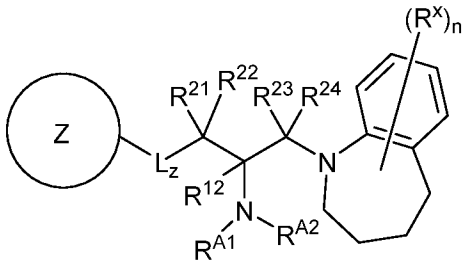
[0085] For example, in some embodiments of Formula (**A-3***), wherein x is 0 and y is 2, 3, or 4, provided is a compound of Formula (**A-3-i***), (**A-3-ii***), or (**A-3-iii***):



(**A-3-i***),



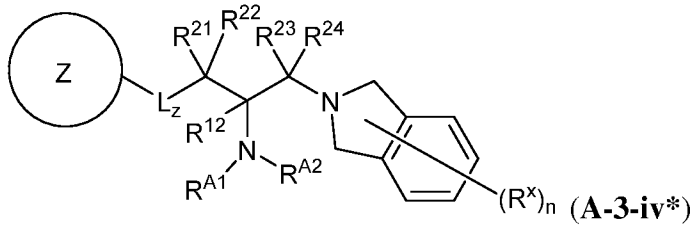
(**A-3-ii***), or



(**A-3-iii***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, R^{A1}, R^{A2}, and n are as described herein.

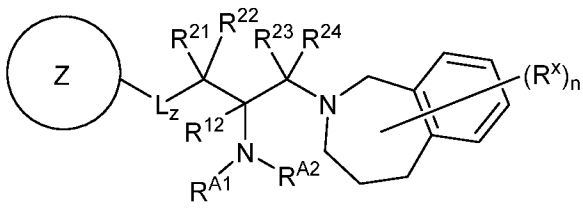
[0086] In some embodiments of Formula (**A-3***), wherein x is 1 and y is 1, provided is a compound of Formula (**A-3-iv***):



(**A-3-iv***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, R^{A1}, R^{A2}, and n are as described herein.

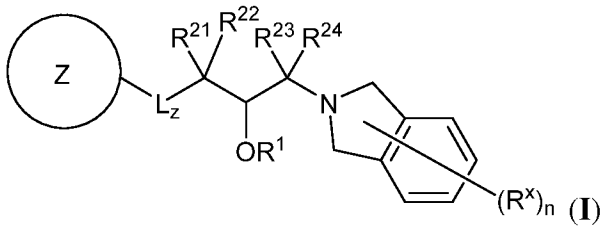
[0087] In some embodiments of Formula (**A**), wherein x is 1 and y is 3, provided is a compound of Formula (**A-v***):



(**A-3-v***)

or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^{12}, R^{21}, R^{22}, R^{23}, R^{24}, R^x, R^{A1}, R^{A2}, and n are as described herein.

[0088] In some embodiments of Formula (**A**), wherein x is 1, y is 1, R^{12} is hydrogen and R^{13} is $-OR^1$, provided is a compound of Formula (**I**):



(**I**)

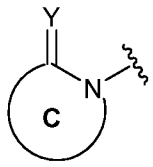
or a pharmaceutically acceptable salt thereof, wherein Ring Z, L_z, R^1, R^{21}, R^{22}, R^{23}, R^{24}, R^x, and n are as described herein.

[0001] As defined generally above, L_z is a linker or is absent. For example, in certain embodiments, L_z is a linker $-X_A-C(R^{2A})(R^{3A})C(=O)N(R)-$, a linker L_B as defined herein, or a linker L_D as defined herein. Alternatively, in certain embodiments, L_z is absent, and the carbon substituted with R^{21} and R^{22} is directly attached to Ring Z.

[0002] In certain embodiments, L_z is a linker $-X_A-C(R^{2A})(R^{3A})C(=O)N(R)-$ and Ring Z is a group Cy^A, as defined herein.

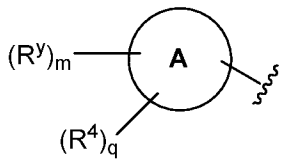
[0003] In certain embodiments, L_z is a linker L_B and Ring Z is a group Ar, as defined herein.

[0004] In certain embodiments, L_z is absent, and Ring Z is a group referred to herein as Ring C:



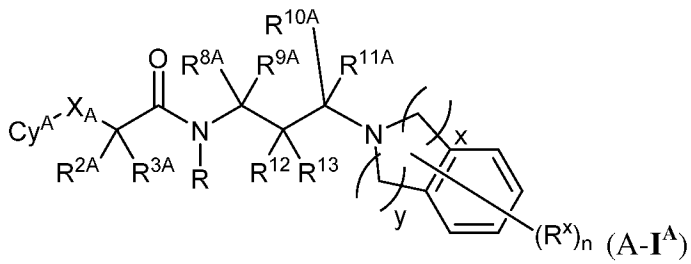
.

[0005] In certain embodiments, L_z is linker L_D, and Ring Z is a group referred to herein as Ring A:



.

[0006] In some embodiments, wherein L_z is a linker -X_A-C(R^{2A})(R^{3A})C(=O)N(R)- and Ring Z is a group Cy^A, provided is a compound of Formula (**A-I^A**):



(A-**I^A**)

or a pharmaceutically acceptable salt thereof, wherein x and y are defined herein, and wherein:

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, –$NR^{A1}R^{A2}$, or –OR^1;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

R^1 is hydrogen, R^z, or –C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl;

X_A is a bond, –O–, –N(R)–, –$CR^{4A}R^{5A}$–, -O-$CR^{4A}R^{5A}$, -N(R)-$CR^{4A}R^{5A}$-, -O-$CR^{4A}R^{5A}$-O-, -N(R)-$CR^{4A}R^{5A}$-O, -N(R)-$CR^{4A}R^{5A}$-N(R)-, -O-$CR^{4A}R^{5A}$-N(R)-, -$CR^{4A}R^{5A}$-O-, -$CR^{4A}R^{5A}$-N(R)-, -O-$CR^{4A}R^{5A}$-$CR^{6A}R^{7A}$-, -N(R)-$CR^{4A}R^{5A}$-$CR^{6A}R^{7A}$-, -$CR^{6A}R^{7A}$-$CR^{4A}R^{5A}$-O-, -$CR^{6A}R^{7A}$-$CR^{4A}R^{5A}$-N(R)-, or –$CR^{6A}R^{7A}$-$CR^{4A}R^{5A}$-;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

R^{2A} and R^{3A} are independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{2A} and R^{3A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^{4A} and R^{5A} are independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{4A} and R^{5A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^{6A} and R^{7A} are independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{6A} and R^{7A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^{8A}, R^{9A}, R^{10A}, and R^{11A} are each independently hydrogen, halo, or optionally substituted aliphatic;

Cy^A is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups;

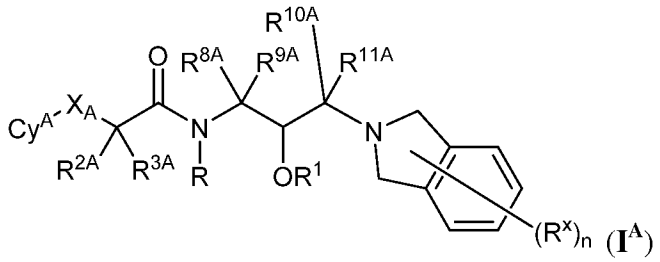
each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

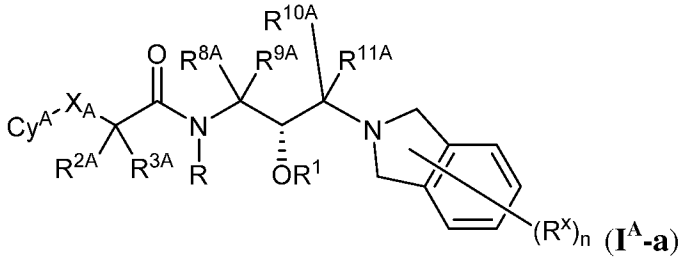
[0007] In certain embodiments of Formula (**A-I^A**), wherein R^{12} is hydrogen, and R^{13} is $-OR^1$, a provided compound is of Formula (**I^A**):



(**I^A**)

or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^{2A}, R^{3A}, R^{8A}, R^{9A}, R^{10A}, R^{11A}, R^x, n, X_A, and Cy^A are as described herein.

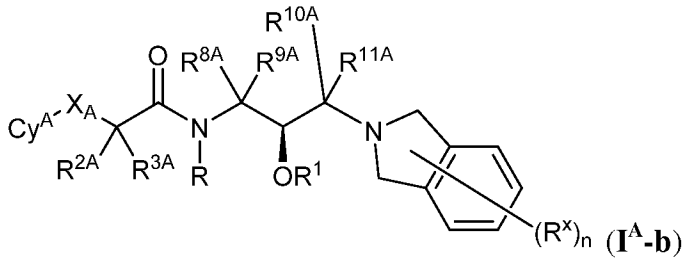
[0008] In certain embodiments, a provided compound is of Formula (**I^A-a**):



(**I^A-a**)

or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^{2A}, R^{3A}, R^{8A}, R^{9A}, R^{10A}, R^{11A}, R^x, n, X_A, and Cy^A are as described herein.

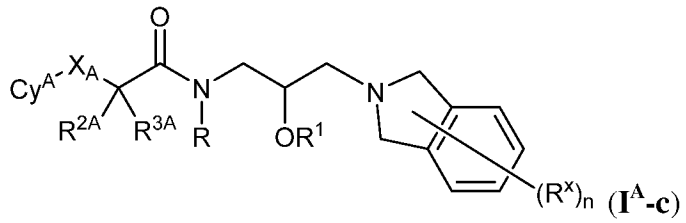
[0009] In certain embodiments, a provided compound is of Formula (**I^A-b**):



(**I^A-b**)

or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^{2A}, R^{3A}, R^{8A}, R^{9A}, R^{10A}, R^{11A}, R^x, n, X_A, and Cy^A are as described herein.

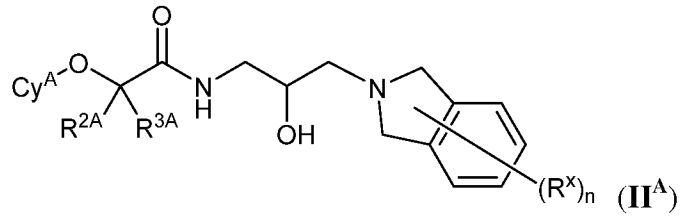
[0010] In certain embodiments, a provided compound is of Formula (**I^A-c**):



(**I^A-c**)

or a pharmaceutically acceptable salt thereof, wherein R, R^1, R^{2A}, R^{3A}, R^x, n, X_A, and Cy^A are as described herein.

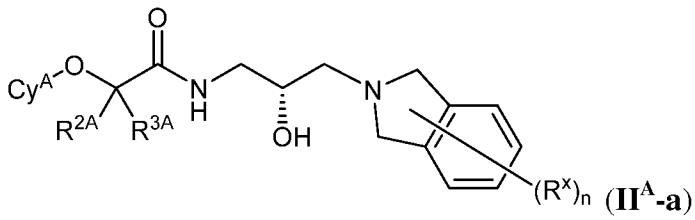
[0011] In certain embodiments, a provided compound is of Formula (**A-II^A**):



(**II^A**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

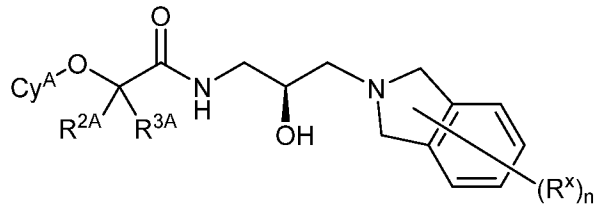
[0012] In certain embodiments, a provided compound is of Formula (**II^A-a**):



(**II^A-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

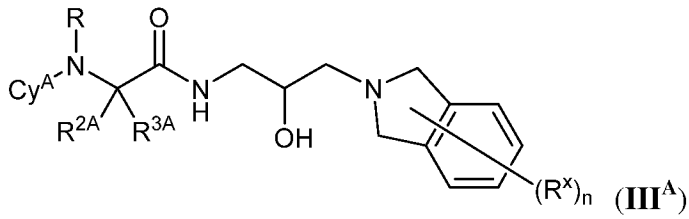
[0013] In certain embodiments, a provided compound is of Formula (**II^A-b**):



(**II^A-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

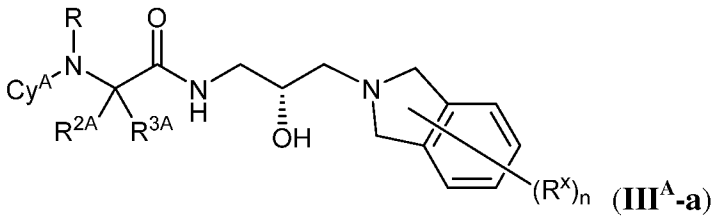
[0014] In certain embodiments, a provided compound is of Formula (**III^A**):



(**III^A**)

or a pharmaceutically acceptable salt thereof, wherein R, R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

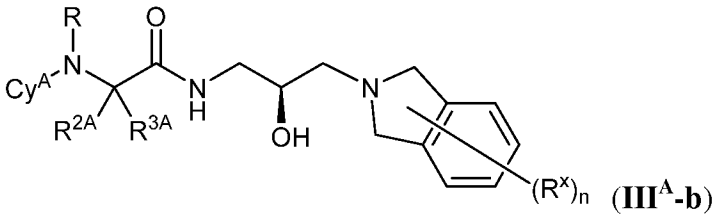
[0015] In certain embodiments, a provided compound is of Formula (**III^A-a**):



(**III^A-a**)

or a pharmaceutically acceptable salt thereof, wherein R, R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

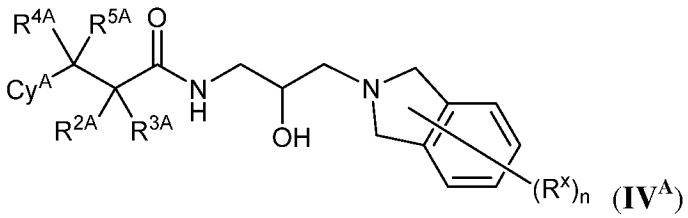
[0016] In certain embodiments, a provided compound is of Formula (**III^A-f**):



(**III^A-b**)

or a pharmaceutically acceptable salt thereof, wherein R, R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

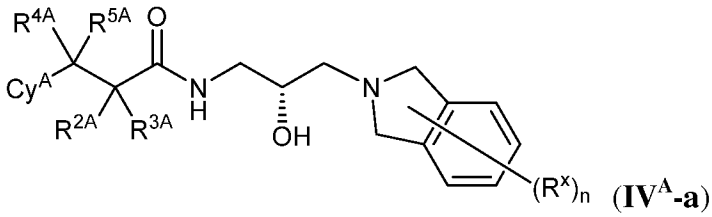
[0017] In certain embodiments, a provided compound is of Formula ($\mathbf{IV^A}$):



($\mathbf{IV^A}$)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^x, n, and Cy^A are as described herein.

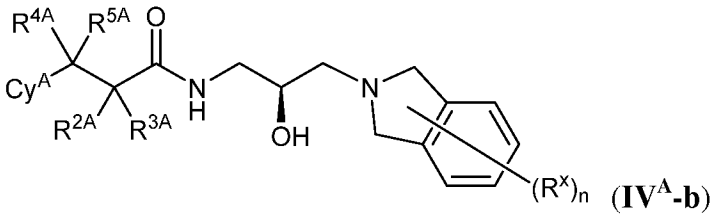
[0018] In certain embodiments, a provided compound is of Formula ($\mathbf{IV^A}$-**a**):



($\mathbf{IV^A}$-**a**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^x, n, and Cy^A are as described herein.

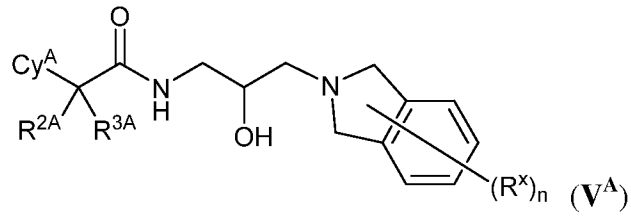
[0019] In certain embodiments, a provided compound is of Formula ($\mathbf{IV^A}$-**b**):



($\mathbf{IV^A}$-**b**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^x, n, and Cy^A are as described herein.

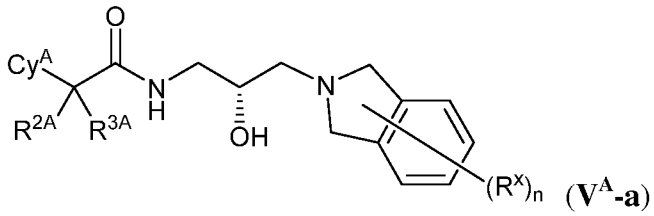
[0020] In certain embodiments, a provided compound is of Formula ($\mathbf{V^A}$):



($\mathbf{V^A}$)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

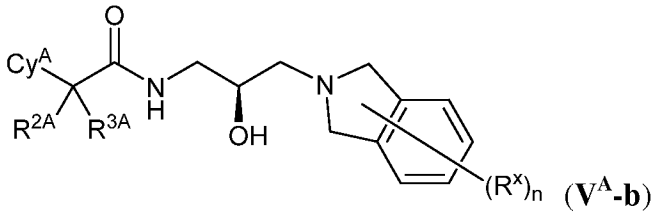
[0021] In certain embodiments, a provided compound is of Formula ($\mathbf{V^A}$-**a**):



($\mathbf{V^A}$-**a**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

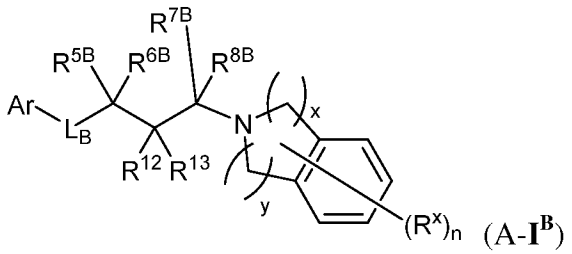
[0022] In certain embodiments, a provided compound is of Formula ($\mathbf{V^A}$-**b**):



($\mathbf{V^A}$-**b**)

or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{3A}, R^x, n, and Cy^A are as described herein.

[0023] In some embodiments, wherein L_z is a linker L_B and Ring Z is a group Ar, provided is a compound of Formula (A-$\mathbf{I^B}$):



(A-$\mathbf{I^B}$)

or a pharmaceutically acceptable salt thereof, wherein x and y are defined herein, and wherein

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^1$;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L_B is $-N(R)C(O)-$, $-C(O)N(R)-$, $-N(R)C(O)N(R)-$,$-N(R)C(O)O-$, or $-OC(O)N(R)-$;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

Ar is a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits; or

Ar is a monocyclic or bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits;

each R^y is independently selected from the group consisting of halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

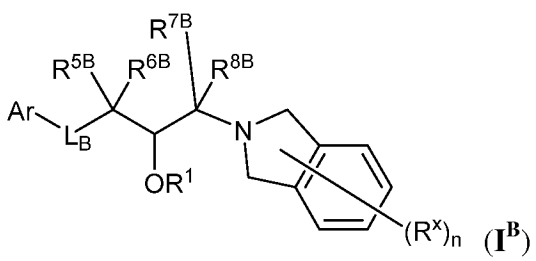
R^{5B}, R^{6B}, R^{7B}, and R^{8B} are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

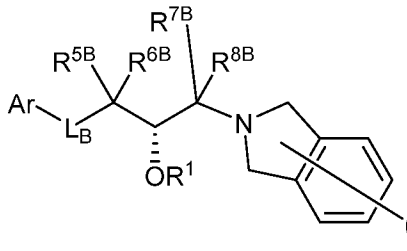
[0024] In certain embodiments, wherein R^{12} is hydrogen, and R^{13} is -OR^1, a provided compound is of Formula ($\mathbf{I^B}$):



($\mathbf{I^B}$)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, n, L_B, and Ar are as described herein.

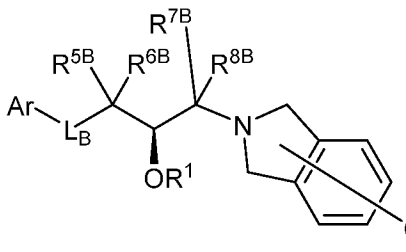
[0025] In certain embodiments, a provided compound is of Formula (**I^B-a**):



(**I^B-a**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, n, L_B, and Ar are as described herein.

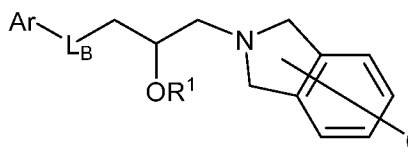
[0026] In certain embodiments, a provided compound is of Formula (**I^B-b**):



(**I^B-b**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, n, L_B, and Ar are as described herein.

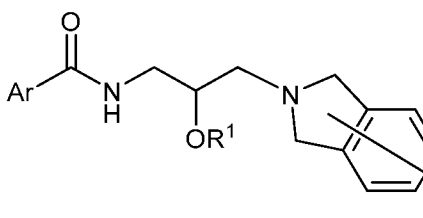
[0027] In certain embodiments, a provided compound is of Formula (**I^B-c**):



(**I^B-c**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, L_B, and Ar are as described herein.

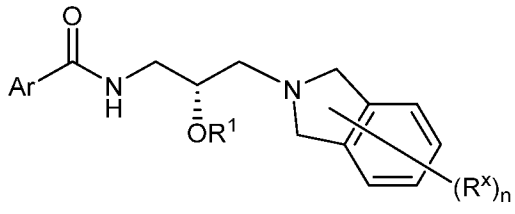
[0028] In certain embodiments, a provided compound is of Formula (**II^B**):



(**II^B**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, and Ar are as described herein.

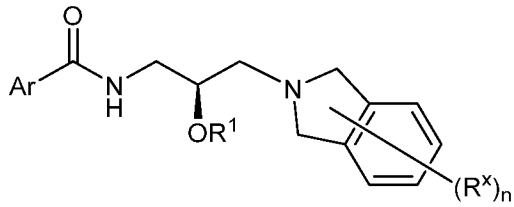
[0029] In certain embodiments, a provided compound is of Formula ($\mathbf{II^B\text{-}a}$):



($\mathbf{II^B\text{-}e}$)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, and Ar are as described herein.

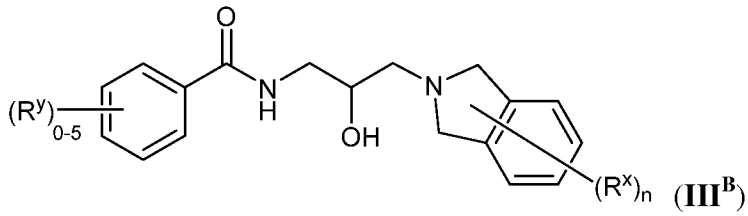
[0030] In certain embodiments, a provided compound is of Formula ($\mathbf{II^B\text{-}f}$):



$\mathbf{II^B\text{-}f}$

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, and Ar are as described herein.

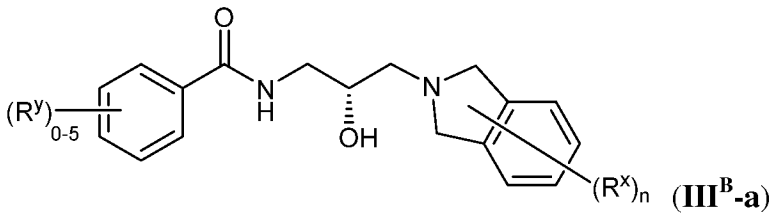
[0031] In certain embodiments, a provided compound is of Formula ($\mathbf{III^B}$):



($\mathbf{III^B}$)

or a pharmaceutically acceptable salt thereof, wherein R^y, R^x, and n are as described herein.

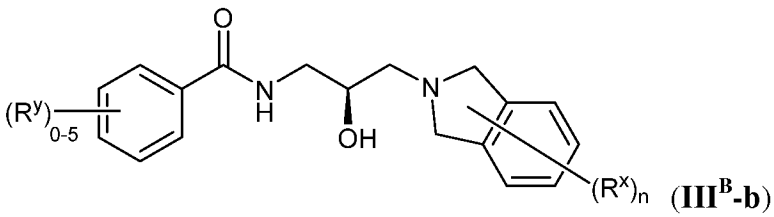
[0032] In certain embodiments, a provided compound is of Formula ($\mathbf{III^B\text{-}a}$):



($\mathbf{III^B\text{-}a}$)

or a pharmaceutically acceptable salt thereof, wherein R^y, R^x, and n are as described herein.

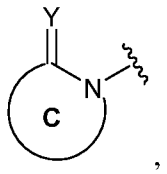
[0033] In certain embodiments, a provided compound is of Formula ($\mathbf{III^B\text{-}b}$):



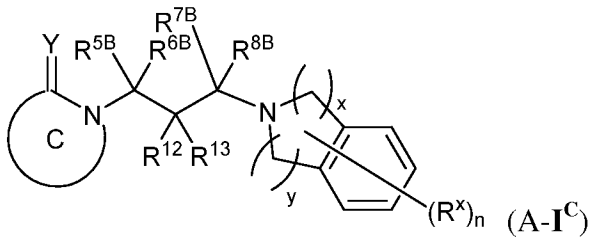
($\mathbf{III^B\text{-}b}$)

or a pharmaceutically acceptable salt thereof, wherein R^y, R^x, and n are as described herein.

[0034] In some embodiments, wherein L_z is absent, and Ring Z is a group of formula (also referred to herein as Ring C):



provided is a compound of Formula (A-$\mathbf{I}^{C}$):



(A-$\mathbf{I}^{C}$)

or a pharmaceutically acceptable salt thereof, wherein x and y are defined herein, and wherein

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^{1}$;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

Ring C is an optionally substituted, 5- to 12-membered, monocyclic or bicyclic, heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{1} is hydrogen, R^{z}, or $-C(O)R^{z}$, wherein R^{z} is optionally substituted C_{1-6} alkyl;

Y is O or S;

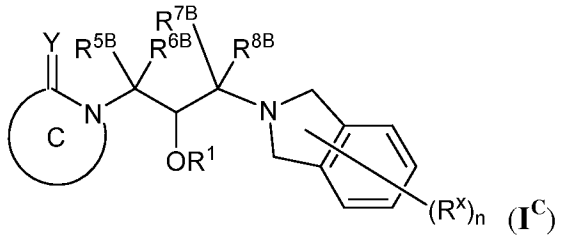
R^{5B}, R^{6B}, R^{7B}, and R^{8B} are independently hydrogen, halo, or optionally substituted aliphatic;

each R^{x} is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

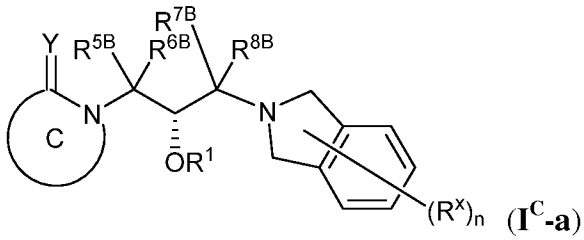
[0035] In certain embodiments, a provided compound is of Formula ($\mathbf{I^C}$):



($\mathbf{I^C}$)

or a pharmaceutically acceptable salt thereof, wherein Ring C, Y, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as described herein.

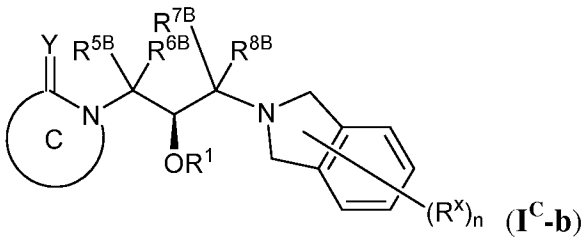
[0036] In certain embodiments, a provided compound is of Formula ($\mathbf{I^C}$-**a**):



($\mathbf{I^C}$-**a**)

or a pharmaceutically acceptable salt thereof, wherein Ring C, Y, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as described herein.

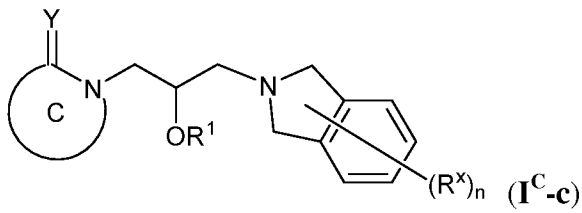
[0037] In certain embodiments, a provided compound is of Formula ($\mathbf{I^C}$-**b**):



($\mathbf{I^C}$-**b**)

or a pharmaceutically acceptable salt thereof, wherein Ring C, Y, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as described herein.

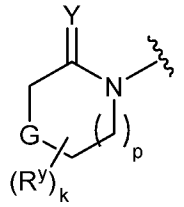
[0038] In certain embodiments, a provided compound is of Formula ($\mathbf{I^C}$-**c**):



($\mathbf{I^C}$-**c**)

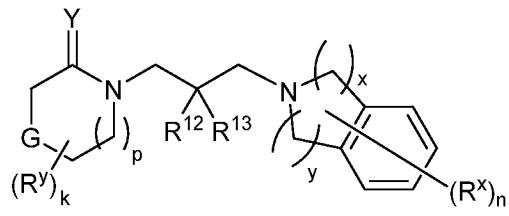
or a pharmaceutically acceptable salt thereof, wherein Ring C, Y, R^1, R^x, and n are as described herein.

[0039] In certain embodiments, wherein Ring C is a group of formula:



,

a provided compound is of Formula (**A-II**^{C}):



(**A-II**^{C})

or a pharmaceutically acceptable salt thereof, wherein x and y are as described herein, and wherein:

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^{1}$;

R^{1} is hydrogen, R^{z}, or $-C(O)R^{z}$, wherein R^{z} is optionally substituted C_{1-6} alkyl;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

Y is O or S;

G is NR^{2C}, $CR^{3C}R^{4C}$, O or S;

R^{2C} is selected from the group consisting of optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(O)R^{A}$, $-C(O)OR^{A}$, $-C(O)SR^{A}$, $-C(O)N(R^{B})_2$, $-C(=NR^{B})R^{A}$, $-C(=NR^{B})N(R^{B})_2$, $-C(=S)R^{A}$, $-C(=S)N(R^{B})_2$, $-S(=O)R^{A}$, $-SO_2R^{A}$, and $-SO_2N(R^{B})_2$;

R^{3C} is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^{A}$, $-N(R^{B})_2$, $-SR^{A}$, $-C(=O)R^{A}$, $-C(O)OR^{A}$, $-C(O)SR^{A}$, $-C(O)N(R^{B})_2$, $-C(O)N(R^{B})N(R^{B})_2$, $-OC(O)R^{A}$, $-OC(O)N(R^{B})_2$, $-NR^{B}C(O)R^{A}$, $-NR^{B}C(O)N(R^{B})_2$, $-NR^{B}C(O)N(R^{B})N(R^{B})_2$, $-NR^{B}C(O)OR^{A}$, $-SC(O)R^{A}$, $-C(=NR^{B})R^{A}$, $-C(=NNR^{B})R^{A}$, $-C(=NOR^{A})R^{A}$, $-C(=NR^{B})N(R^{B})_2$, $-NR^{B}C(=NR^{B})R^{B}$, $-C(=S)R^{A}$, $-C(=S)N(R^{B})_2$, $-NR^{B}C(=S)R^{A}$, $-S(O)R^{A}$, $-OS(O)_2R^{A}$, $-SO_2R^{A}$, $-NR^{B}SO_2R^{A}$, or $-SO_2N(R^{B})_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^{4C} is selected from the group consisting of hydrogen, halo, and optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic;

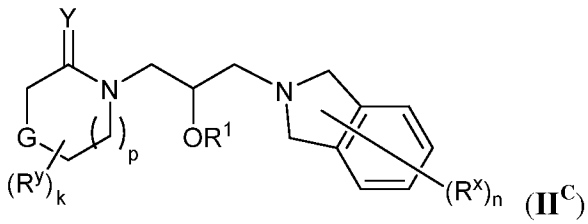
each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$, or two adjacent R^y groups may be taken together with their intervening atoms to form a saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8, as valency permits;

p is 0, 1, or 2; and

k is 0, 1, 2, 3, or 4, as valency permits.

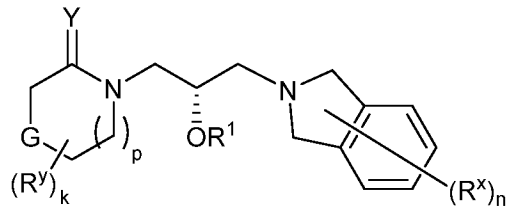
[0040] In certain embodiments, a provided compound is of Formula ($\mathbf{II}^C$):



($\mathbf{II}^C$)

or a pharmaceutically acceptable salt thereof, wherein R^1, G, Y, R^y, k, p, R^x, and n are as described herein.

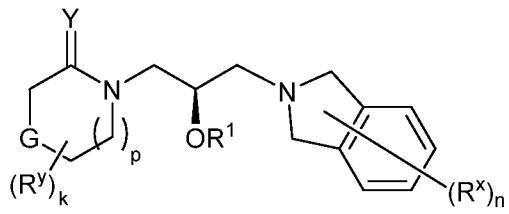
[0041] In certain embodiments, a provided compound is of Formula (**II^C-a**):



(**II^C-a**)

or a pharmaceutically acceptable salt thereof, wherein R^1, G, Y, R^y, k, p, R^x, and n are as described herein.

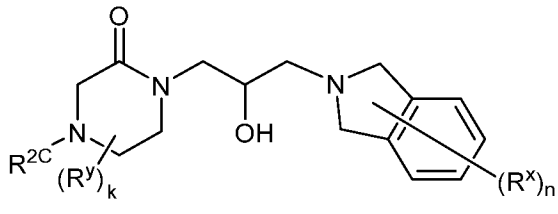
[0042] In certain embodiments, a provided compound is of Formula (**II^C-b**):



(**II^C-b**)

or a pharmaceutically acceptable salt thereof, wherein R^1, G, Y, R^y, k, p, R^x, and n are as described herein.

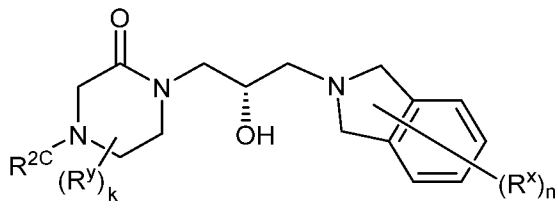
[0043] In certain embodiments, a provided compound is of Formula (**III^C**):



(**III^C**)

or a pharmaceutically acceptable salt thereof, wherein R^{2C}, R^y, k, R^x, and n are as described herein.

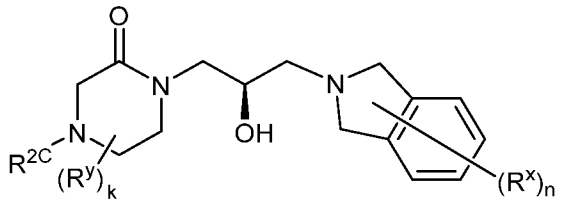
[0044] In certain embodiments, a provided compound is of Formula (**III^C-e**):



(**III^C-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{2C}, R^y, k, R^x, and n are as described herein.

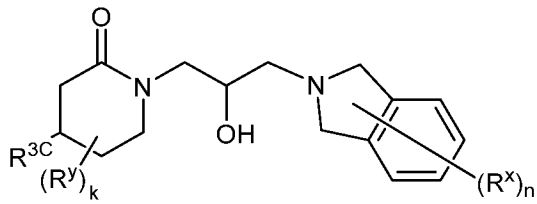
[0045] In certain embodiments, a provided compound is of Formula (**III^C-b**):



(**III^C-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{2C}, R^y, k, R^x, and n are as described herein.

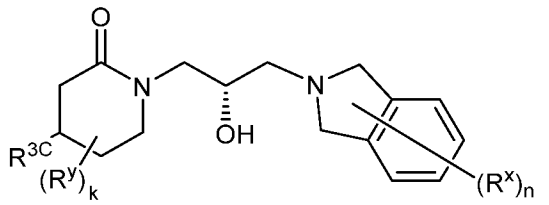
[0046] In certain embodiments, a provided compound is of Formula (**IV^C**):



(**IV^C**)

or a pharmaceutically acceptable salt thereof, wherein R^{3C}, R^y, k, R^x, and n are as described herein.

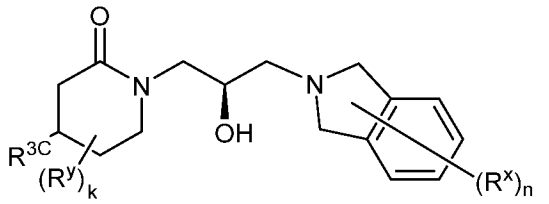
[0047] In certain embodiments, a provided compound is of Formula (**IV^C-a**):



(**IV^C-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{3C}, R^y, k, R^x, and n are as described herein.

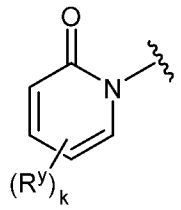
[0048] In certain embodiments, a provided compound is of Formula (**IV^C-f**):



(**IV^C-b**)

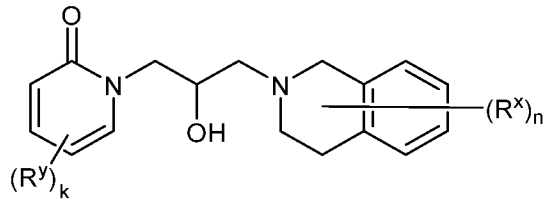
or a pharmaceutically acceptable salt thereof, wherein R^{3C}, R^y, k, R^x, and n are as described herein.

[0049] In certain embodiments, wherein Ring C is a group of formula:



,

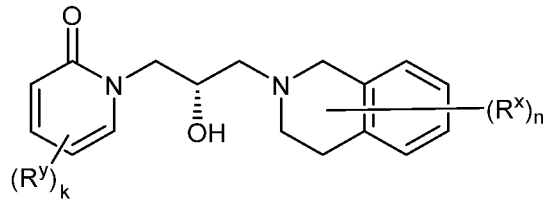
a provided compound is of Formula ($\mathbf{V^C}$):



($\mathbf{V^C}$)

or a pharmaceutically acceptable salt thereof, wherein R^y, k, R^x, and n are as described herein.

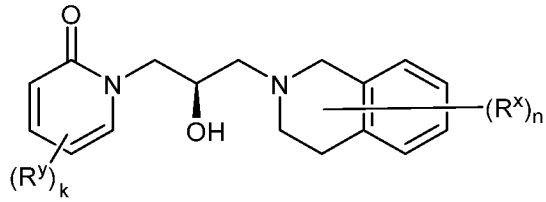
[0050] In certain embodiments, a provided compound is of Formula ($\mathbf{V^C\text{-}a}$):



($\mathbf{V^C\text{-}a}$)

or a pharmaceutically acceptable salt thereof, wherein R^y, k, R^x, and n are as described herein.

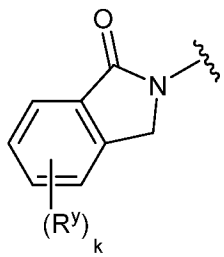
[0051] In certain embodiments, a provided compound is of Formula ($\mathbf{V^C\text{-}f}$):



($\mathbf{V^C\text{-}b}$)

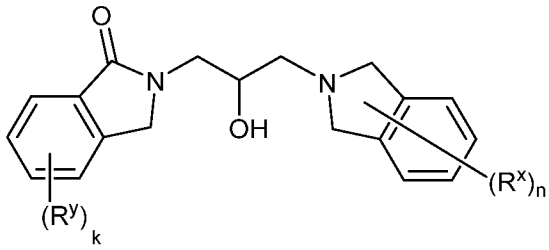
or a pharmaceutically acceptable salt thereof, wherein R^y, k, R^x, and n are as described herein.

[0052] In certain embodiments, wherein Ring C is a group of formula:



,

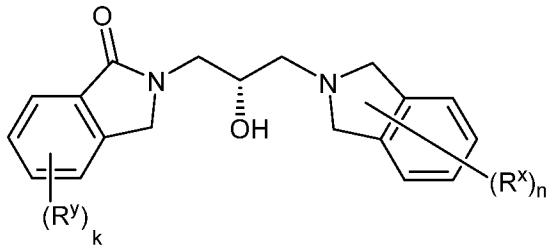
a provided compound is of Formula ($\mathbf{VI}^{C}$):



($\mathbf{VI}^{C}$)

or a pharmaceutically acceptable salt thereof, wherein R^y, k, R^x, and n are as described herein.

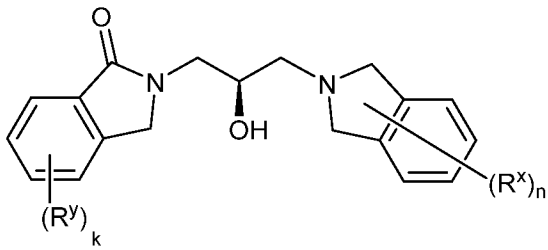
[0053] In certain embodiments, a provided compound is of Formula ($\mathbf{VI}^{C}$-**a**):



($\mathbf{VI}^{C}$-**a**)

or a pharmaceutically acceptable salt thereof, wherein R^y, k, R^x, and n are as described herein.

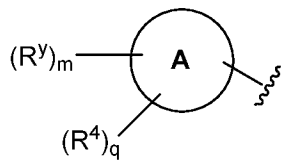
[0054] In certain embodiments, a provided compound is of Formula ($\mathbf{VI}^{C}$-**b**):



($\mathbf{VI}^{C}$-**b**)

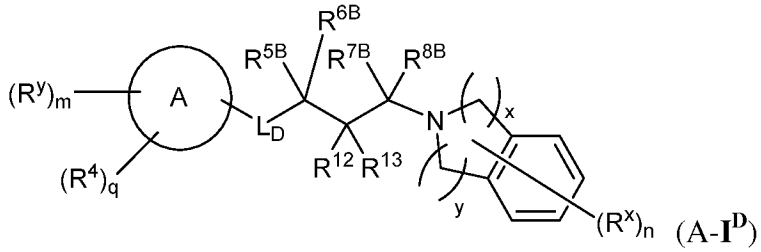
or a pharmaceutically acceptable salt thereof, wherein R^y, k, R^x, and n are as described herein.

[0055] In certain embodiments, wherein L_z is L_D, and Ring Z is a group of formula (also referred to herein as Ring A):



,

provided is a compound of Formula (A-$\mathbf{I}^{D}$):



(A-$\mathbf{I}^{D}$)

or a pharmaceutically acceptable salt thereof, wherein x and y are defined herein, and wherein:

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^{1}$;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

R^{1} is hydrogen, R^{z}, or $-C(O)R^{z}$, wherein R^{z} is optionally substituted C_{1-6} alkyl;

L_D is the linker L_B wherein L_B is –N(R)C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–,–N(R)C(O)O–, or –OC(O)N(R)– and each R is independently hydrogen or optionally substituted C_{1-6} aliphatic; or

L_D is –O–, –N(R)–,$-C(R^{2A})(R^{3A})-$, -O-$CR^{2A}R^{3A}$-, -N(R)-$CR^{2A}R^{3A}$-, -O-$CR^{2A}R^{3A}$-O-, -N(R)-$CR^{2A}R^{3A}$-O, -N(R)-$CR^{2A}R^{3A}$-N(R)-, -O-$CR^{2A}R^{3A}$-N(R)-, -$CR^{2A}R^{3A}$-O-, -$CR^{2A}R^{3A}$-N(R)-, -O-$CR^{2A}R^{3A}$-$CR^{9}R^{10}$-, -N(R)-$CR^{2A}R^{3A}$-$CR^{9}R^{10}$-, -$CR^{2A}R^{3A}$-$CR^{9}R^{10}$-O-, -$CR^{2A}R^{3A}$-$CR^{9}R^{10}$-N(R)-, or $-CR^{2A}R^{3A}$-$CR^{9}R^{10}$-;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

R^{2A} and R^{3A} are independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl; optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^{A}, -$N(R^{B})_2$, -SR^{A}, -$C(=O)R^{A}$, -$C(O)OR^{A}$, -$C(O)SR^{A}$, -$C(O)N(R^{B})_2$, -$C(O)N(R^{B})N(R^{B})_2$, -$OC(O)R^{A}$, -$OC(O)N(R^{B})_2$, -$NR^{B}C(O)R^{A}$, -$NR^{B}C(O)N(R^{B})_2$, -$NR^{B}C(O)N(R^{B})N(R^{B})_2$, -$NR^{B}C(O)OR^{A}$, -$SC(O)R^{A}$, -$C(=NR^{B})R^{A}$, -$C(=NNR^{B})R^{A}$, -$C(=NOR^{A})R^{A}$, -$C(=NR^{B})N(R^{B})_2$, -$NR^{B}C(=NR^{B})R^{B}$, -$C(=S)R^{A}$, -$C(=S)N(R^{B})_2$, -$NR^{B}C(=S)R^{A}$, -$S(O)R^{A}$, -$OS(O)_2R^{A}$, -$SO_2R^{A}$, -$NR^{B}SO_2R^{A}$, and -$SO_2N(R^{B})_2$; or R^{2A} and R^{3A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^{A} is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

Ring A is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^4 is $–L_1\text{-}Cy^D$;

L_1 is a bond, –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, $–SO_2–$, $–SO_2N(R)–$, $–N(R)SO_2–$, –OC(O)–, –C(O)O–, or an optionally substituted, straight or branched, C_{1-6} aliphatic chain wherein one, two, or three methylene units of L_1 are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, $–SO_2–$, $–SO_2N(R)–$, $–N(R)SO_2–$, –OC(O)–, or –C(O)O–;

Cy^D is an optionally substituted, monocyclic, bicyclic or tricyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{5B}, R^{6B}, R^{7B}, and R^{8B} are each independently hydrogen, halo, or optionally substituted aliphatic;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl; optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$; or R^9 and R^{10} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl; optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$,

$-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

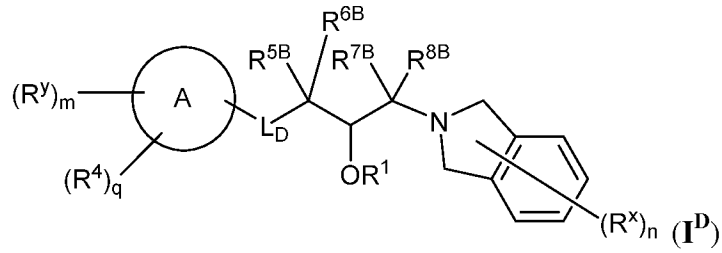
R' is hydrogen or optionally substituted aliphatic;

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8, as valency permits;

m is 0, 1, 2, 3, 4, 5, 6, 7, or 8, as valency permits; and

q is 0 or 1, as valency permits.

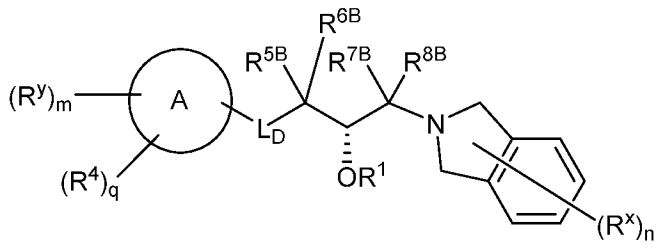
[0056] In certain embodiments, a provided compound is of Formula ($\mathbf{I^D}$):



($\mathbf{I^D}$)

or a pharmaceutically acceptable salt thereof, wherein Ring A, L_D, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

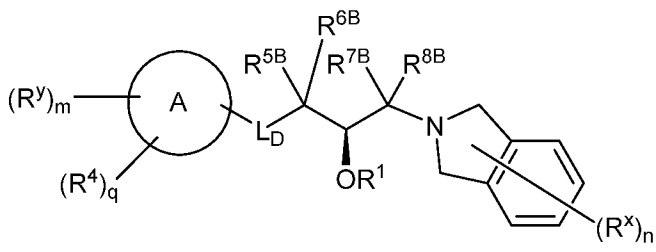
[0057] In certain embodiments, a provided compound is of Formula ($\mathbf{I^D}$-**a**):



($\mathbf{I^D}$-**a**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, L_D, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

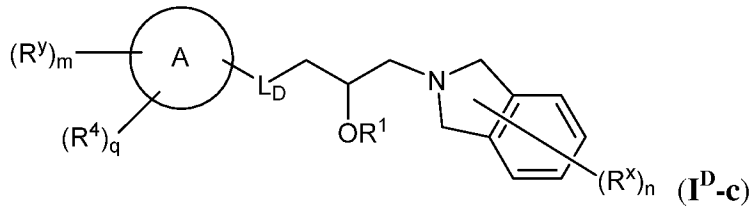
[0058] In certain embodiments, a provided compound is of Formula ($\mathbf{I^D}$-**b**):



($\mathbf{I^D}$-**b**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, L_D, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

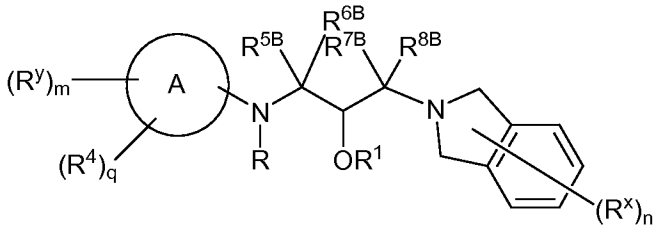
[0059] In certain embodiments, a provided compound is of Formula ($\mathbf{I^D}$-c):



($\mathbf{I^D}$-c)

or a pharmaceutically acceptable salt thereof, wherein Ring A, L_D, R^1, R^4, R^y, m, q, R^x, and n are as defined herein.

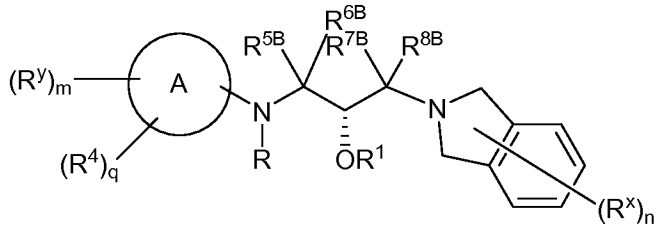
[0060] In certain embodiments, a provided compound is of Formula ($\mathbf{II^D}$):



$\mathbf{II^D}$

or a pharmaceutically acceptable salt thereof, wherein Ring A, R, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

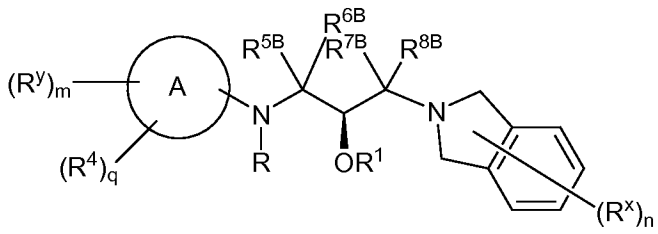
[0061] In certain embodiments, a provided compound is of Formula ($\mathbf{II^D}$-a):



($\mathbf{II^D}$-a)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

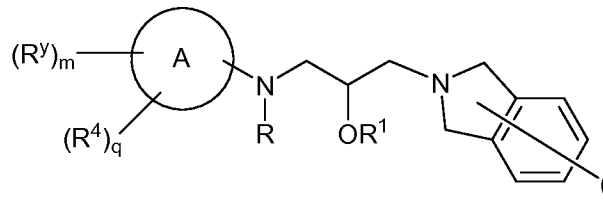
[0062] In certain embodiments, a provided compound is of Formula ($\mathbf{II^D}$-b):



($\mathbf{II^D}$-b)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

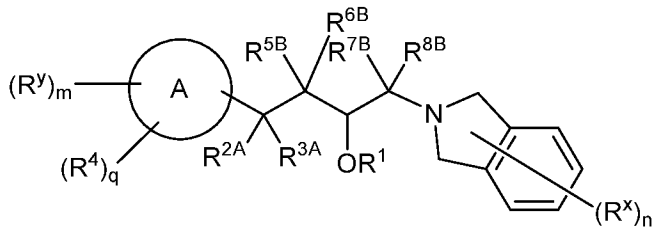
[0063] In certain embodiments, a provided compound is of Formula (**II^D-c**):



(**II^D-c**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R, R^1, R^4, R^y, m, q, R^x, and n are as defined herein.

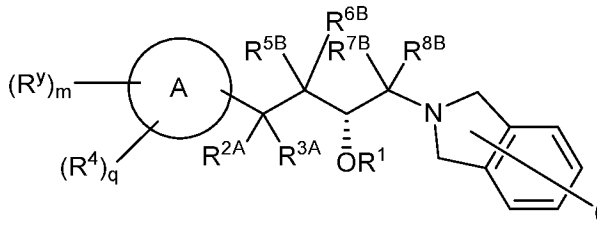
[0064] In certain embodiments, a provided compound is of Formula (**III^D**):



(**III^D**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^{2A}, R^{3A}, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

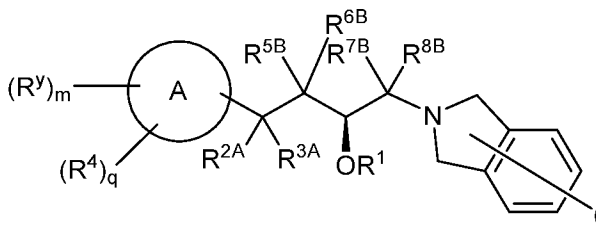
[0065] In certain embodiments, a provided compound is of Formula (**III^D-a**):



(**III^D-a**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^{2A}, R^{3A}, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

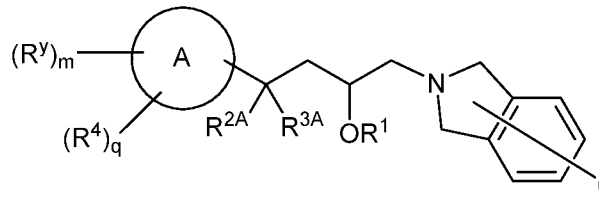
[0066] In certain embodiments, a provided compound is of Formula (**III^D-b**):



(**III^D-b**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^{2A}, R^{3A}, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, q, R^x, and n are as defined herein.

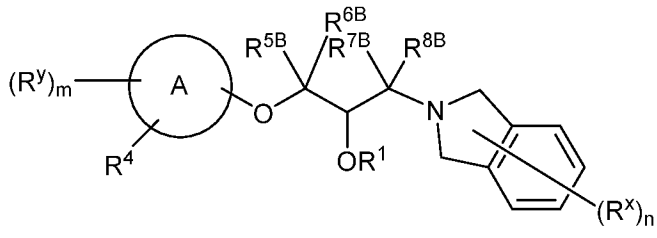
[0067] In certain embodiments, a provided compound is of Formula (**III^D-c**):



(**III^D-c**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^{2A}, R^{3A}, R^4, R^y, m, q, R^x, and n are as defined herein.

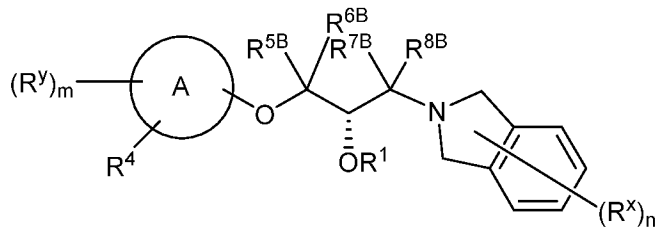
[0068] In certain embodiments, a provided compound is of Formula (**IV^D**):



(**IV^D**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, R^x, and n are as defined herein.

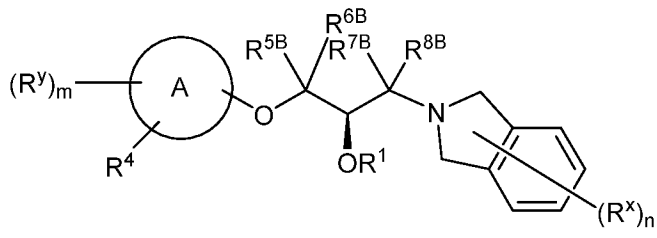
[0069] In certain embodiments, a provided compound is of Formula (**IV^D-a**):



(**IV^D-a**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, R^x, and n are as defined herein.

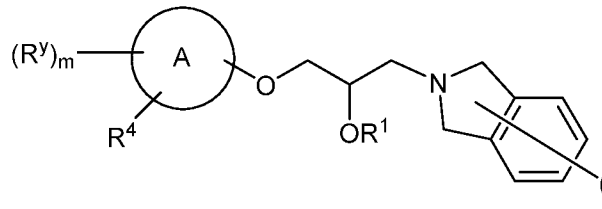
[0070] In certain embodiments, a provided compound is of Formula (**IV^D-b**):



(**IV^D-b**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^4, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^y, m, R^x, and n are as defined herein.

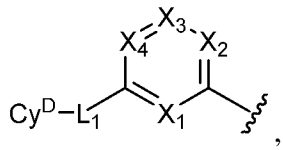
[0071] In certain embodiments, a provided compound is of Formula (**IV^D-c**):



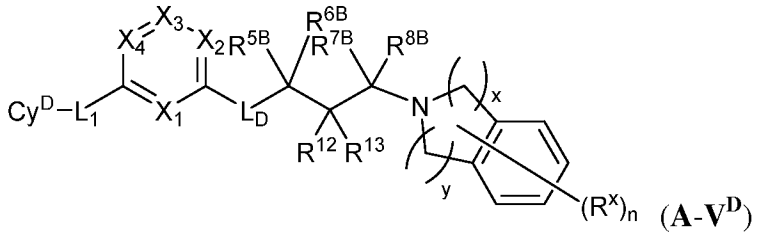
(**IV^D-c**)

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^1, R^4, R^y, m, R^x, and n are as defined herein.

[0072] In certain embodiments, wherein Ring A is a monocyclic aromatic ring having 0, 1, 2, or 3 nitrogen heteroatoms:



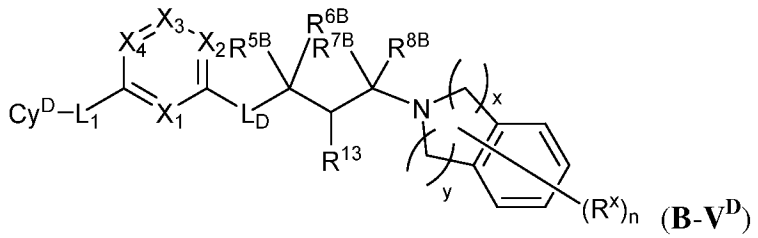
a provided compound is of Formula (**A-V^D**):



(**A-V^D**)

or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, and X_4 are each independently selected from the group consisting of N, CH, and CR^y, provided that at least one of X_2, X_3, and X_4 is not N; and L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, R^{12}, R^{13}, x, y, and n are as defined herein.

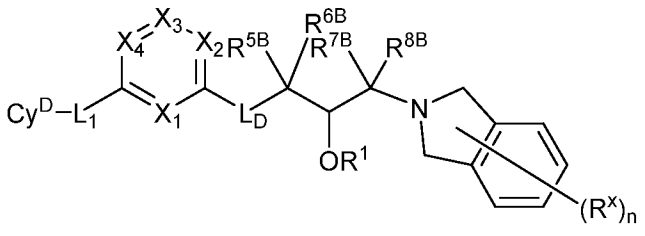
[0073] In certain embodiments, a provided compound is of Formula (**B-V^D**):



(**B-V^D**)

or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, and X_4 are each independently selected from the group consisting of N, CH, and CR^y, provided that at least one of X_2, X_3, and X_4 is not N; and L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, R^{13}, x, y, and n are as defined herein.

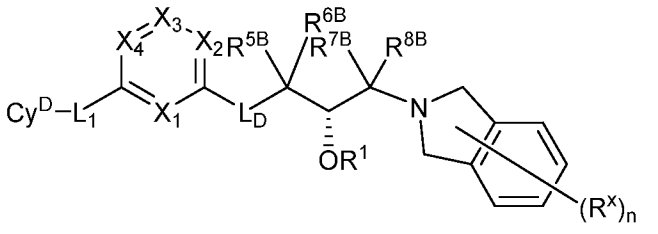
[0074] In certain embodiments, a provided compound is of Formula ($\mathbf{V^D}$):



($\mathbf{V^D}$)

or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, X_4, L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

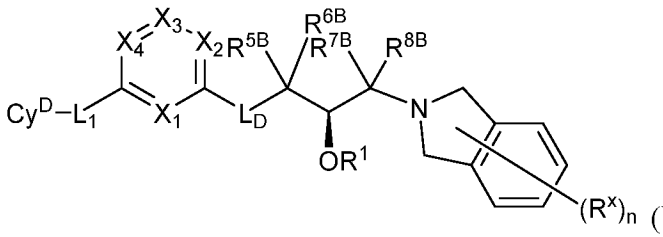
[0075] In certain embodiments, a provided compound is of Formula ($\mathbf{V^D\text{-}a}$):



($\mathbf{V^D\text{-}a}$)

or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, X_4, L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

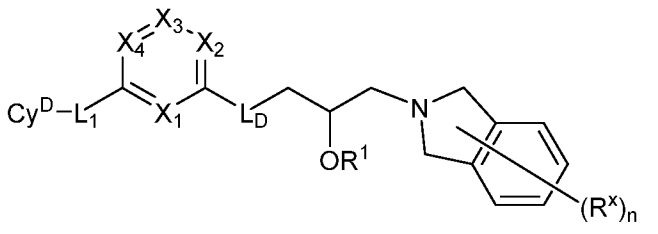
[0076] In certain embodiments, a provided compound is of Formula ($\mathbf{V^D\text{-}b}$):



($\mathbf{V^D\text{-}b}$)

or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, X_4, L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

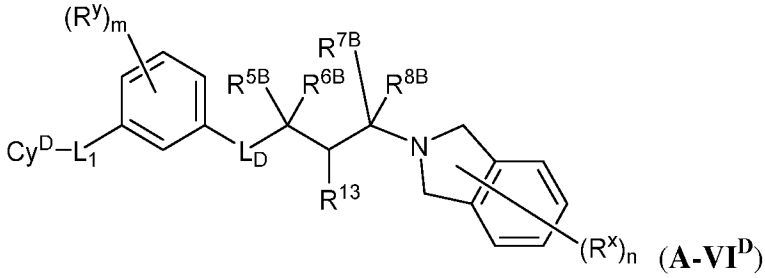
[0077] In certain embodiments, a provided compound is of Formula ($\mathbf{V^D\text{-}c}$):



($\mathbf{V^D\text{-}c}$)

or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, X_4, L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

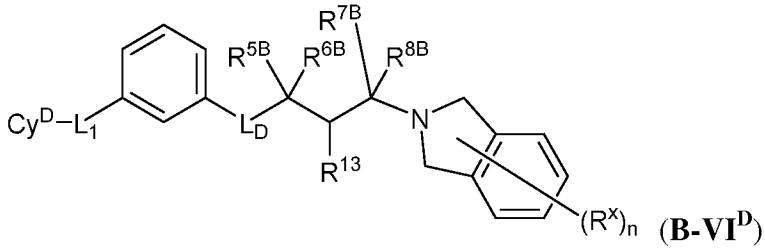
[0078] In certain embodiments, a provided compound is of Formula (**A-VI^D**):



(**A-VI^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

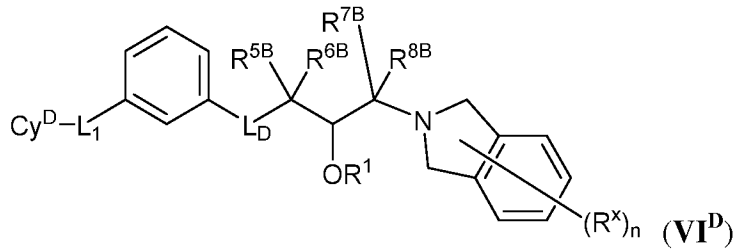
[0079] In certain embodiments, a provided compound is of Formula (**B-VI^D**):



(**B-VI^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

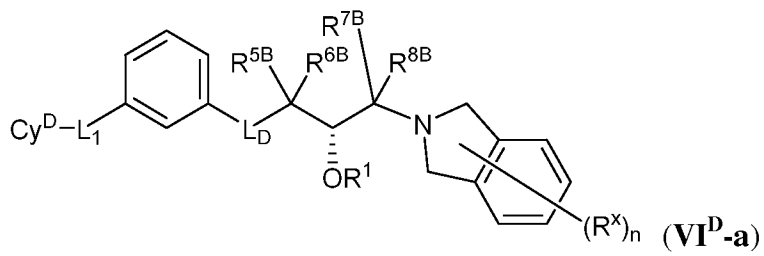
[0080] In certain embodiments, a provided compound is of Formula (**VI^D**):



(**VI^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

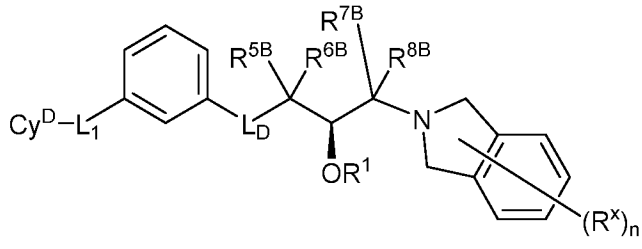
[0081] In certain embodiments, a provided compound is of Formula (**VI^D-a**):



(**VI^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

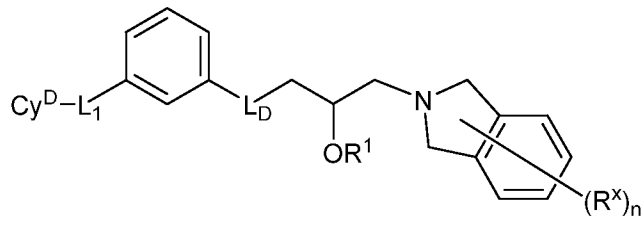
[0082] In certain embodiments, a provided compound is of Formula (**VI^D-b**):



(**VI^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

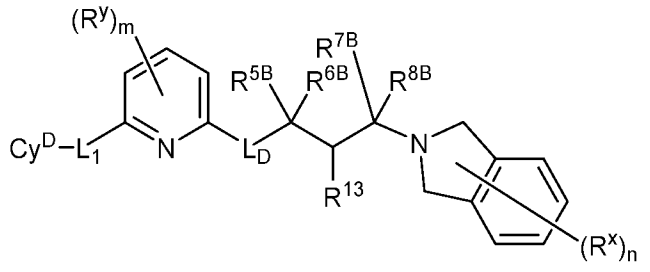
[0083] In certain embodiments, a provided compound is of Formula (**VI^D-c**):



(**VI^D-c**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

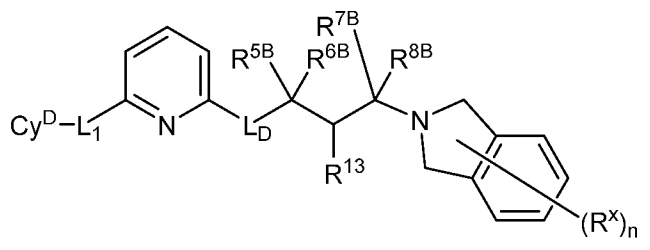
[0084] In certain embodiments, a provided compound is of Formula (**A-VII^D**):



(**A-VII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

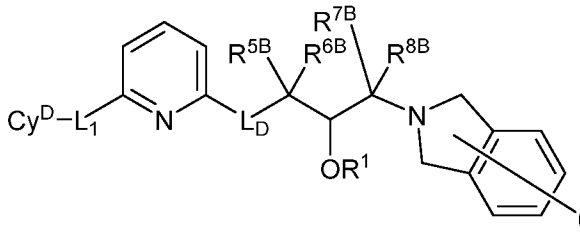
[0085] In certain embodiments, a provided compound is of Formula (**B-VII^D**):



(**B-VII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

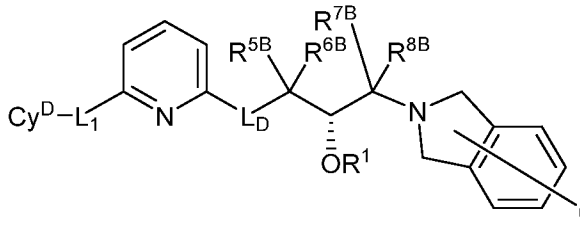
[0086] In certain embodiments, a provided compound is of Formula (**VII^D**):



(**VII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

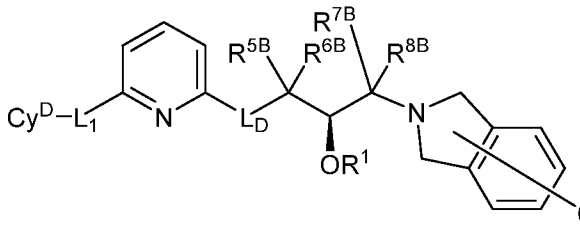
[0087] In certain embodiments, a provided compound is of Formula (**VII^D-a**):



(**VII^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

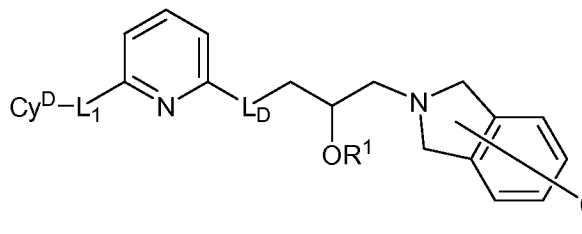
[0088] In certain embodiments, a provided compound is of Formula (**VII^D-b**):



(**VII^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

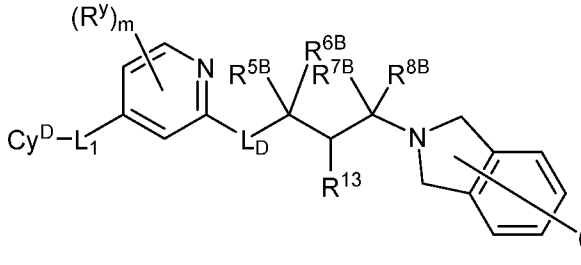
[0089] In certain embodiments, a provided compound is of Formula (**VII^D-g**):



(**VII^D-c**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

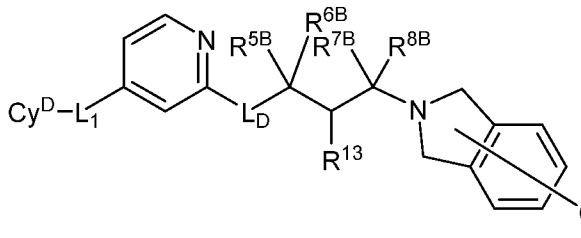
[0090] In certain embodiments, a provided compound is of Formula (**A-VIII^D**):



(**A-VIII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

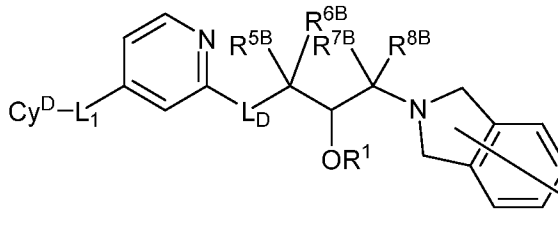
[0091] In certain embodiments, a provided compound is of Formula (**B-VIII^D**):



(**B-VIII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

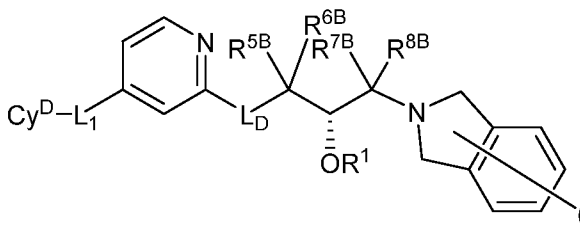
[0092] In certain embodiments, a provided compound is of Formula (**VIII^D**):



(**VIII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

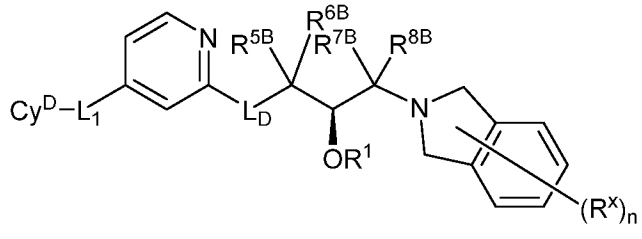
[0093] In certain embodiments, a provided compound is of Formula (**VIII^D-a**):



(**VIII^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

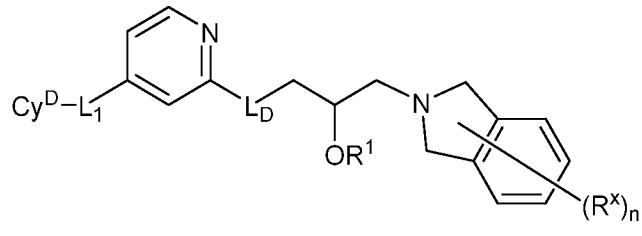
[0094] In certain embodiments, a provided compound is of Formula (**VIII^D-b**):



(**VIII^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

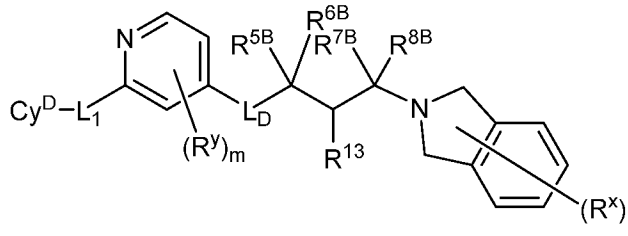
[0095] In certain embodiments, a provided compound is of Formula (**VIII^D-c**):



(**VIII^D-c**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

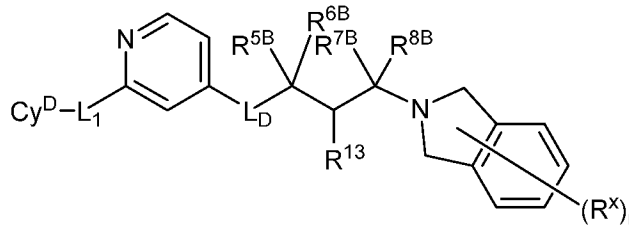
[0096] In certain embodiments, a provided compound is of Formula (**A-IX^D**):



(**A-IX^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

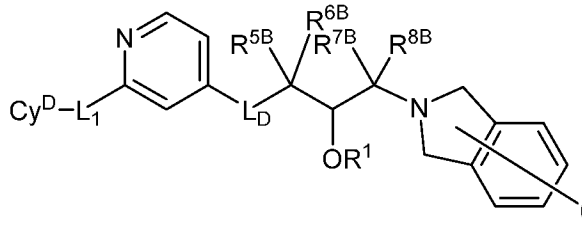
[0097] In certain embodiments, a provided compound is of Formula (**B-IX^D**):



(**B-IX^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

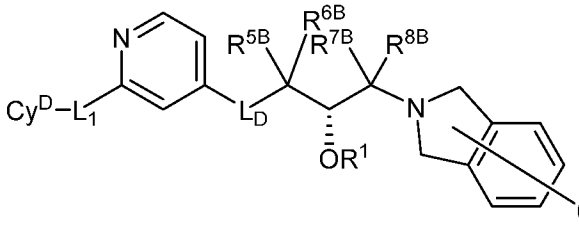
[0098] In certain embodiments, a provided compound is of Formula (**IX^D**):



(**IX^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

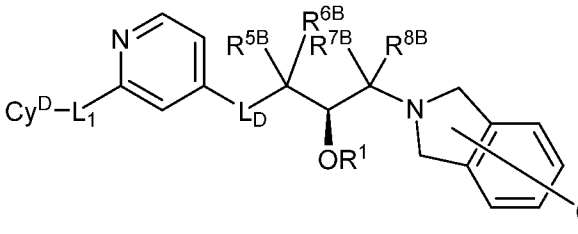
[0099] In certain embodiments, a provided compound is of Formula (**IX^D-a**):



(**IX^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

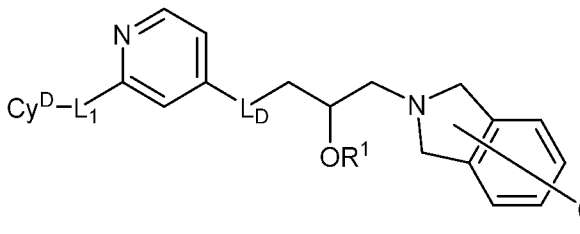
[00100] In certain embodiments, a provided compound is of Formula (**IX^D-b**):



(**IX^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

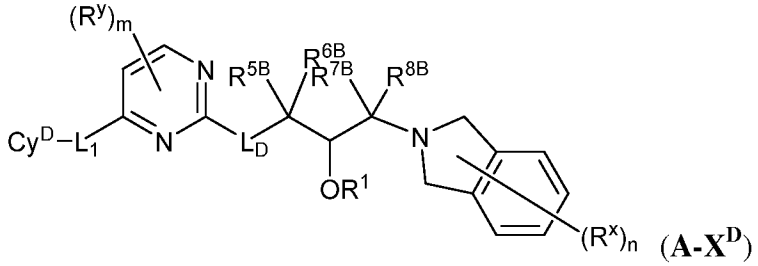
[00101] In certain embodiments, a provided compound is of Formula (**IX^D-c**):



(**IX^D-c**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

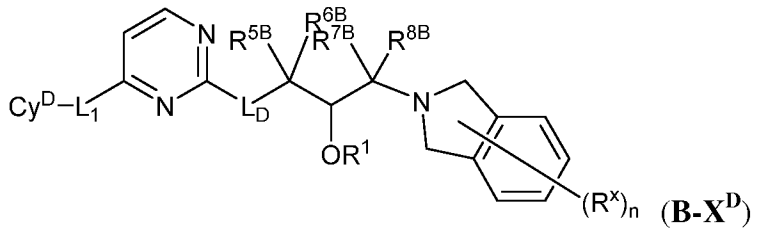
[00102] In certain embodiments, a provided compound is of Formula (**A-X^D**):



(**A-X^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

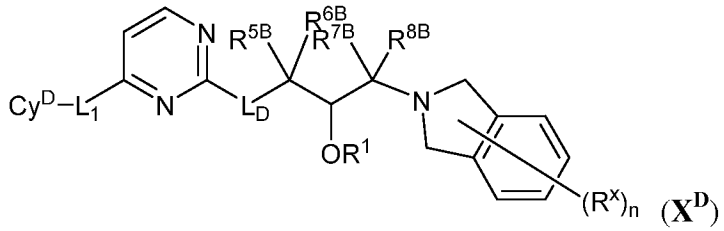
[00103] In certain embodiments, a provided compound is of Formula (**B-X^D**):



(**B-X^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

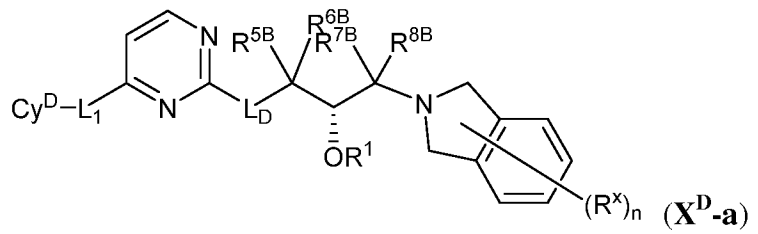
[00104] In certain embodiments, a provided compound is of Formula (**X^D**):



(**X^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

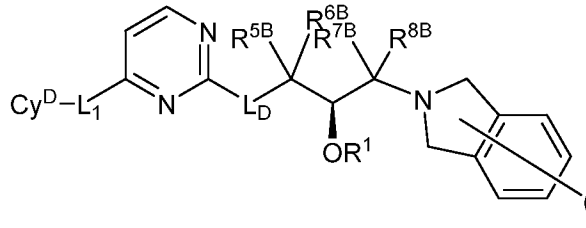
[00105] In certain embodiments, a provided compound is of Formula (**X^D-a**):



(**X^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

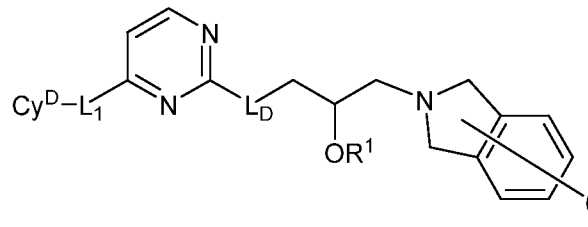
[00106] In certain embodiments, a provided compound is of Formula ($\mathbf{X^D}$-**b**):



($\mathbf{X^D}$-**b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

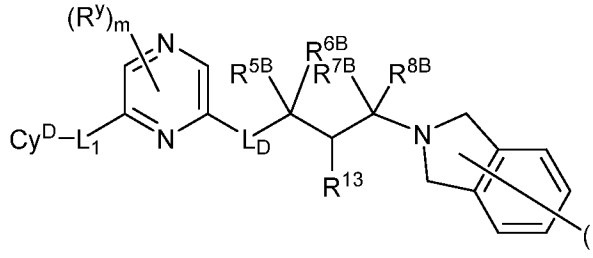
[00107] In certain embodiments, a provided compound is of Formula ($\mathbf{X^D}$-**c**):



($\mathbf{X^D}$-**c**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

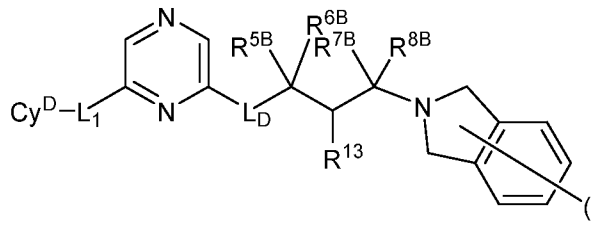
[00108] In certain embodiments, a provided compound is of Formula (**A-XI^D**):



(**A-XI^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

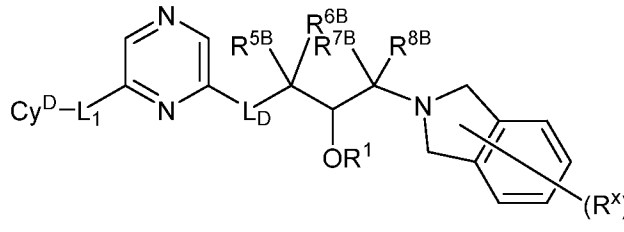
[00109] In certain embodiments, a provided compound is of Formula (**B-XI^D**):



(**B-XI^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

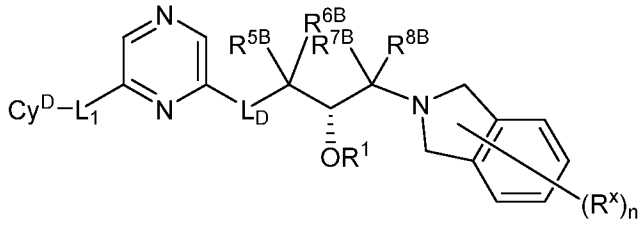
[00110] In certain embodiments, a provided compound is of Formula ($\mathbf{XI^D}$):



($\mathbf{XI^D}$)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

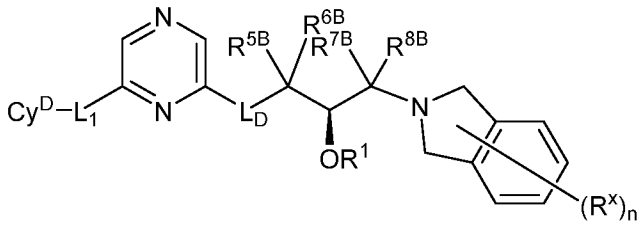
[00111] In certain embodiments, a provided compound is of Formula ($\mathbf{XI^D\text{-}a}$):



($\mathbf{XI^D\text{-}a}$)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

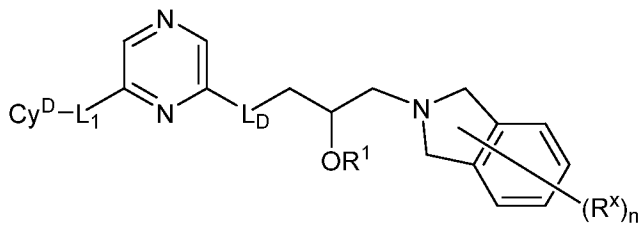
[00112] In certain embodiments, a provided compound is of Formula ($\mathbf{XI^D\text{-}b}$):



($\mathbf{XI^D\text{-}b}$)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

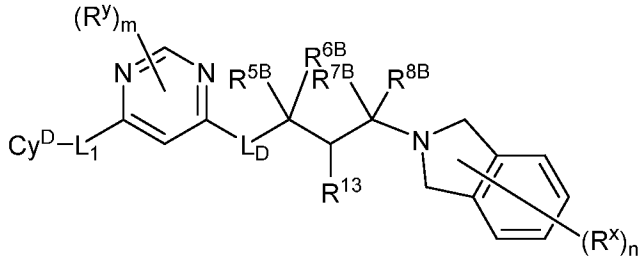
[00113] In certain embodiments, a provided compound is of Formula ($\mathbf{XI^D\text{-}c}$):



($\mathbf{XI^D\text{-}c}$)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^x, and n are as defined herein.

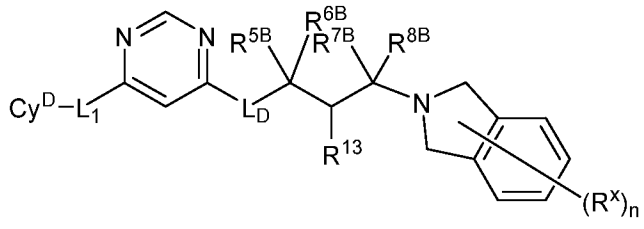
[00114] In certain embodiments, a provided compound is of Formula (**A-XII^D**):



(**A-XII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

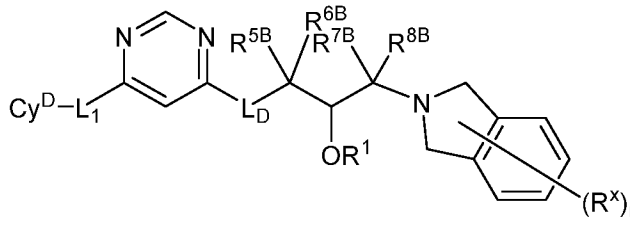
[00115] In certain embodiments, a provided compound is of Formula (**B-XII^D**):



(**B-XII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

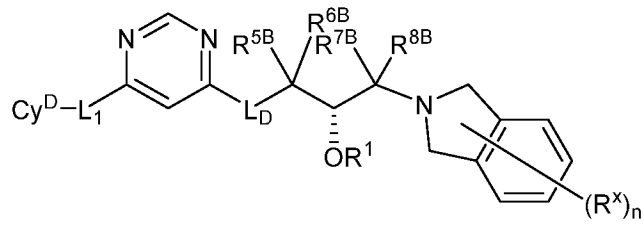
[00116] In certain embodiments, a provided compound is of Formula (**XII^D**):



(**XII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

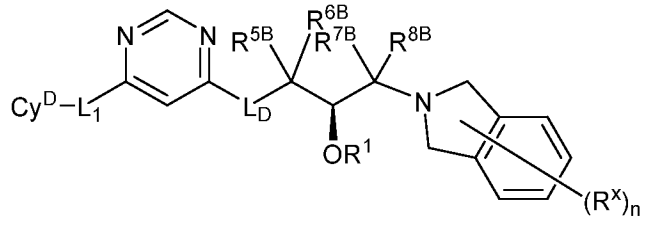
[00117] In certain embodiments, a provided compound is of Formula (**XII^D-a**):



(**XII^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

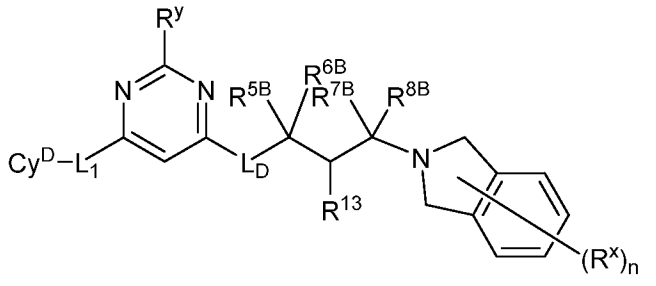
[00118] In certain embodiments, a provided compound is of Formula (**XII^D-b**):



(**XII^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

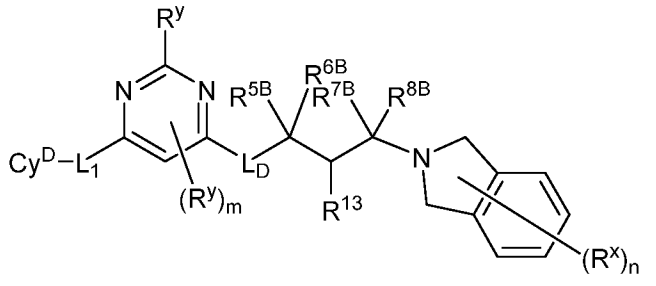
[00119] In certain embodiments, a provided compound is of Formula (**A-XIII^D**):



(**A-XIII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

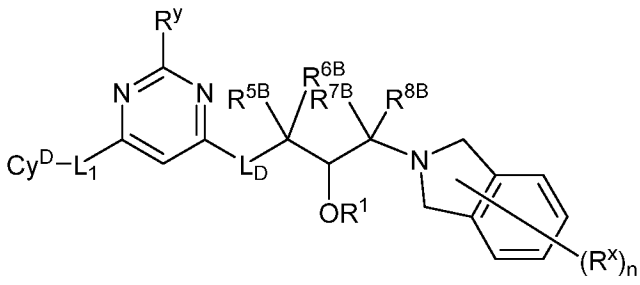
[00120] In certain embodiments, a provided compound is of Formula (**B-XIII^D**):



(**B-XIII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

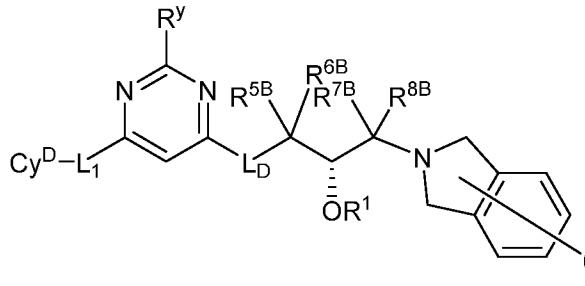
[00121] In certain embodiments, a provided compound is of Formula (**XIII^D**):



(**XIII^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

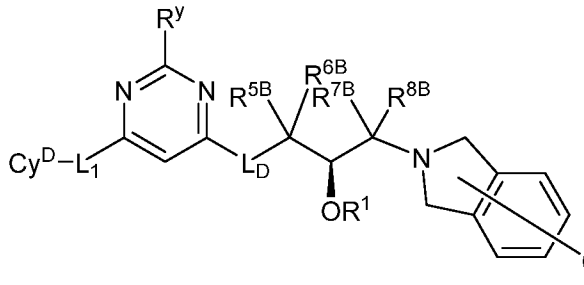
[00122] In certain embodiments, a provided compound is of Formula (**XIII^D-a**):



(**XIII^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

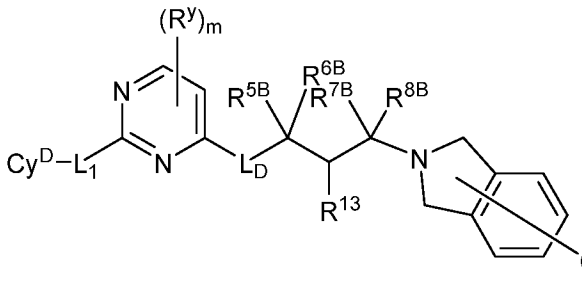
[00123] In certain embodiments, a provided compound is of Formula (**XIII^D-b**):



(**XIII^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

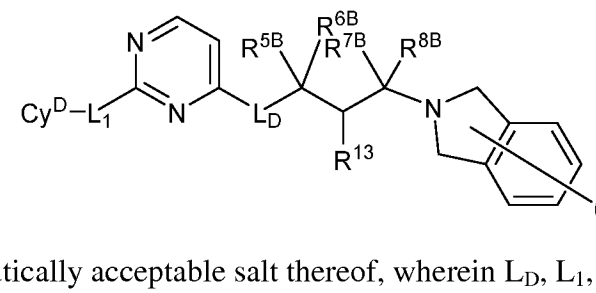
[00124] In certain embodiments, a provided compound is of Formula (**A-XIV^D**):



(**A-XIV^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^y, m, R^x, and n are as defined herein.

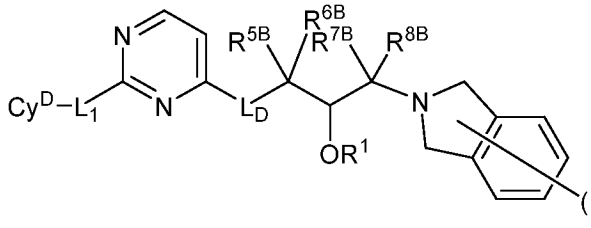
[00125] In certain embodiments, a provided compound is of Formula (**B-XIV^D**):



(**B-XIV^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{13}, R^x, and n are as defined herein.

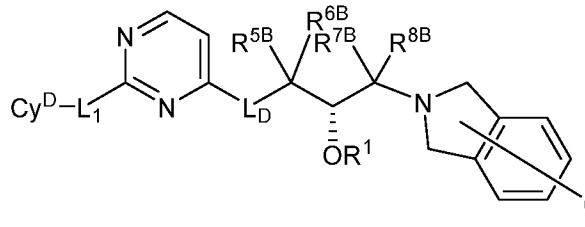
[00126] In certain embodiments, a provided compound is of Formula (**XIV^D**):



(**XIV^D**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

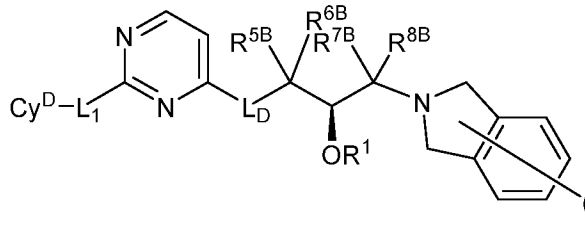
[00127] In certain embodiments, a provided compound is of Formula (**XIV^D-a**):



(**XIV^D-a**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

[00128] In certain embodiments, a provided compound is of Formula (**XIV^D-b**):



(**XIV^D-b**)

or a pharmaceutically acceptable salt thereof, wherein L_D, L_1, Cy^D, R^1, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^x, and n are as defined herein.

[00129] As defined generally above, R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is methyl, ethyl, or propyl. In some embodiments, R^1 is $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is $-C(O)R^z$, wherein R^z is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is acetyl.

[00130] As defined generally above, L_z is a linker or is absent. In certain embodiments, L_z is $-X_A-C(R^{2A})(R^{3A})C(=O)N(R)-$, L_B, or L_D as described herein.

[00131] As defined generally above, Ring Z is an optionally substituted, monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring Z is Ring A, Ring C, Cy^A, or Ar as described herein.

[00132] As defined generally above, R^{21}, R^{22}, R^{23}, and R^{24} are independently hydrogen, halo, or optionally substituted aliphatic. In some embodiments, R^{21}, R^{22}, R^{23}, and R^{24} are hydrogen. In some embodiments, R^{22}, R^{23}, and R^{24} are hydrogen, and R^{21} is optionally substituted aliphatic. In some embodiments, R^{22}, R^{23}, and R^{24} are hydrogen, and R^{21} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{22}, R^{23}, and R^{24} are hydrogen, and R^{21} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{22}, R^{23}, and R^{24} are hydrogen, and R^{21} is methyl. In some embodiments, R^{21}, R^{22}, and $R^{23}$are hydrogen, and R^{24} is optionally substituted aliphatic. In some embodiments, R^{21}, R^{22}, and $R^{23}$are hydrogen, and R^{24} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{21}, R^{22}, and $R^{23}$are hydrogen, and R^{24} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{21}, R^{22}, and $R^{23}$are hydrogen, and R^{24} is methyl.

[00133] As defined generally above, X_A is a bond, –O–, –N(R)–, $–CR^{4A}R^{5A}–$, $-O-CR^{4A}R^{5A}$, $-N(R)-CR^{4A}R^{5A}-$, $-O-CR^{4A}R^{5A}-O-$, $-N(R)-CR^{4A}R^{5A}-O$, $-N(R)-CR^{4A}R^{5A}-N(R)-$, $-O-CR^{4A}R^{5A}-N(R)-$, $-CR^{4A}R^{5A}-O-$, $-CR^{4A}R^{5A}-N(R)-$, $-O-CR^{4A}R^{5A}-CR^{6A}R^{7A}-$, $-N(R)-CR^{4A}R^{5A}-CR^{6A}R^{7A}-$, $-CR^{6A}R^{7A}-CR^{4A}R^{5A}-O-$, $-CR^{6A}R^{7A}-CR^{4A}R^{5A}-N(R)-$, or $–CR^{6A}R^{7A}-CR^{4A}R^{5A}-$. In certain embodiments, X_A is a bond, –O–, –N(R)–, or $–CR^4R^5–$, wherein R, R^4, and R^5 are as described herein. In certain embodiments, X_A is a bond. In certain embodiments, X_A is –O–. In some embodiments, X_A is –N(R)–. In certain embodiments, X_A is –NH-. In certain embodiments, X_A is –N(R)–, wherein R is optionally substituted C_{1-6} aliphatic. In certain embodiments, X_A is –N(R)–, wherein R is optionally substituted C_{1-6} alkyl. In certain embodiments, X_A is –N(R)–, wherein R is unsubstituted C_{1-6} alkyl. In certain embodiments, X_A is –N(Me)–. In some embodiments, X_A is $–CR^{4A}R^{5A}–$. In certain embodiments, X_A is $–CH_2–$. In certain embodiments, X_A is $–CH_2-O-$.

[00134] As defined generally above, each R is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, R is hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is substituted C_{1-6} aliphatic. In some embodiments, R is unsubstituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is substituted C_{1-6} alkyl. In some embodiments, R is unsubstituted C_{1-6} alkyl. In some embodiments, R is methyl, ethyl, or propyl.

[00135] As defined generally above, R^{2A} and R^{3A} are each independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally

substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$; or R^{2A} and R^{3A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring. In certain embodiments, R^{2A} and R^{3A} are independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-OC(O)R^A$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$; or R^{2A} and R^{3A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

[00136] In certain embodiments, R^{2A} is hydrogen. In some embodiments, R^{2A} is not hydrogen. In some embodiments, R^{2A} is halo. In certain embodiments, R^{2A} is fluoro. In some embodiments, R^{2A} is optionally substituted aliphatic. In certain embodiments, R^{2A} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{2A} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{2A} is substituted C_{1-6} alkyl. In certain embodiments, R^{2A} is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{2A} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{2A} is methyl, ethyl, or propyl. In certain embodiments, R^{3A} is hydrogen. In some embodiments, R^{3A} is not hydrogen. In some embodiments, R^{3A} is halo. In certain embodiments, R^{3A} is fluoro. In some embodiments, R^{3A} is optionally substituted aliphatic. In certain embodiments, R^3 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{3A} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{3A} is substituted C_{1-6} alkyl. In certain embodiments, R^{3A} is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{3A} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{3A} is methyl, ethyl, or propyl. In some embodiments, R^{2A} and R^{3A} are the same. In some embodiments, R^{2A} and R^{3A} are different. In some embodiments, R^{2A} and R^{3A} are each hydrogen. In some embodiments, R^{2A} is hydrogen and R^{3A} is not hydrogen. In some embodiments, R^{2A} is hydrogen and R^{3A} is optionally substituted aliphatic. In some embodiments, R^{2A} is hydrogen and R^{3A} is C_{1-6} alkyl. In some embodiments, R^{2A} is hydrogen and R^{3A} is methyl.

[00137] As defined generally above, R^{4A} and R^{5A} are each independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$OC(O)R^A$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{4A} and R^{5A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring. In certain embodiments, R^{4A} and R^{5A} are each independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$OC(O)R^A$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{4A} and R^{5A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

[00138] In certain embodiments, R^{4A} is hydrogen. In some embodiments, R^{4A} is not hydrogen. In some embodiments, R^{4A} is halo. In certain embodiments, R^{4A} is fluoro. In some embodiments, R^{4A} is optionally substituted aliphatic. In certain embodiments, R^{4A} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{4A} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{4A} is substituted C_{1-6} alkyl. In certain embodiments, R^{4A} is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{4A} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{4A} is methyl, ethyl, or propyl. In certain embodiments, R^{5A} is hydrogen. In some embodiments, R^{5A} is not hydrogen. In some embodiments, R^{5A} is halo. In certain embodiments, R^{5A} is fluoro. In some embodiments, R^{5A} is optionally substituted aliphatic. In certain embodiments, R^{5A} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{5A} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{5A} is substituted C_{1-6} alkyl. In certain embodiments, R^{5A} is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{5A} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{5A} is methyl, ethyl, or propyl. In some embodiments, R^{4A} and R^{5A} are the same. In some embodiments, R^{4A} and R^{5A} are different. In some embodiments, R^{4A} and R^{5A} are each hydrogen. In some embodiments, R^{4A} is hydrogen and R^{5A} is not hydrogen. In some embodiments, R^{4A} is hydrogen and R^{5A} is optionally substituted aliphatic. In some embodiments, R^{4A} is hydrogen and R^{5A} is C_{1-6} alkyl. In some embodiments, R^{4A} is hydrogen and R^{5A} is methyl.

[00139] As defined generally above, R^{6A} and R^{7A} are each independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, or -$SO_2N(R^B)_2$; or R^{6A} and R^{7A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring. In certain embodiments, R^{6A} and R^{7A} are each independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$OC(O)R^A$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{6A} and R^{7A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

[00140] In certain embodiments, R^{6A} is hydrogen. In some embodiments, R^{6A} is not hydrogen. In some embodiments, R^{6A} is halo. In certain embodiments, R^{6A} is fluoro. In some embodiments, R^{6A} is optionally substituted aliphatic. In certain embodiments, R^{6A} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{6A} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{6A} is substituted C_{1-6} alkyl. In certain embodiments, R^{6A} is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{6A} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{6A} is methyl, ethyl, or propyl. In certain embodiments, R^{7A} is hydrogen. In some embodiments, R^{7A} is not hydrogen. In some embodiments, R^{7A} is halo. In certain embodiments, R^{7A} is fluoro. In some embodiments, R^{7A} is optionally substituted aliphatic. In certain embodiments, R^{7A} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{7A} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{7A} is substituted C_{1-6} alkyl. In certain embodiments, R^{7A} is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{7A} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{7A} is methyl, ethyl, or propyl. In some embodiments, R^{6A} and R^{7A} are the same. In some embodiments, R^{6A} and R^{7A} are different. In some embodiments, R^{6A} and R^{7A} are each hydrogen. In some embodiments, R^{6A} is hydrogen and R^{7A} is not hydrogen. In some embodiments, R^{6A} is hydrogen and R^{7A} is

optionally substituted aliphatic. In some embodiments, R^{6A} is hydrogen and R^{7A} is C_{1-6} alkyl. In some embodiments, R^{6A} is hydrogen and R^{7A} is methyl.

[00141] As defined generally above, R^{8A}, R^{9A}, R^{10A}, and R^{11A} are independently hydrogen, halo, or optionally substituted aliphatic. In some embodiments, R^{8A}, R^{9A}, R^{10A}, and R^{11A} are hydrogen. In some embodiments, R^{9A}, R^{10A}, and R^{11A} are hydrogen, and R^{8A} is optionally substituted aliphatic. In some embodiments, R^{9A}, R^{10A}, and R^{11A} are hydrogen, and R^{8A} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{9A}, R^{10A}, and R^{11A} are hydrogen, and R^{8A} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{9A}, R^{10A}, and R^{11A} are hydrogen, and R^{8A} is methyl. In some embodiments, R^{8A}, R^{9A}, and R^{10A} are hydrogen, and R^{11A} is optionally substituted aliphatic. In some embodiments, R^{8A}, R^{9A}, and R^{10A} are hydrogen, and R^{11A} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{8A}, R^{9A}, and R^{10A} are hydrogen, and R^{11A} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{8A}, R^{9A}, and R^{10A} are hydrogen, and R^{11A} is methyl.

[00142] As defined generally above, R^{5B}, R^{6B}, R^{7B}, and R^{8B} are each independently hydrogen, halo, or optionally substituted aliphatic. In some embodiments, R^{5B}, R^{6B}, R^{7B}, and R^{8B} are hydrogen. In some embodiments, R^{6B}, R^{7B}, and R^{8B} are hydrogen, and R^{5B} is optionally substituted aliphatic. In some embodiments, R^{6B}, R^{7B}, and R^{8B} are hydrogen, and R^{5B} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{6B}, R^{7B}, and R^{8B} are hydrogen, and R^{5B} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{6B}, R^{7B}, and R^{8B} are hydrogen, and R^{5B} is methyl. In some embodiments, R^{5B}, R^{6B}, and R^{7B} are hydrogen, and R^{8B} is optionally substituted aliphatic. In some embodiments, R^{5B}, R^{6B}, and R^{7B} are hydrogen, and R^{8B} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{5B}, R^{6B}, and R^{7B} are hydrogen, and R^{8B} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{5B}, R^{6B}, and R^{7B} are hydrogen, and R^{8B} is methyl.

[00143] As generally defined above, R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl. In certain embodiments, R^{12} is hydrogen. In certain embodiments, R^{12} is optionally substituted C_{1-3}alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{12} is optionally substituted C_1alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{12} is optionally substituted C_2 alkyl, *e.g.,* ethyl. In certain embodiments, R^{12} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{12} is fluoro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is chloro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is bromo, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is iodo, provided that R^{13} is not $-OR^1$.

[00144] As generally defined above, R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$ or $-OR^{1}$. In certain embodiments, R^{13} is hydrogen. In certain embodiments, R^{13} is optionally substituted C_{1-3}alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{13} is optionally substituted C_1alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{13} is optionally substituted C_2 alkyl, *e.g.,* ethyl. In certain embodiments, R^{13} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{13} is fluoro. In certain embodiments, R^{13} is chloro. In certain embodiments, R^{13} is bromo. In certain embodiments, R^{13} is iodo.

[00145] As defined generally above, L_B is –N(R)C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)O–, or –OC(O)N(R)–, wherein R is as described herein. In some embodiments, L_B is –N(R)C(O)–. In some embodiments, L_B is –NHC(O)–. In some embodiments, L_B is –N(C_{1-6} alkyl)C(O)–. In some embodiments, L_B is –N(CH_3)C(O)–. In some embodiments, L_B is –C(O)N(R)–. In some embodiments, L_B is –C(O)NH–. In some embodiments, L_B is –C(O)N(C_{1-6} alkyl)–. In some embodiments, L_B is –C(O)N(CH_3)–. In some embodiments, L_B is –N(R)C(O)N(R)–. In some embodiments, L_B is –NHC(O)NH–. In some embodiments, L_B is –NHC(O)N(R)–. In some embodiments, L_B is –N(R)C(O)NH–. In some embodiments, L_B is –N(CH_3)C(O)N(R)–. In some embodiments, L_B is –N(R)C(O)N(CH_3)–. In some embodiments, L_B is –N(CH_3)C(O)N(CH_3)–. In some embodiments, L_B is –N(R)C(O)O–. In some embodiments, L_B is –NHC(O)O–. In some embodiments, L_B is –N(C_{1-6} alkyl)C(O)O–. In some embodiments, L_B is –N(CH_3)C(O)O–. In some embodiments, L_B is –OC(O)N(R)–. In some embodiments, L_B is –OC(O)NH–. In some embodiments, L_B is –OC(O)N(C_{1-6} alkyl)–. In some embodiments, L_B is –OC(O)N(CH_3)–.

[00146] For avoidance of confusion, though Ar is sometimes used to denote the element argon, as used herein Ar denotes a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits, and various embodiments thereof as described herein, or Ar is a monocyclic or bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits, and various embodiments thereof as described herein. In certain embodiments, Ar is unsubstituted. In certain embodiments, Ar is substituted with one or two R^y groups. In certain embodiments, Ar is substituted with one R^y group. In certain embodiments, Ar is substituted with two R^y groups. In certain embodiments, Ar is substituted with three R^y groups. In certain embodiments, Ar

is substituted with four R^y groups. In certain embodiments, Ar is substituted with five R^y groups.

[00147] In certain embodiments, Ar is phenyl substituted with 0, 1, 2, 3, 4, or 5 R^y groups. In certain embodiments, Ar is phenyl substituted with one or two R^y groups. In certain embodiments, Ar is unsubstituted phenyl. In certain embodiments, Ar is phenyl substituted with one R^y group. In certain embodiments, Ar is phenyl substituted with two R^y groups. In certain embodiments, Ar is phenyl substituted with three R^y groups. In certain embodiments, Ar is phenyl substituted with four R^y groups. In certain embodiments, Ar is phenyl substituted with five R^y groups.

[00148] In certain embodiments, Ar is heteroaryl substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is an unsubstituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one or two R^y groups. In certain embodiments, Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one R^y group. In certain embodiments, Ar is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl), and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is a 6-membered heteroaryl having 1-3 nitrogens (*e.g.*, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl), and is substituted with 0, 1, 2, 3, 4, or 5 R^y groups.

[00149] In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is an 8- to 12-membered bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is an unsubstituted bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with one or two R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar

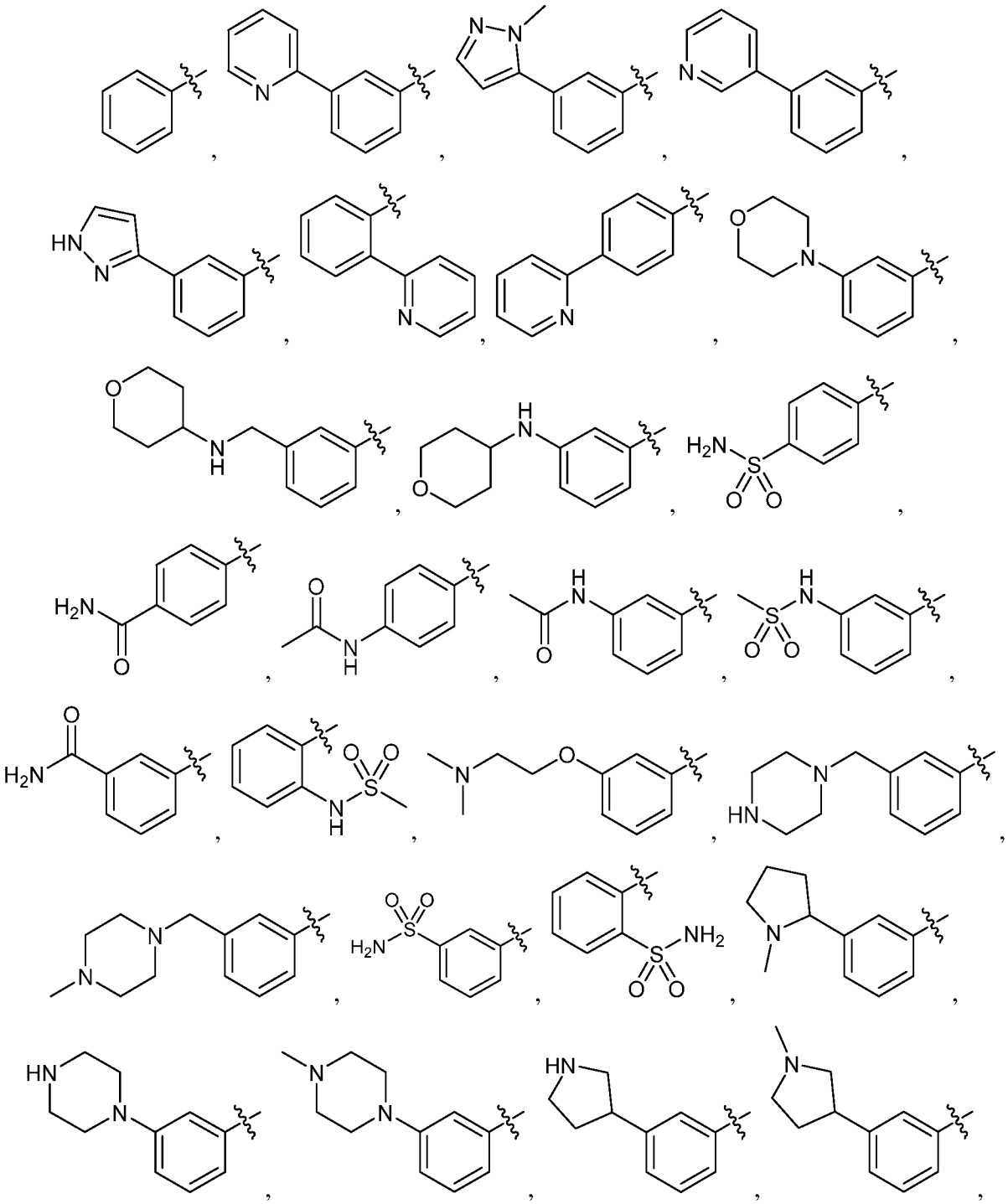
is substituted with one R^y group. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with two R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with three R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with four R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with five R^y groups. In certain embodiments, Ar is naphthalene substituted with 0, 1, 2, 3, 4, or 5 R^y groups.

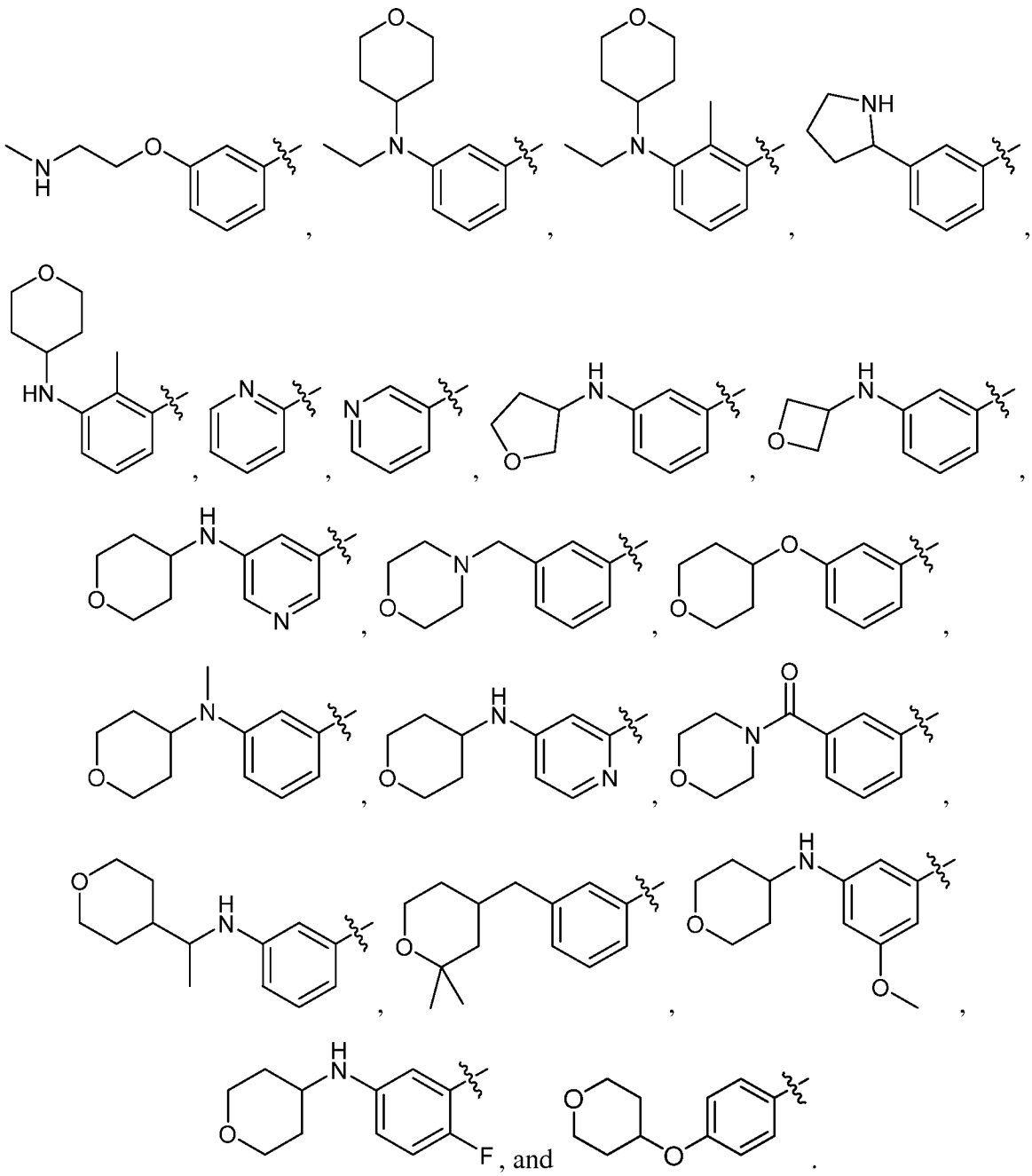
[00150] In certain embodiments, Ar is an 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is a 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl), wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups. In certain embodiments, Ar is a 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl), wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups. In certain embodiments, Ar is selected from the group consisting of quinoline, benzimidazole, benzopyrazole, quinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, naphthalene, tetrahydronaphthalene, 2,3-dihydrobenzo[*b*][1,4]dioxine, isoindole, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, and quinoxalin-2(1*H*)-one, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups.

[00151] As generally defined above, in certain embodiments, Ar is a monocyclic or bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a monocyclic heterocyclic ring, *e.g.*, a monocyclic 5-membered or 6-membered heterocyclic ring substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a bicyclic heterocyclic ring, *e.g.*, a 6,6-bicyclic or 5,6-bicyclic heterocyclic ring substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a 5,6-bicyclic heterocyclic ring wherein the

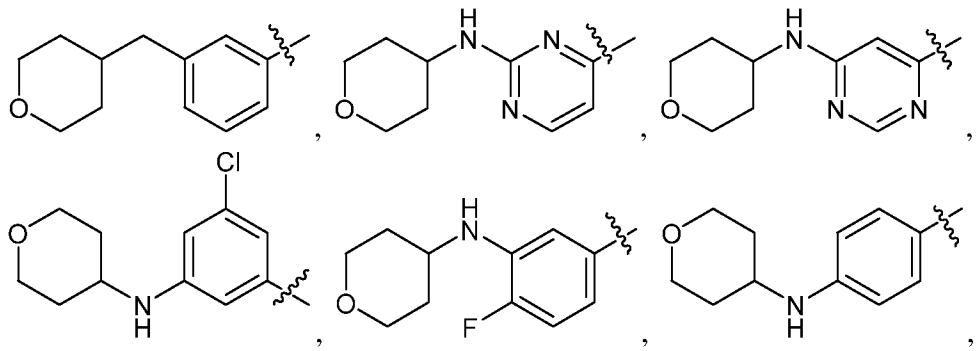
point of attachment is on the 6-membered ring. In certain embodiments, wherein Ar is a 5,6-bicyclic heterocyclic ring, Ar is an optionally substituted dihydroimidazo pyrimidinyl ring.

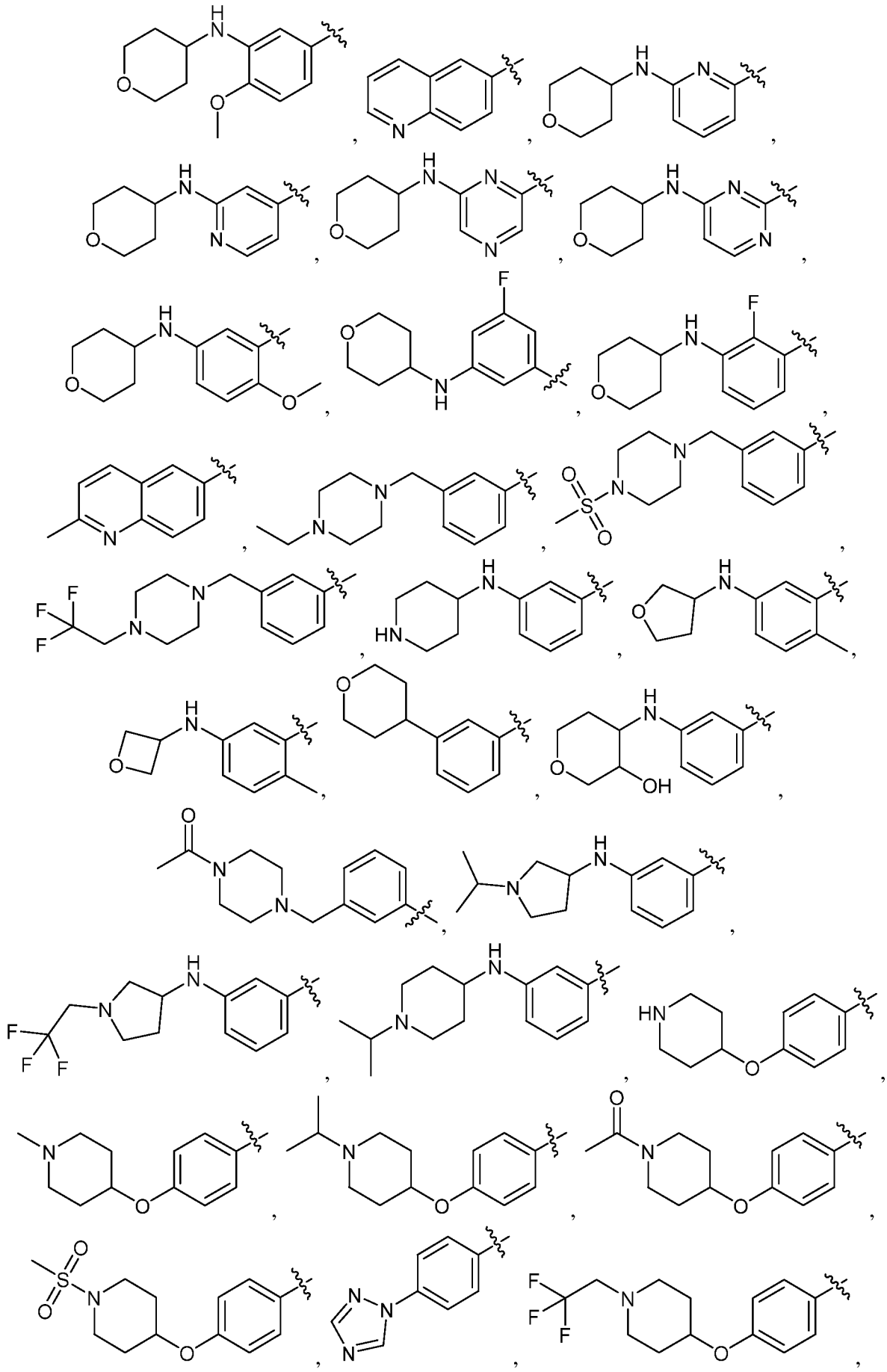
[00152] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:

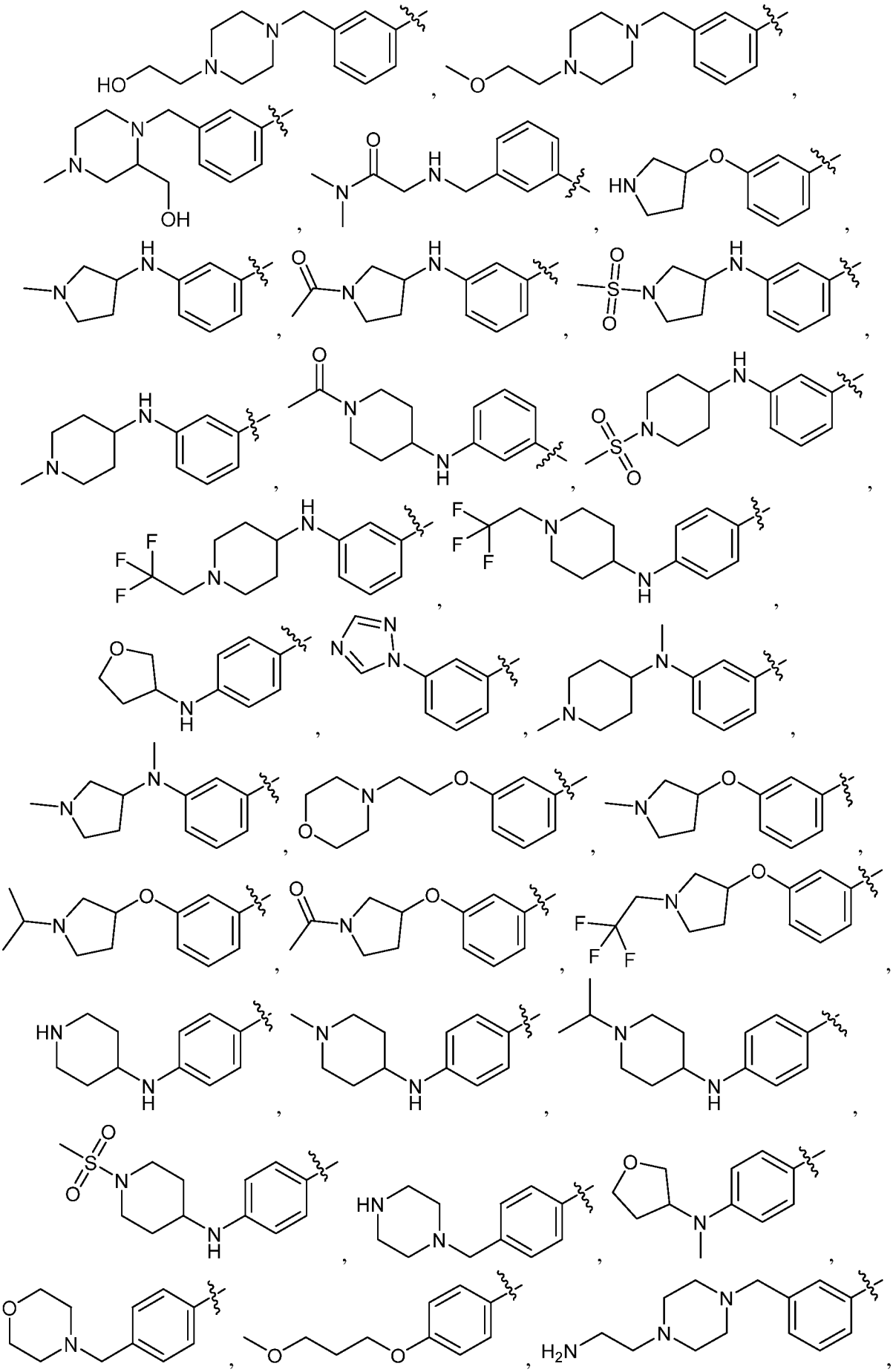


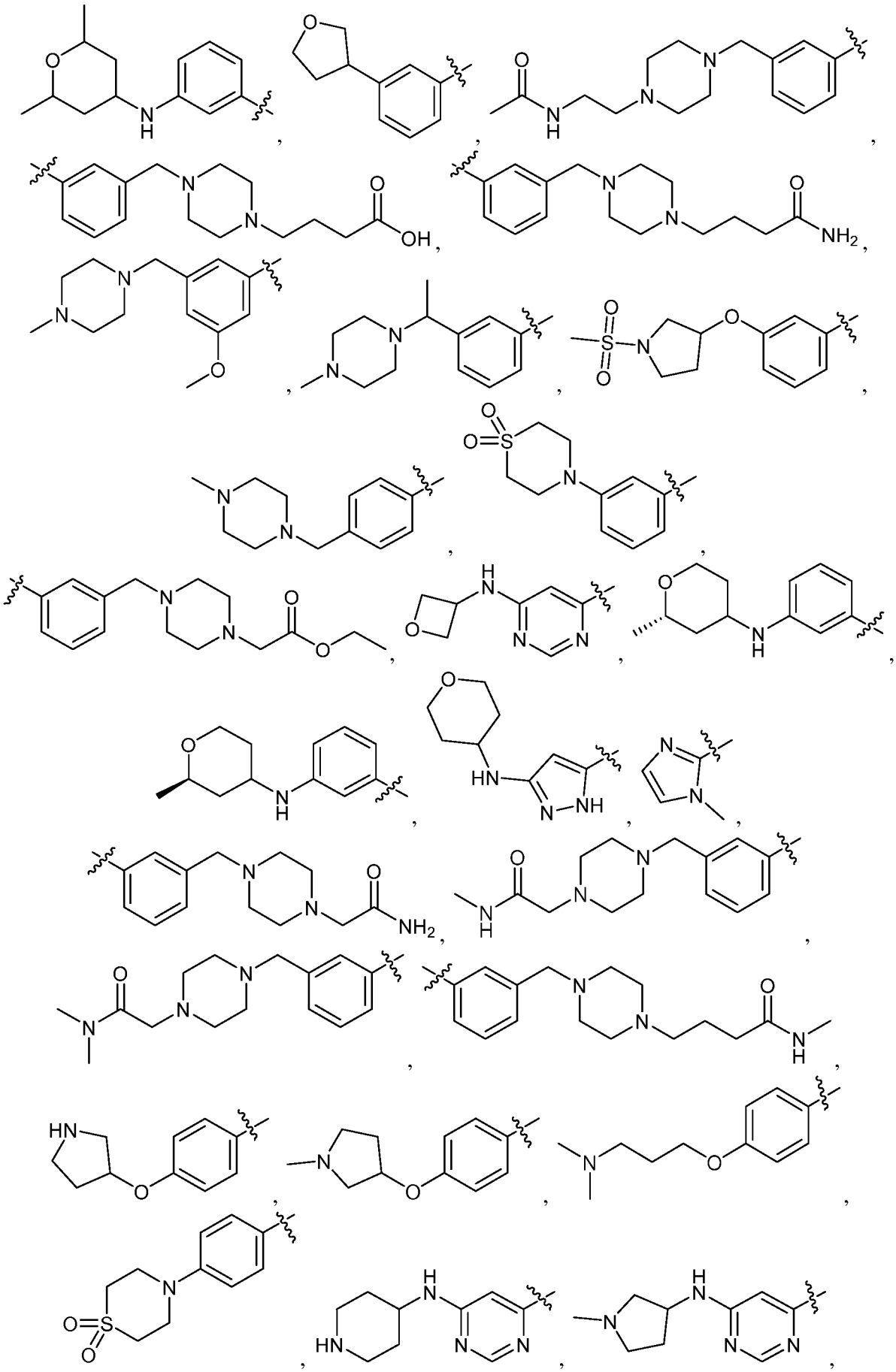


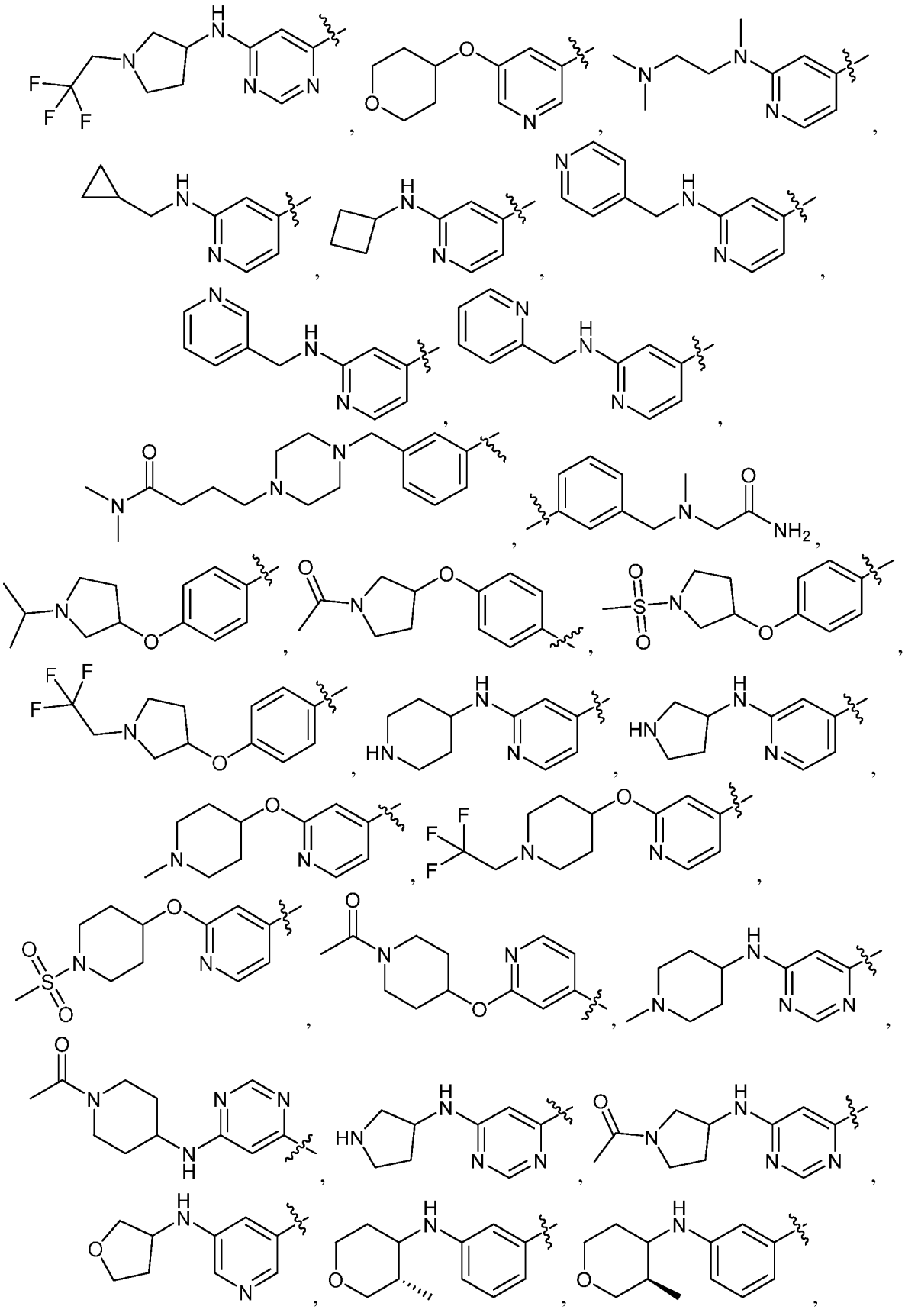
[00153] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:

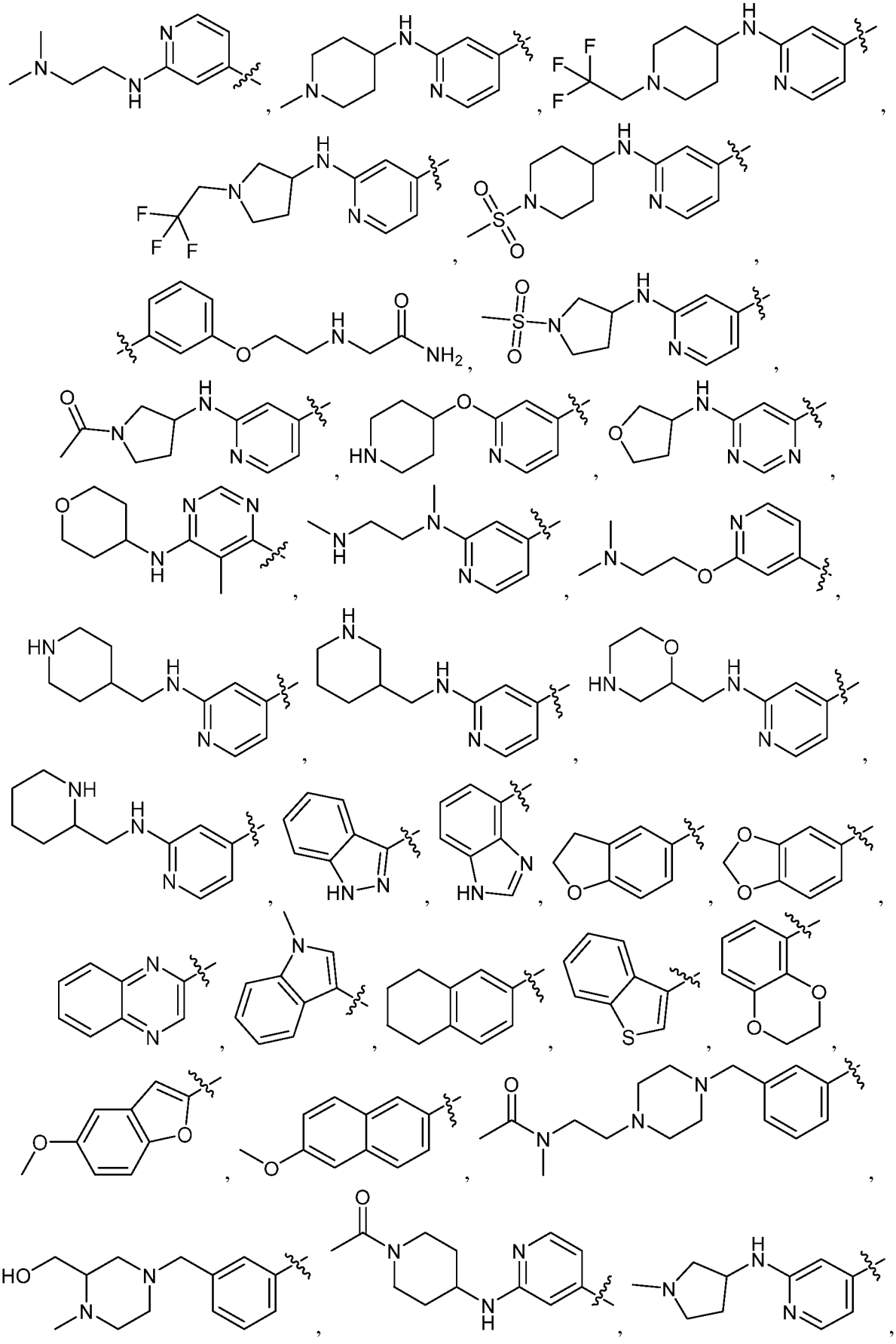


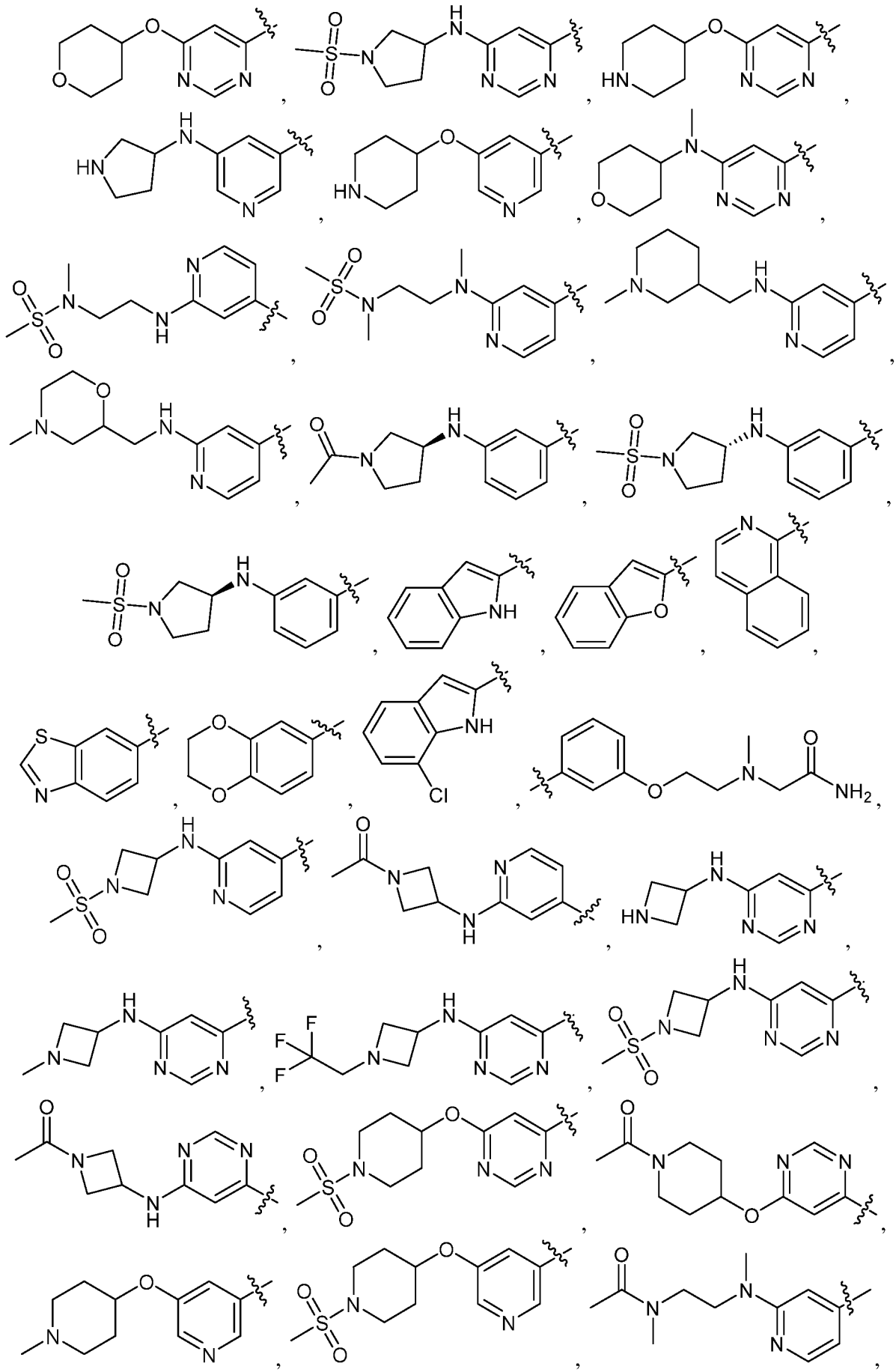


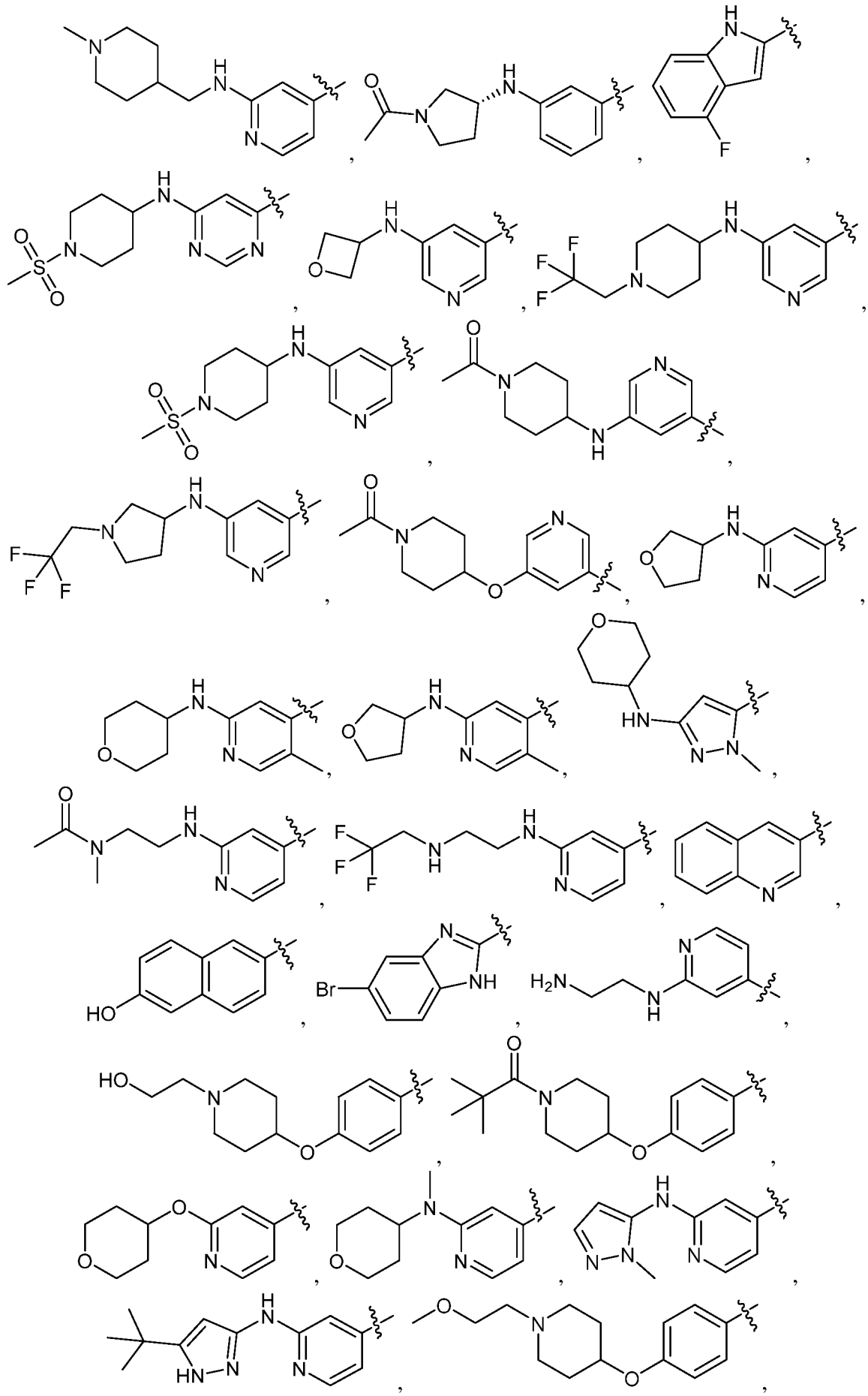


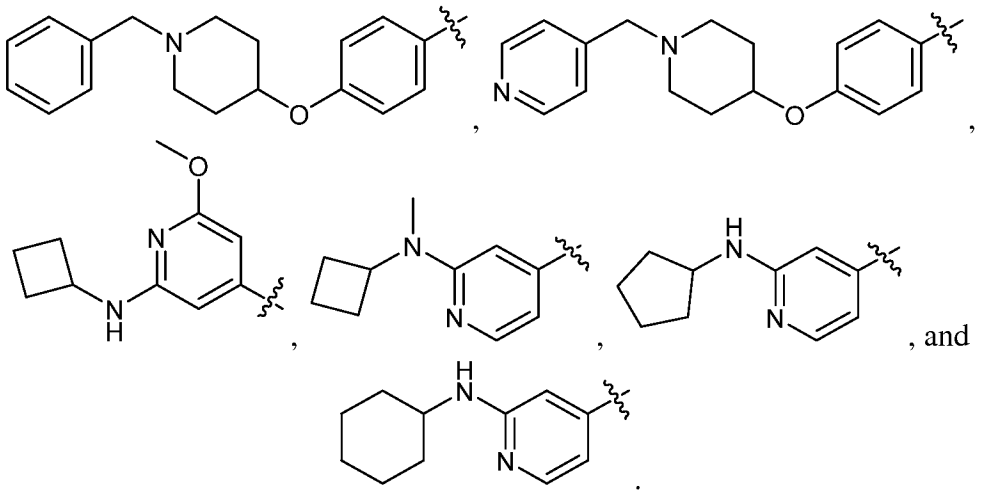












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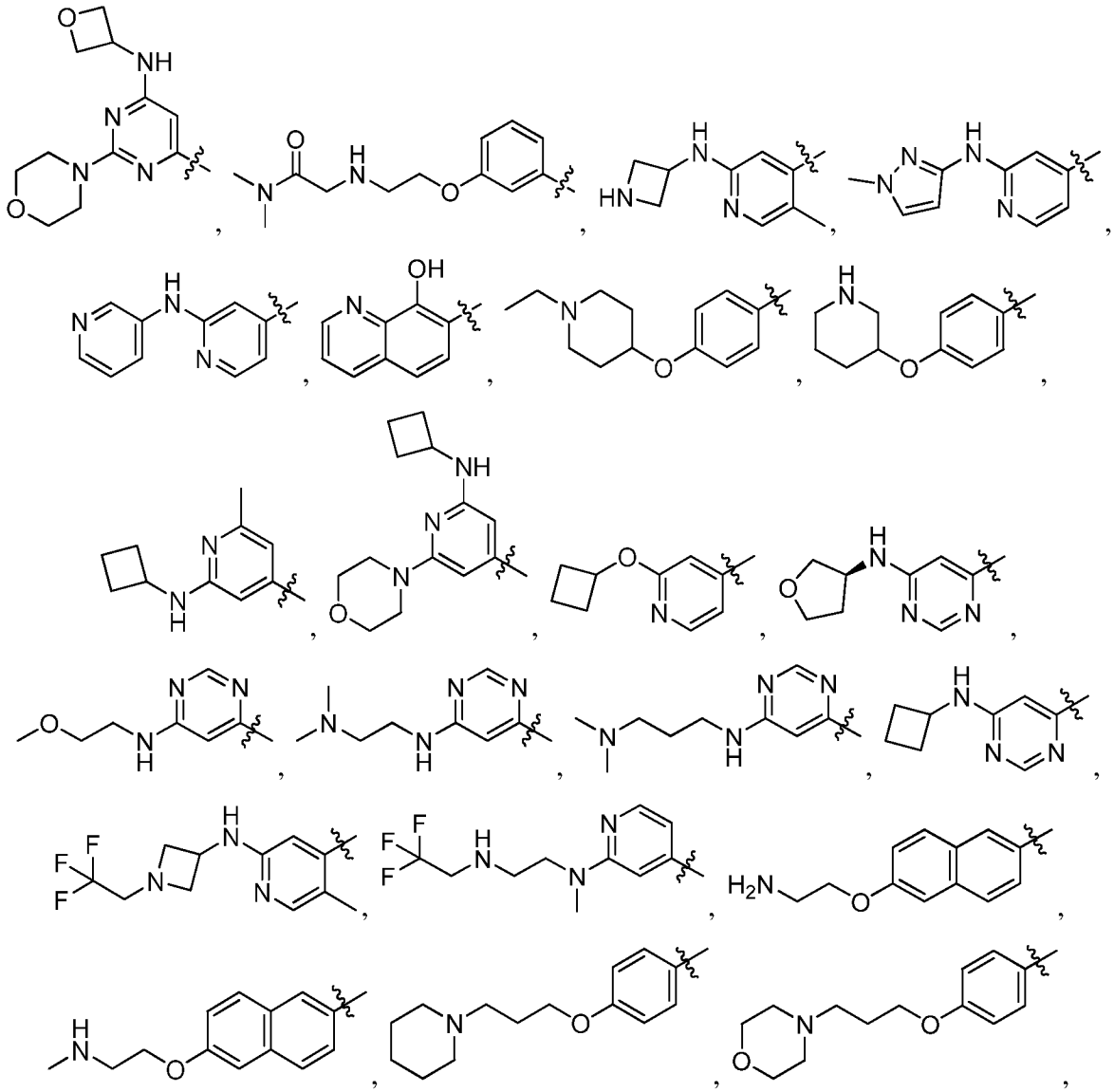
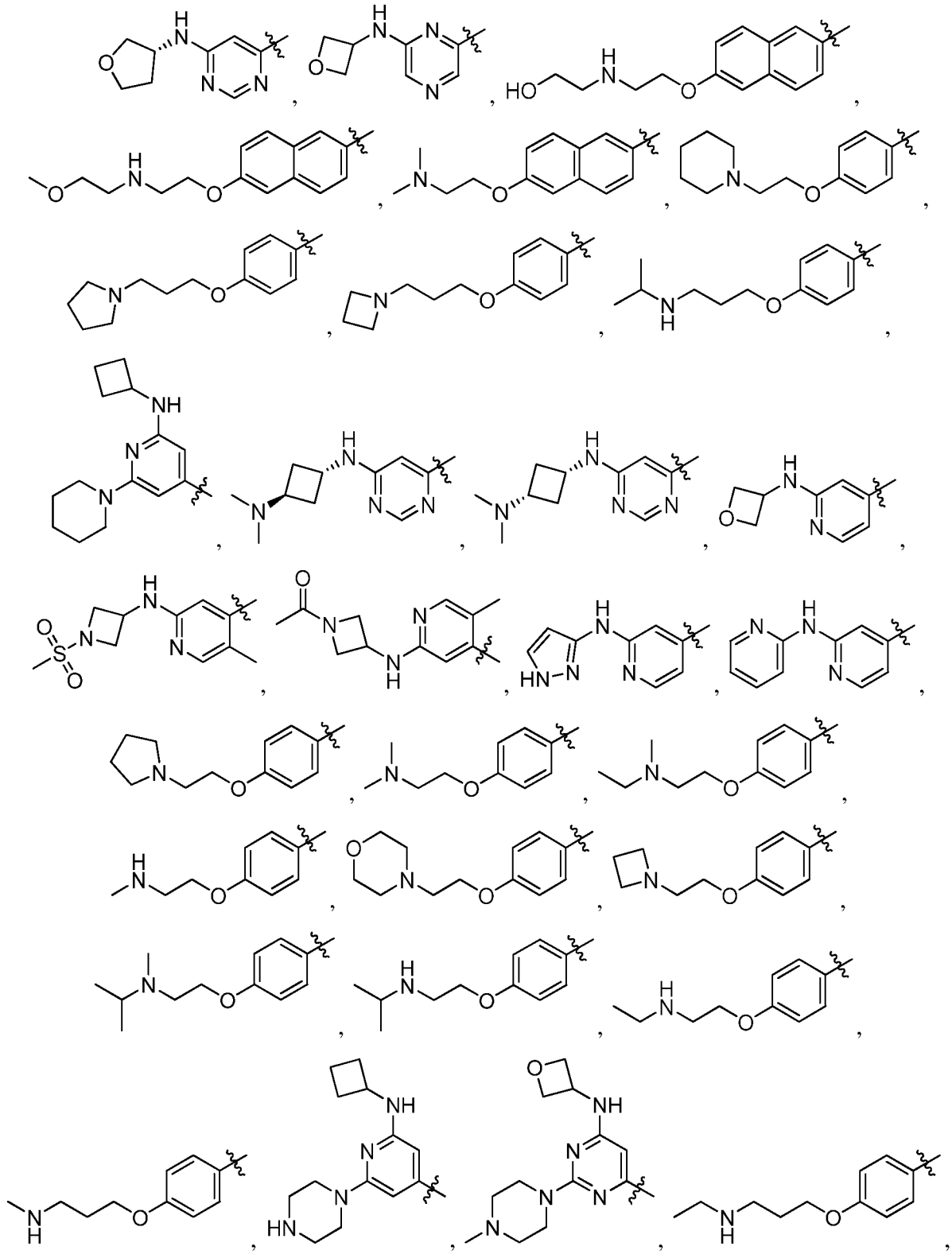
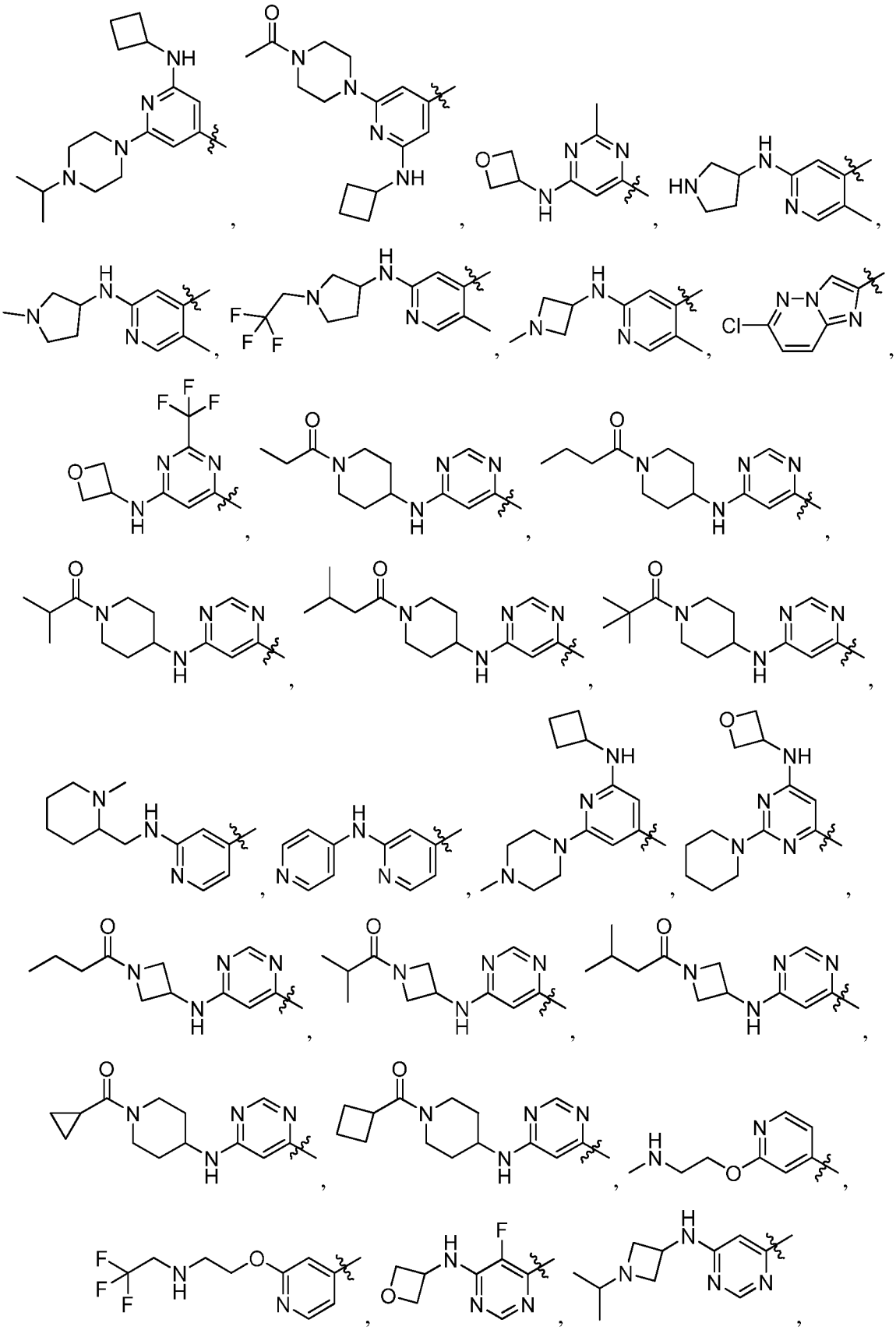
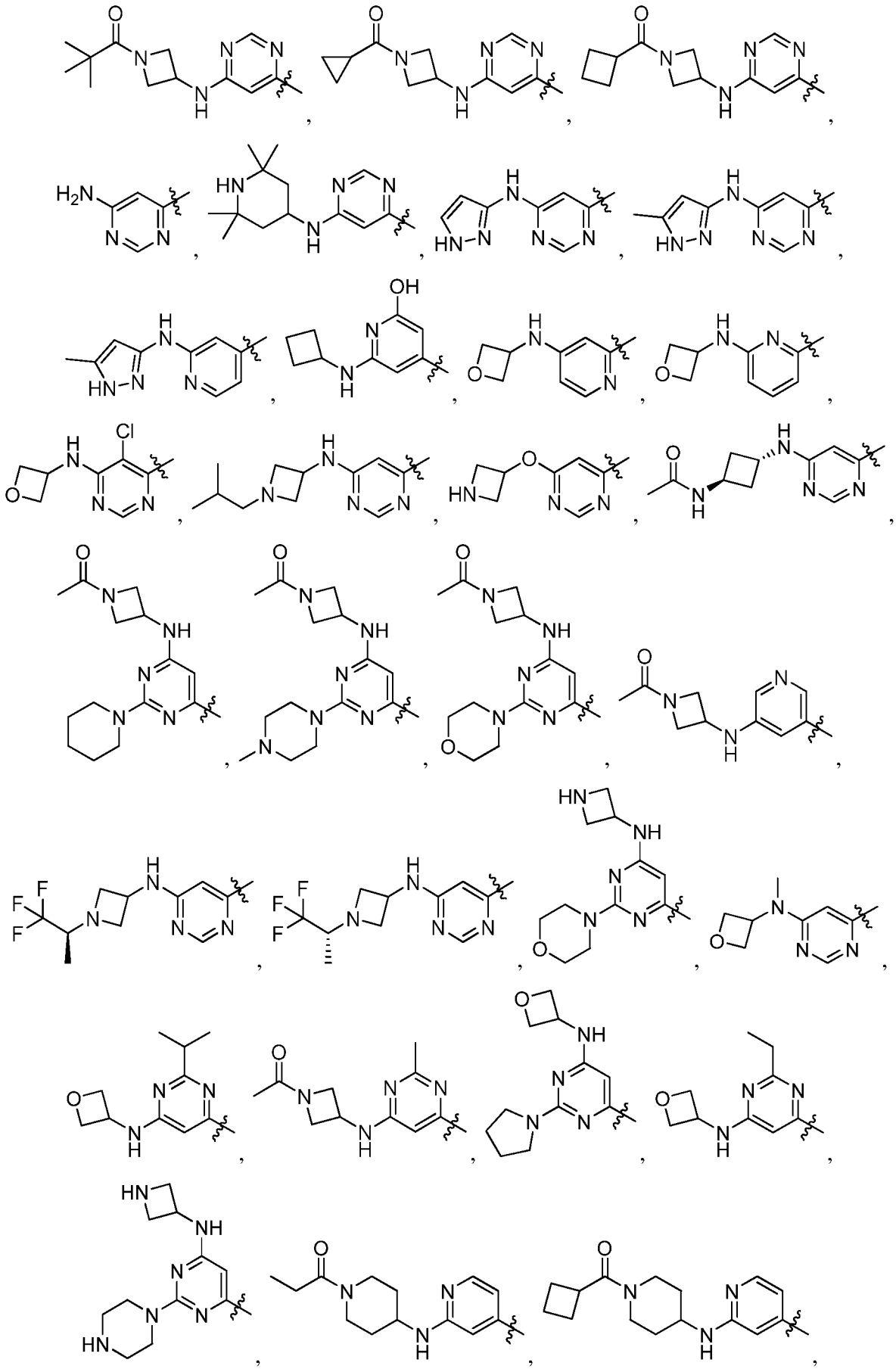
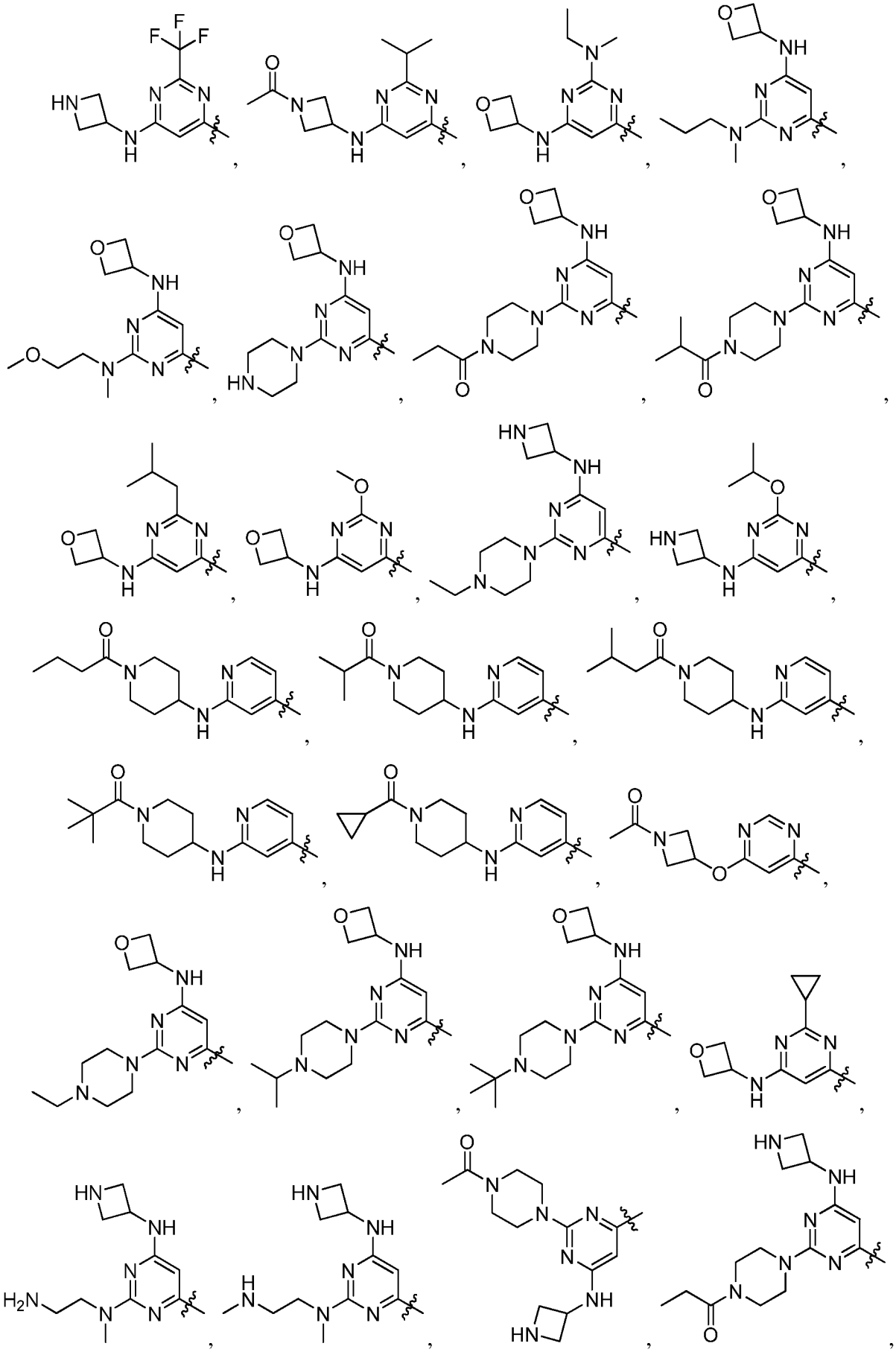
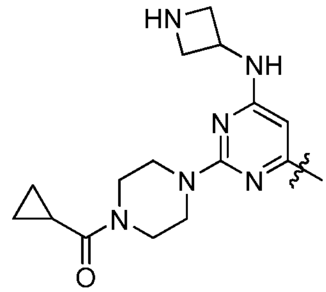
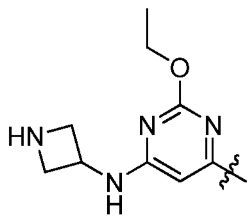
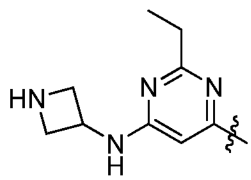
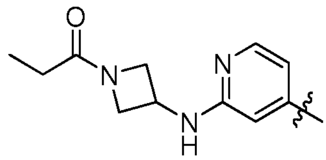


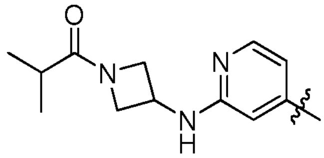
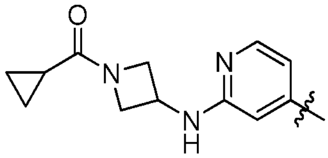
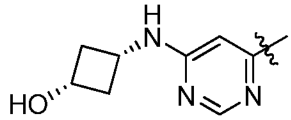


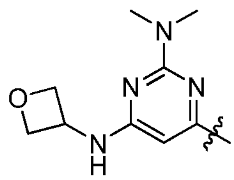
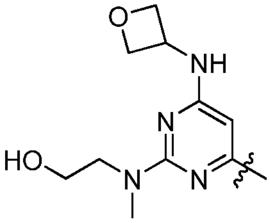
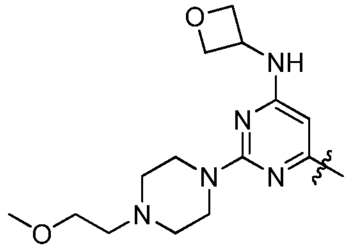
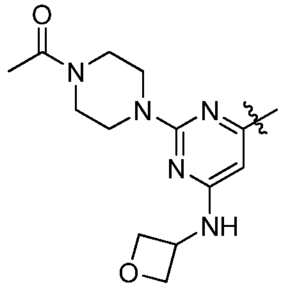


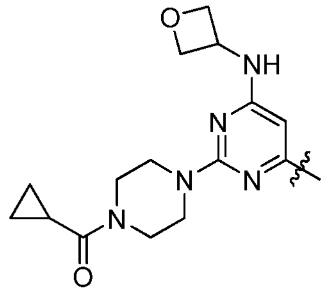
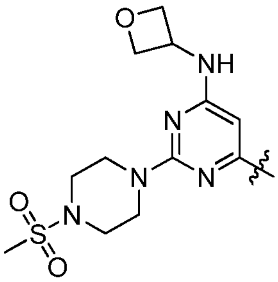
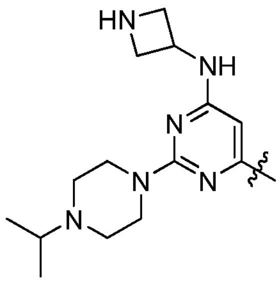
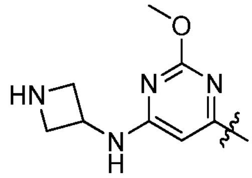


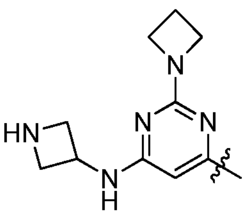
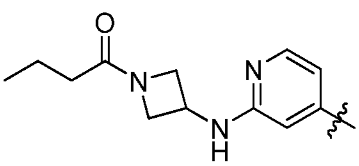
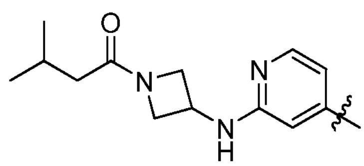


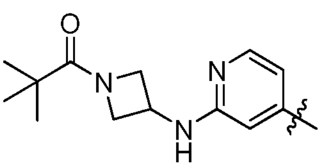
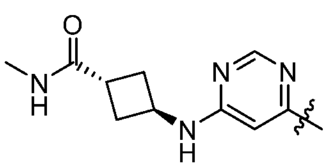
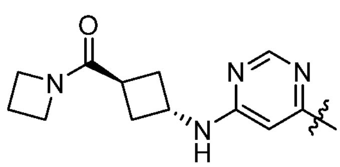
 ,  ,  ,  ,

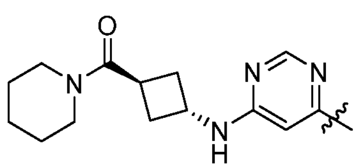
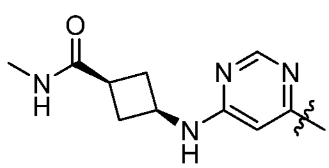
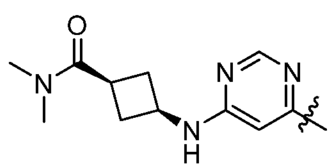
 ,  ,  ,

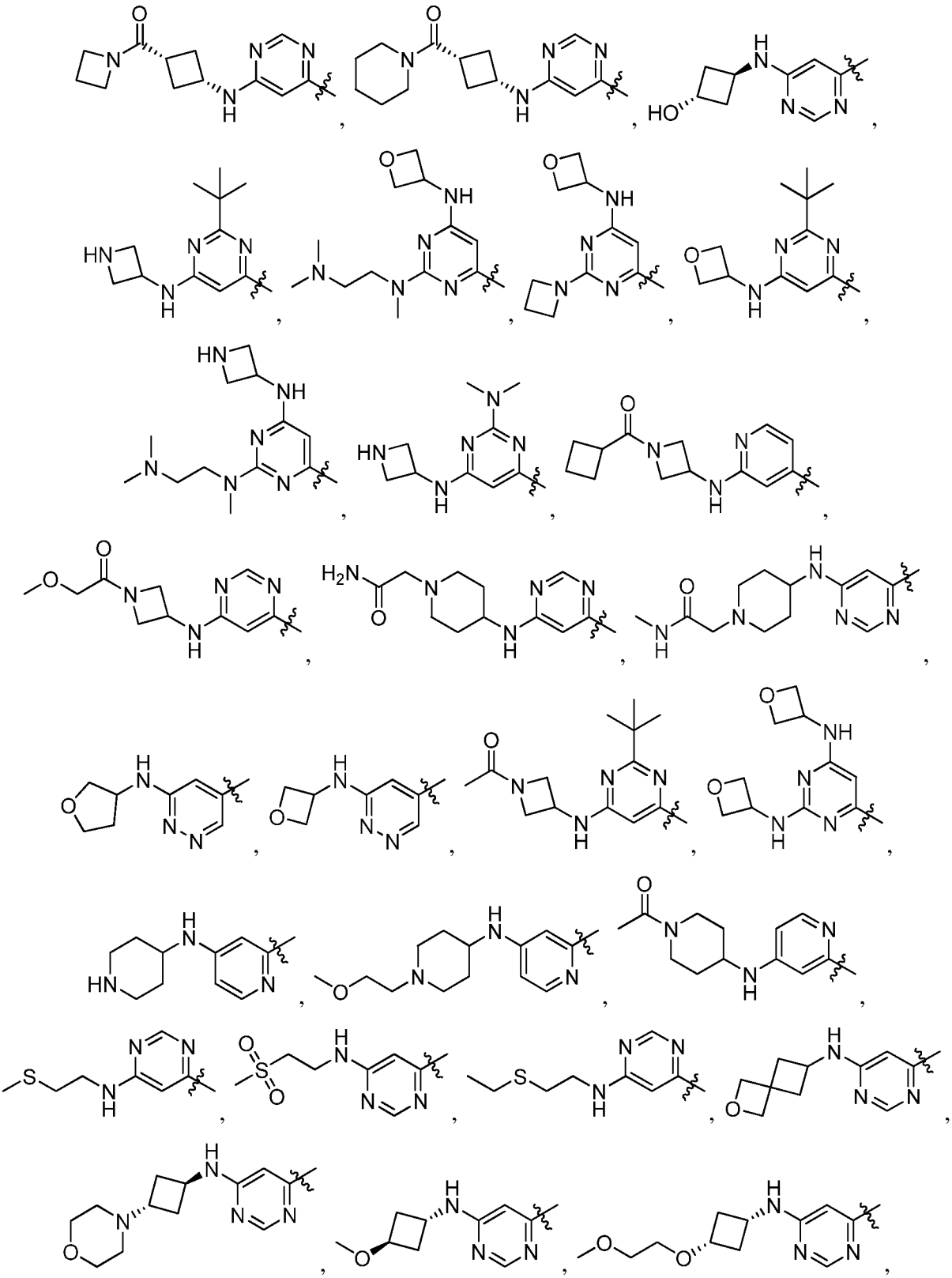
 ,  ,  ,  ,

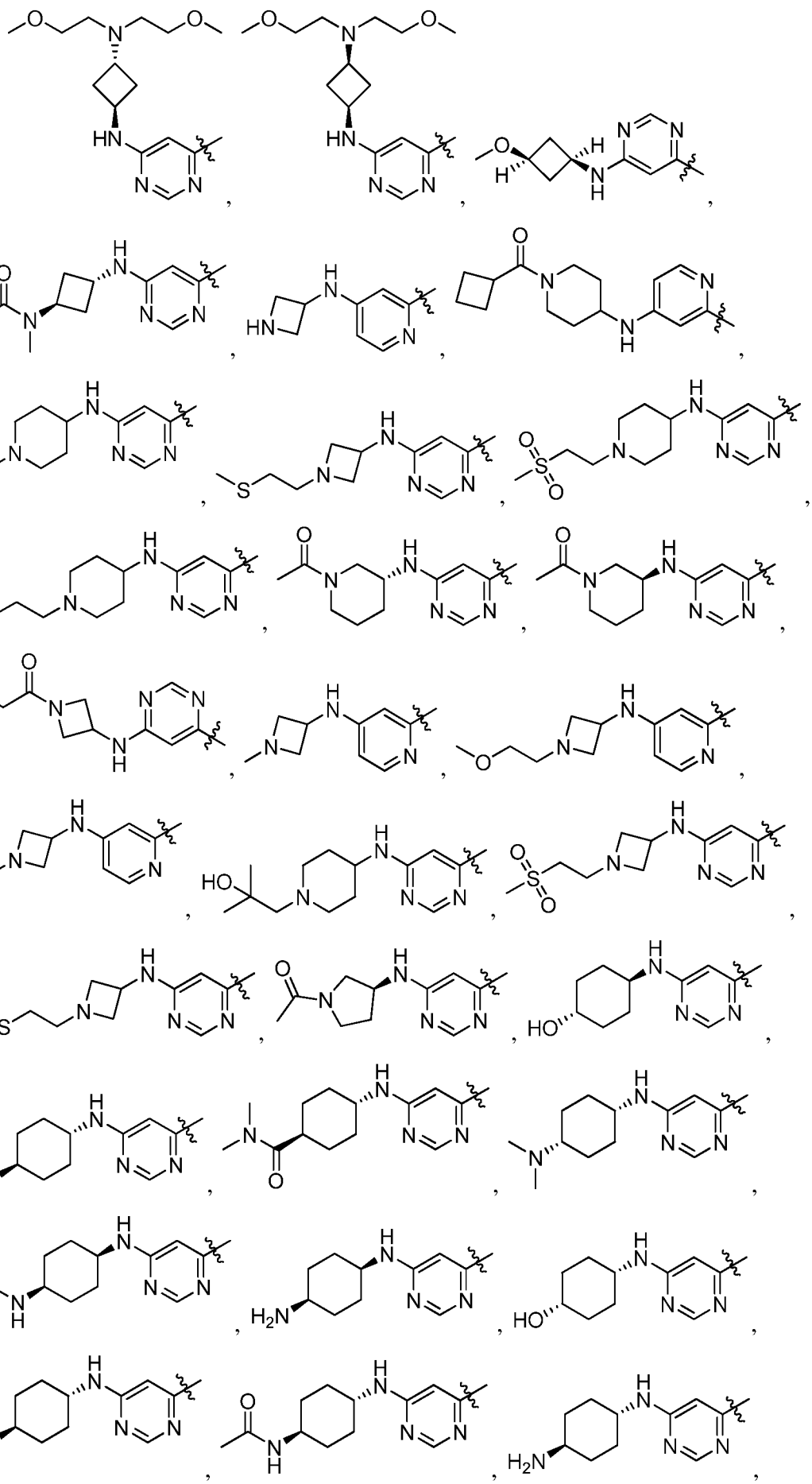
 ,  ,  ,  ,

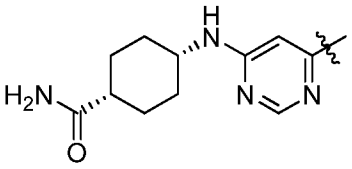
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,



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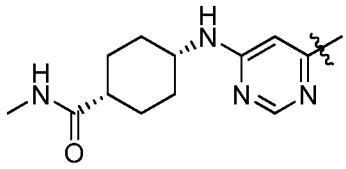
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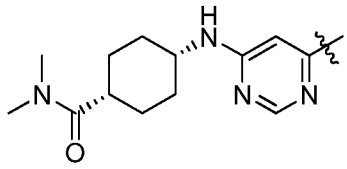
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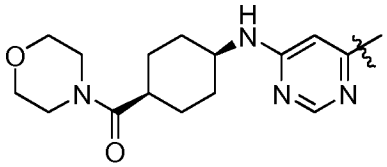
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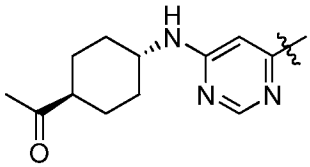
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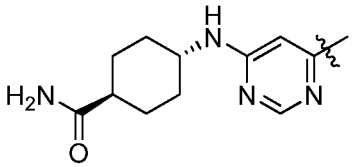
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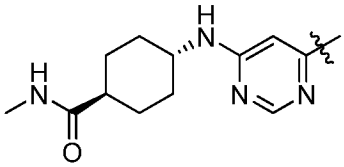
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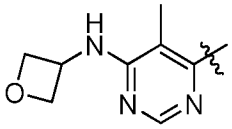
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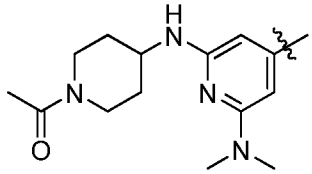
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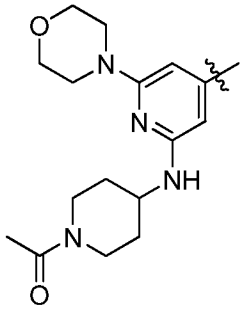
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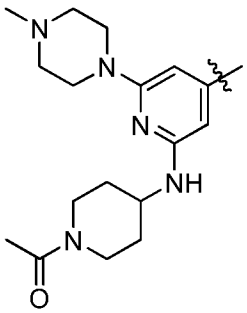
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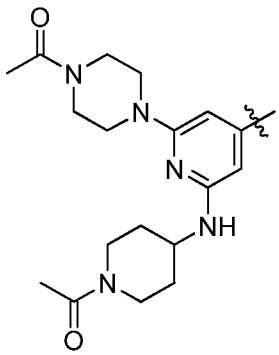
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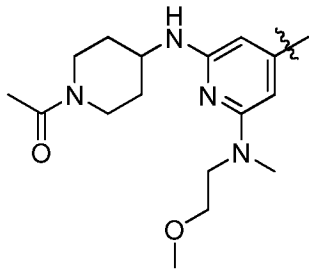
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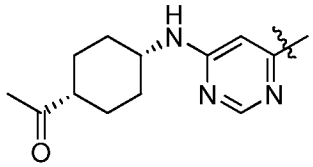
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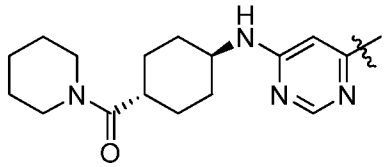
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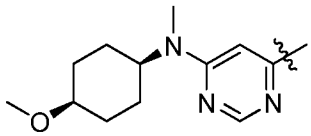
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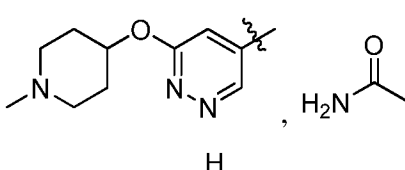
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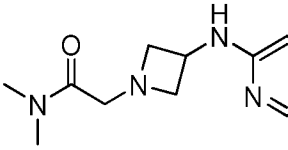
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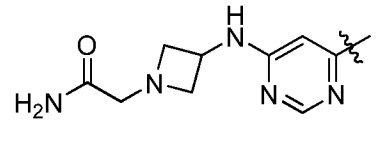
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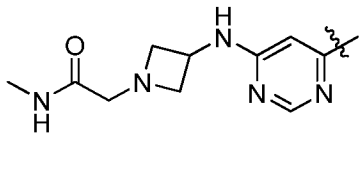
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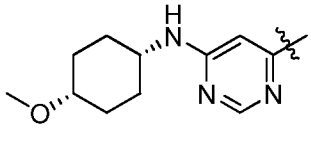
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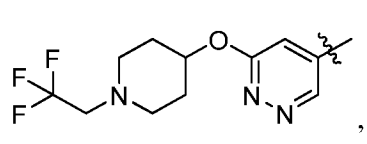
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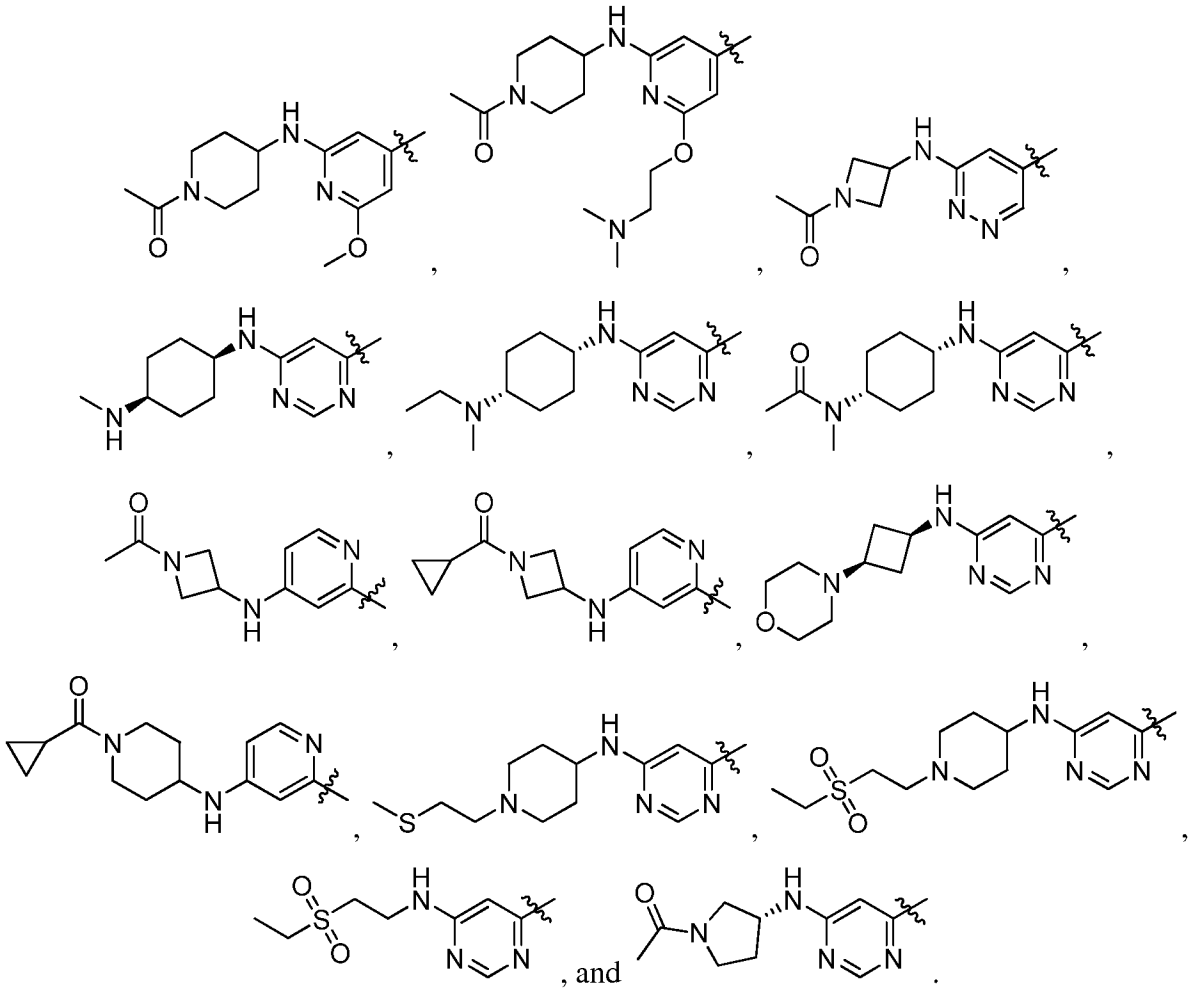

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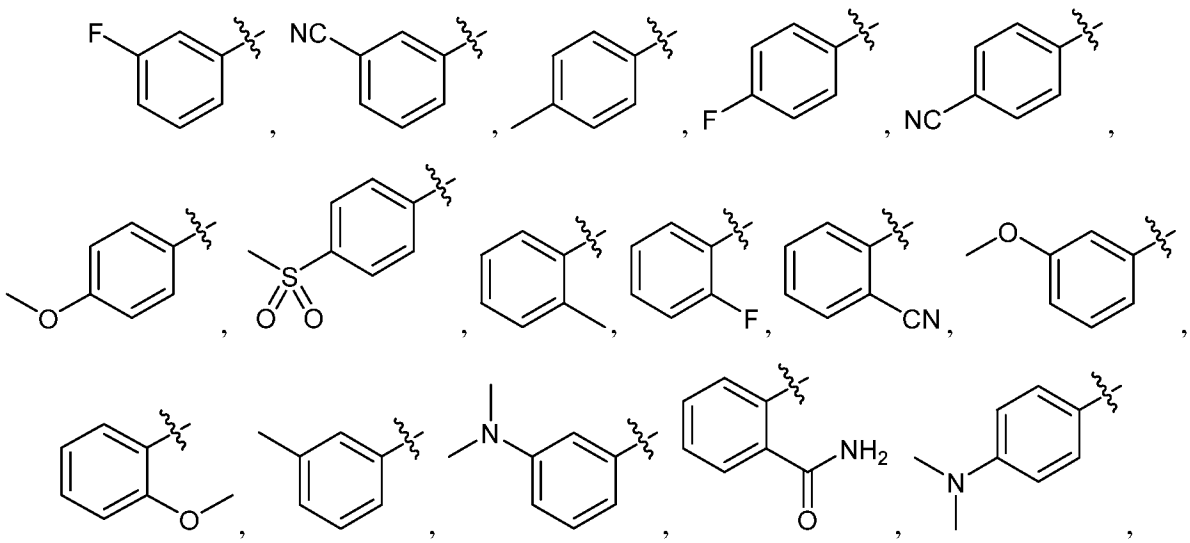
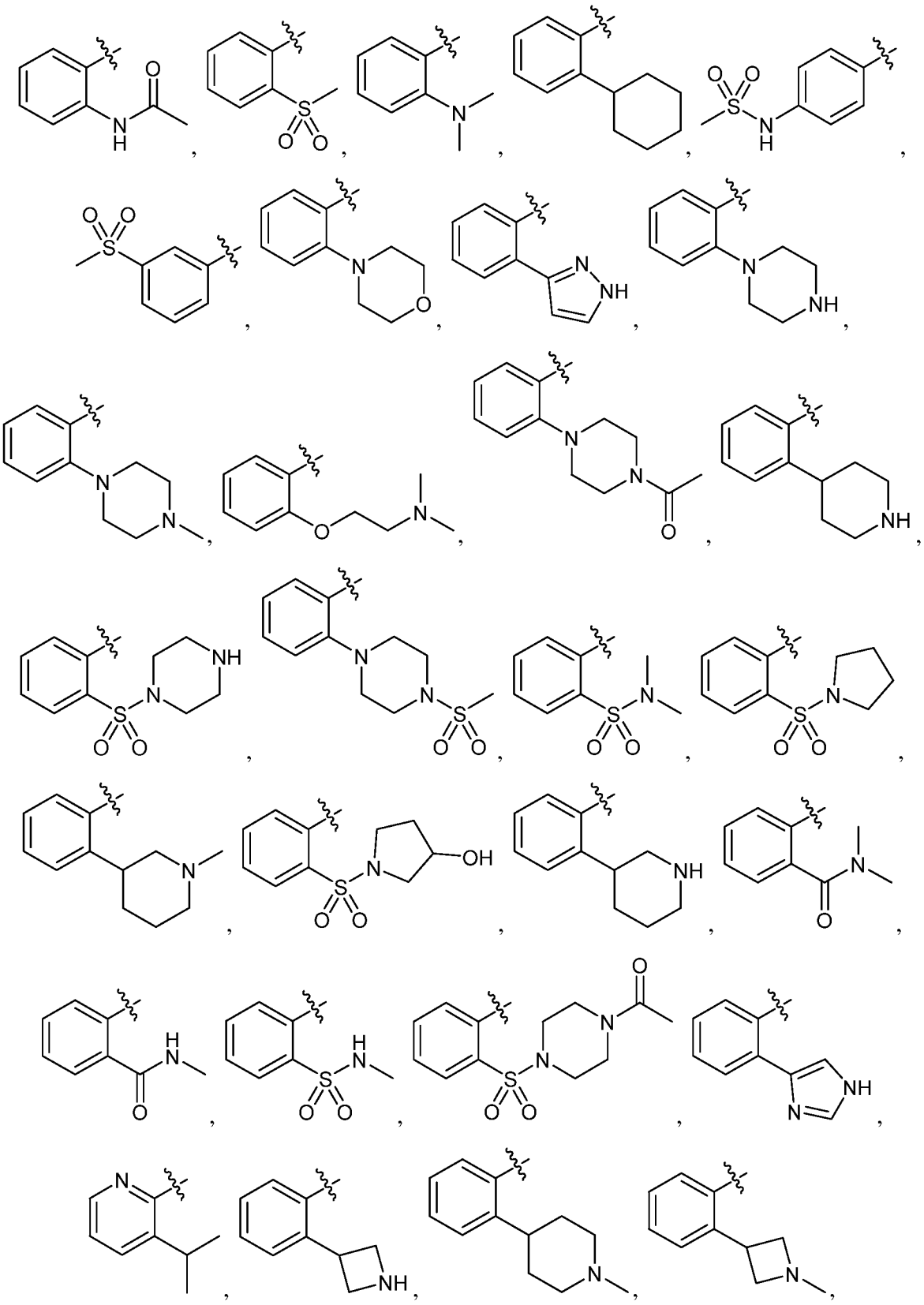
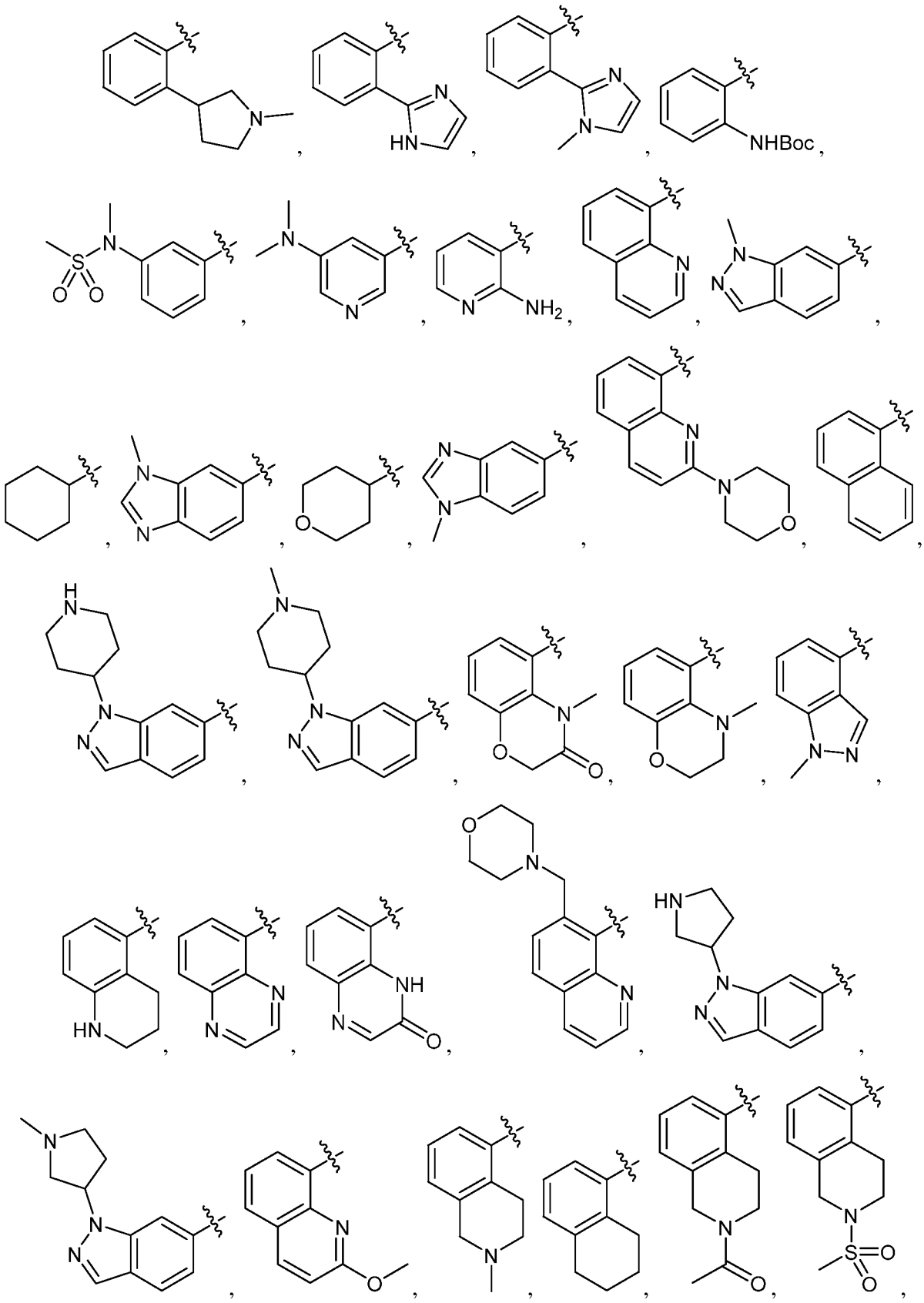
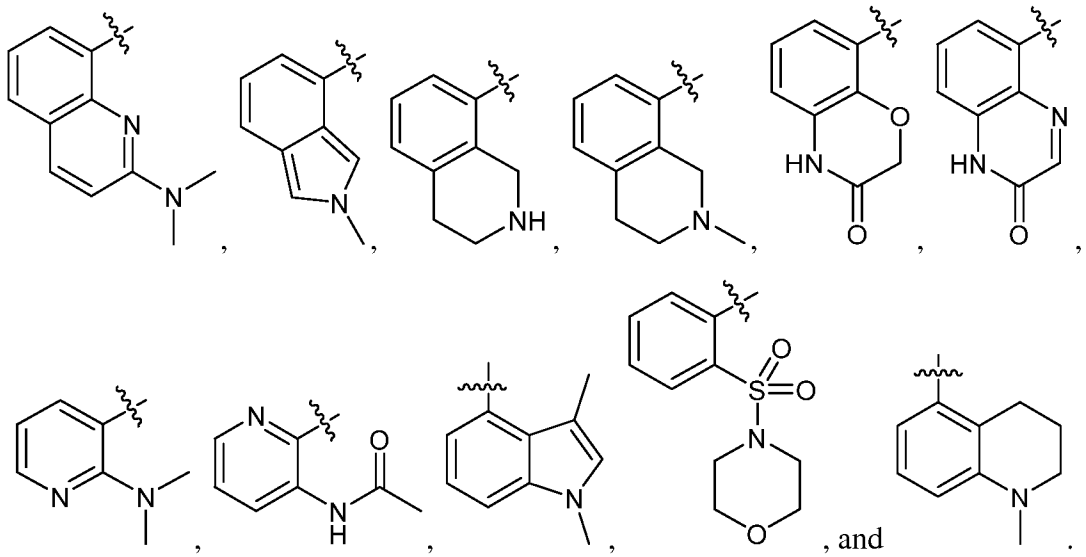
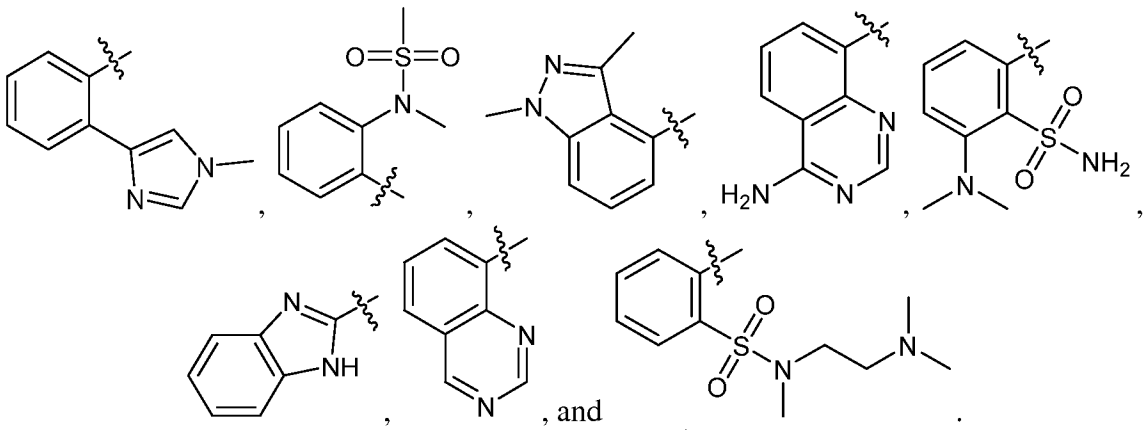




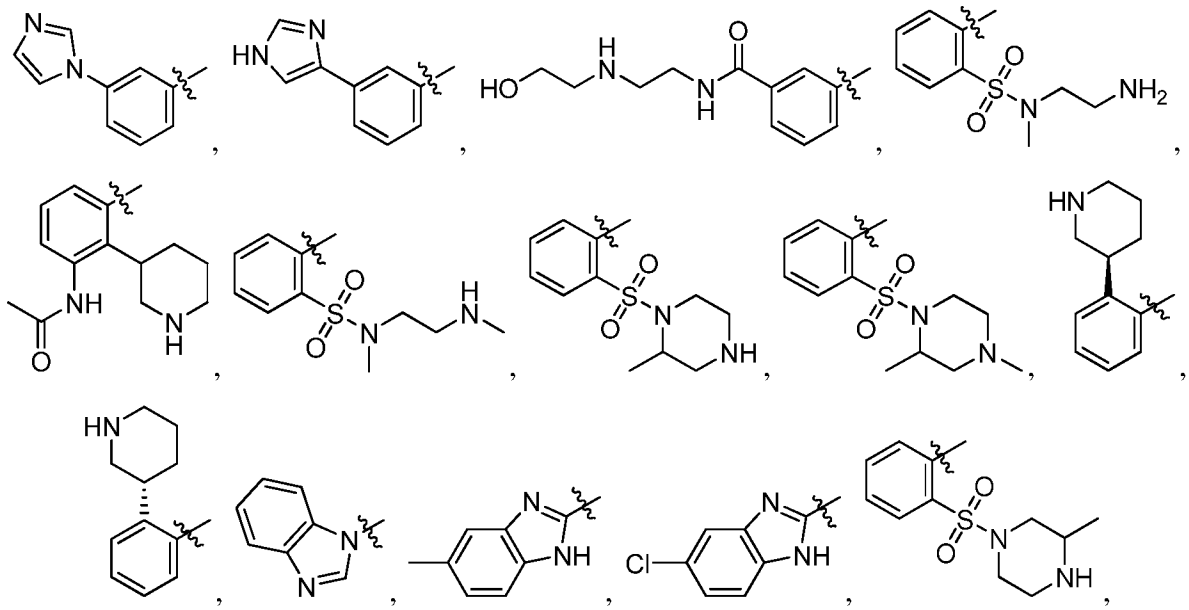


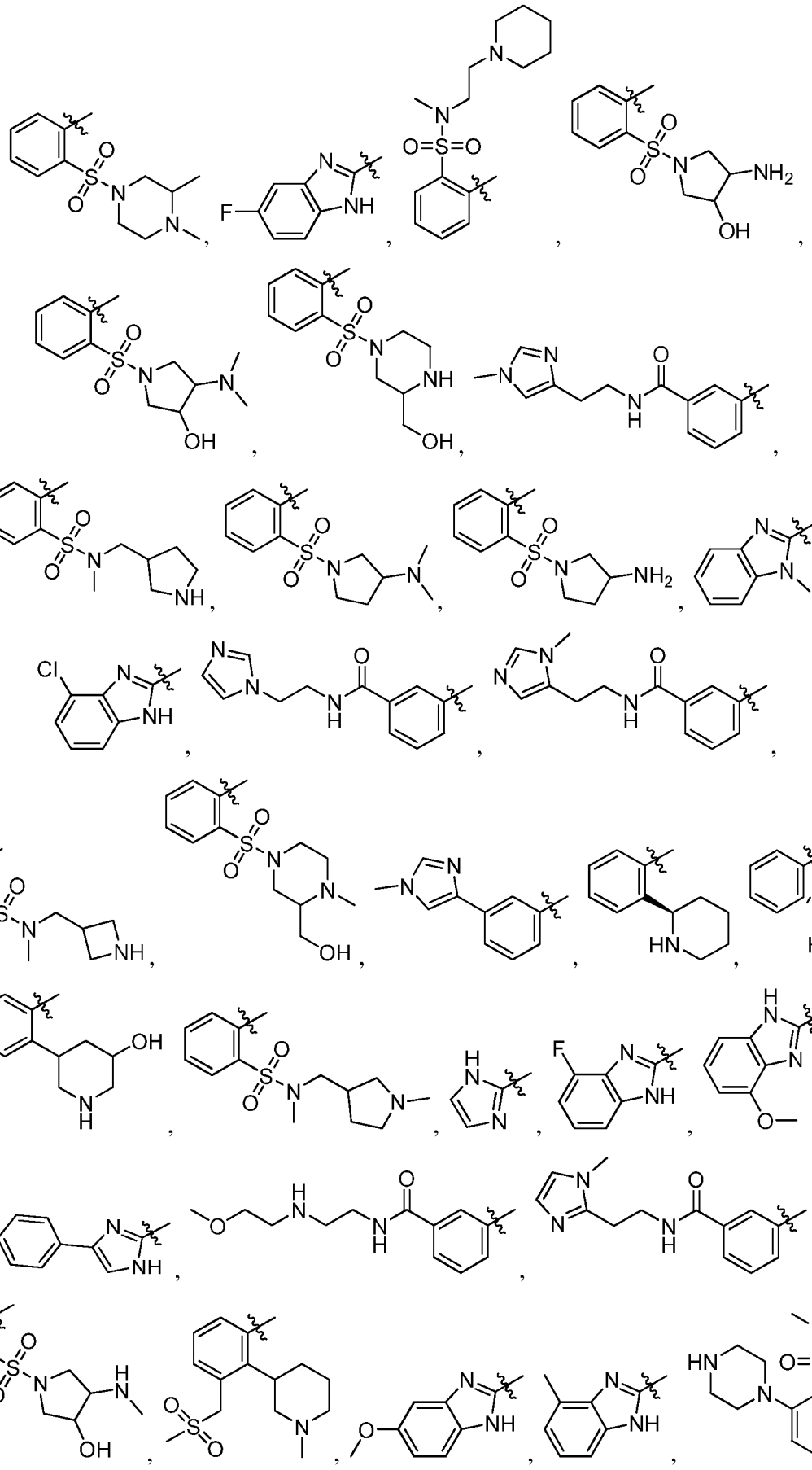


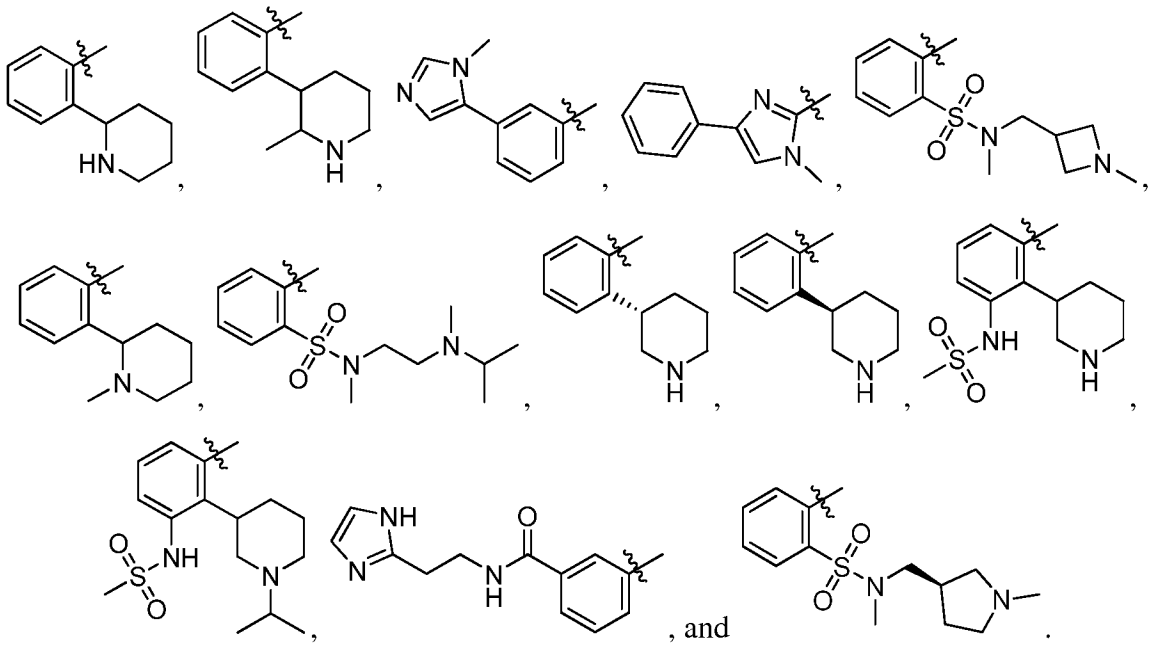
[00156] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:



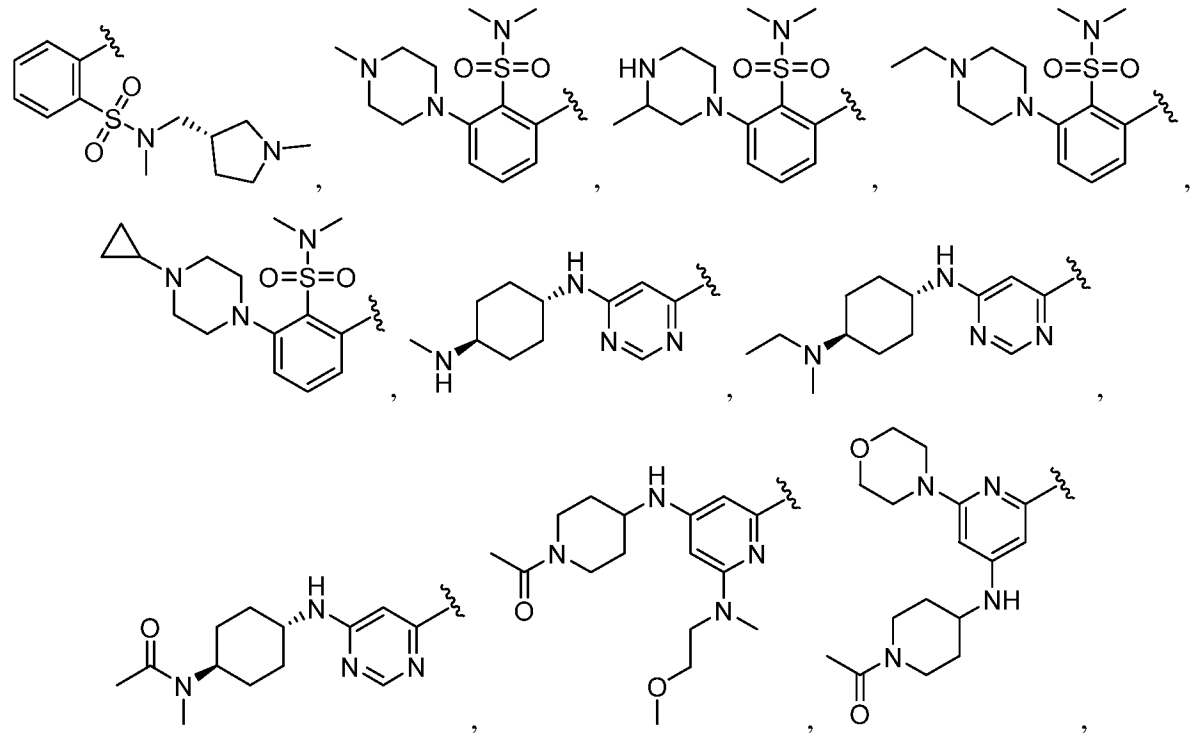
[00157] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:

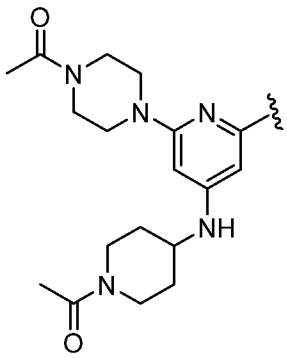
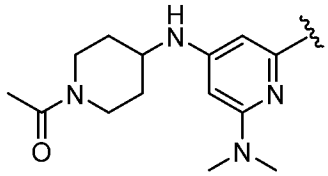
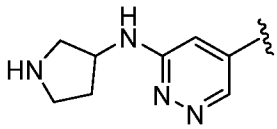
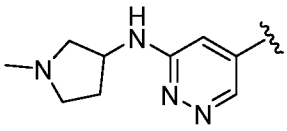






[00158] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:

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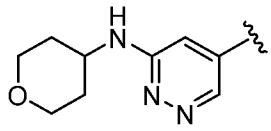
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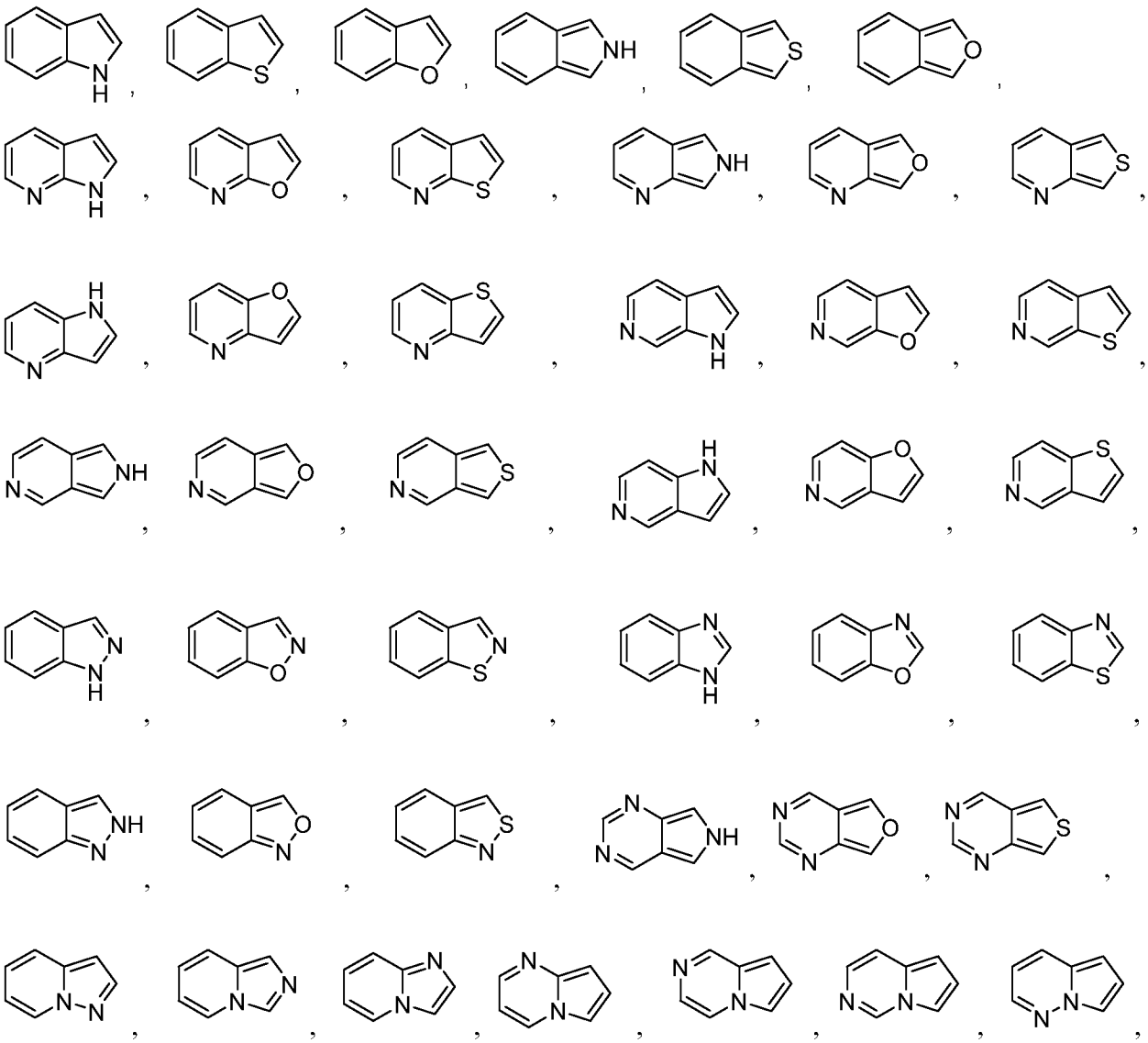
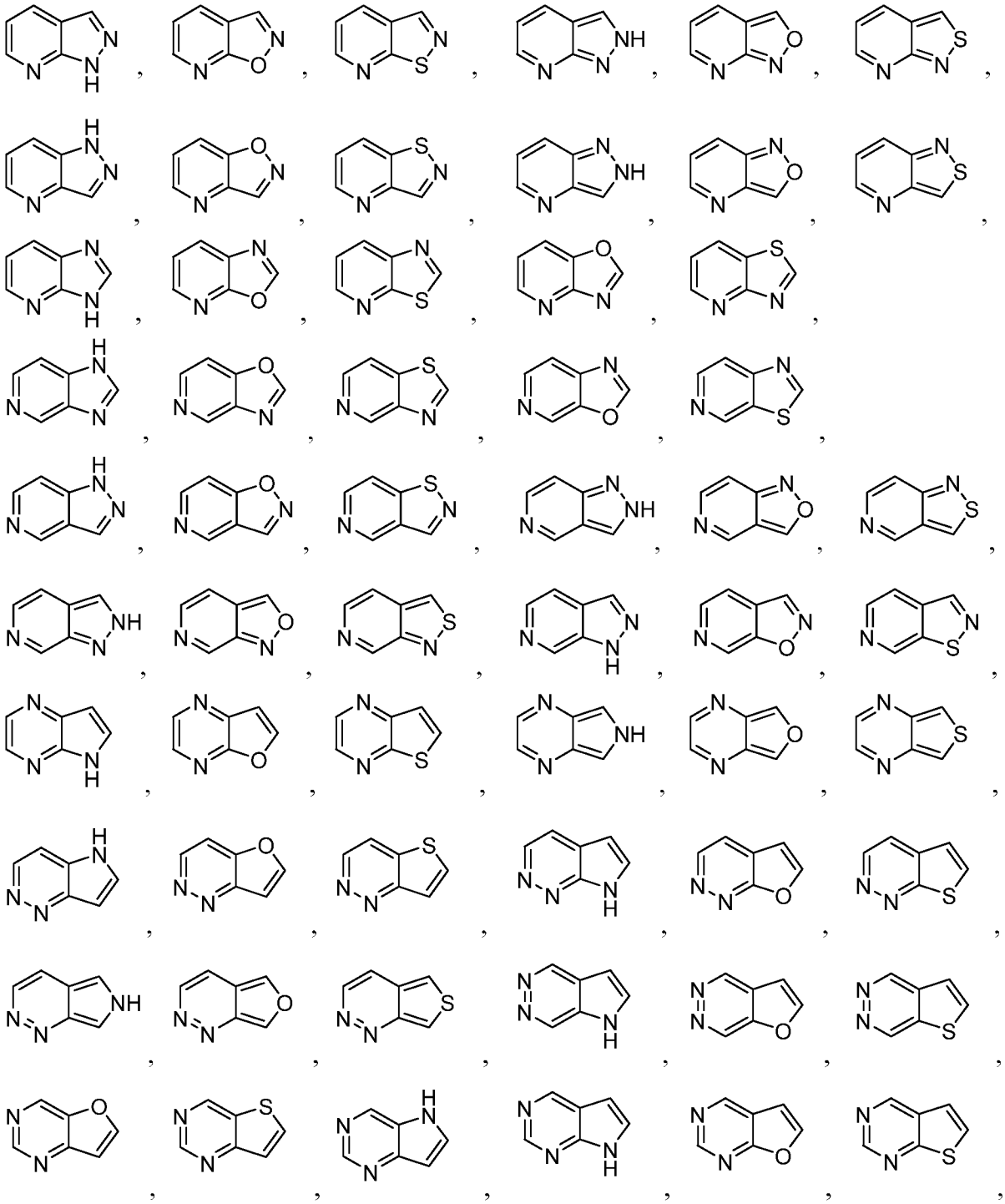
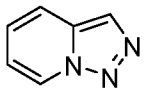
[00159] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:



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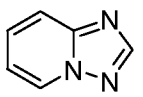
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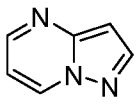
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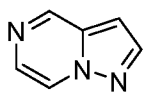
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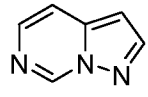
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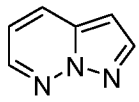
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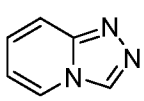
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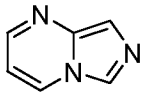
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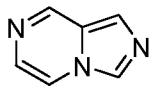
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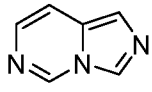
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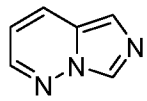
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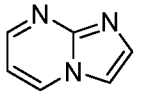
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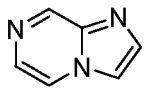
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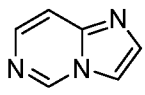
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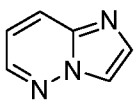
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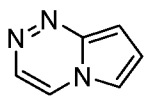
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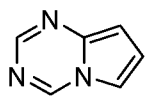
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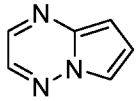
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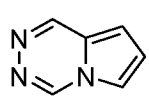
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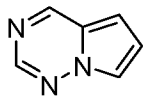
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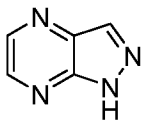
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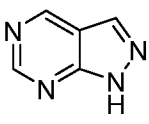
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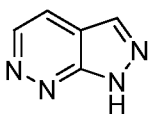
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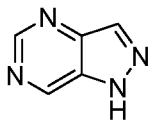
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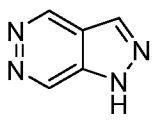
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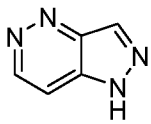
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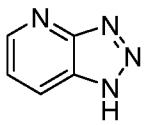
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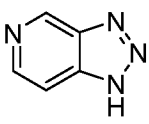
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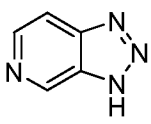
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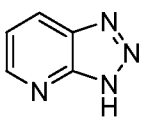
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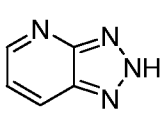
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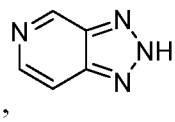
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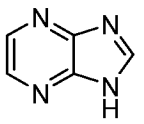
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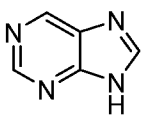
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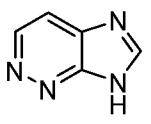
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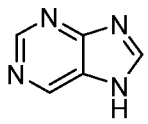
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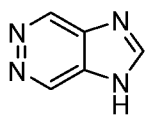
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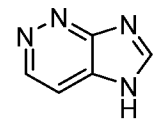
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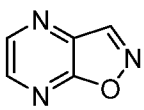
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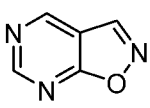
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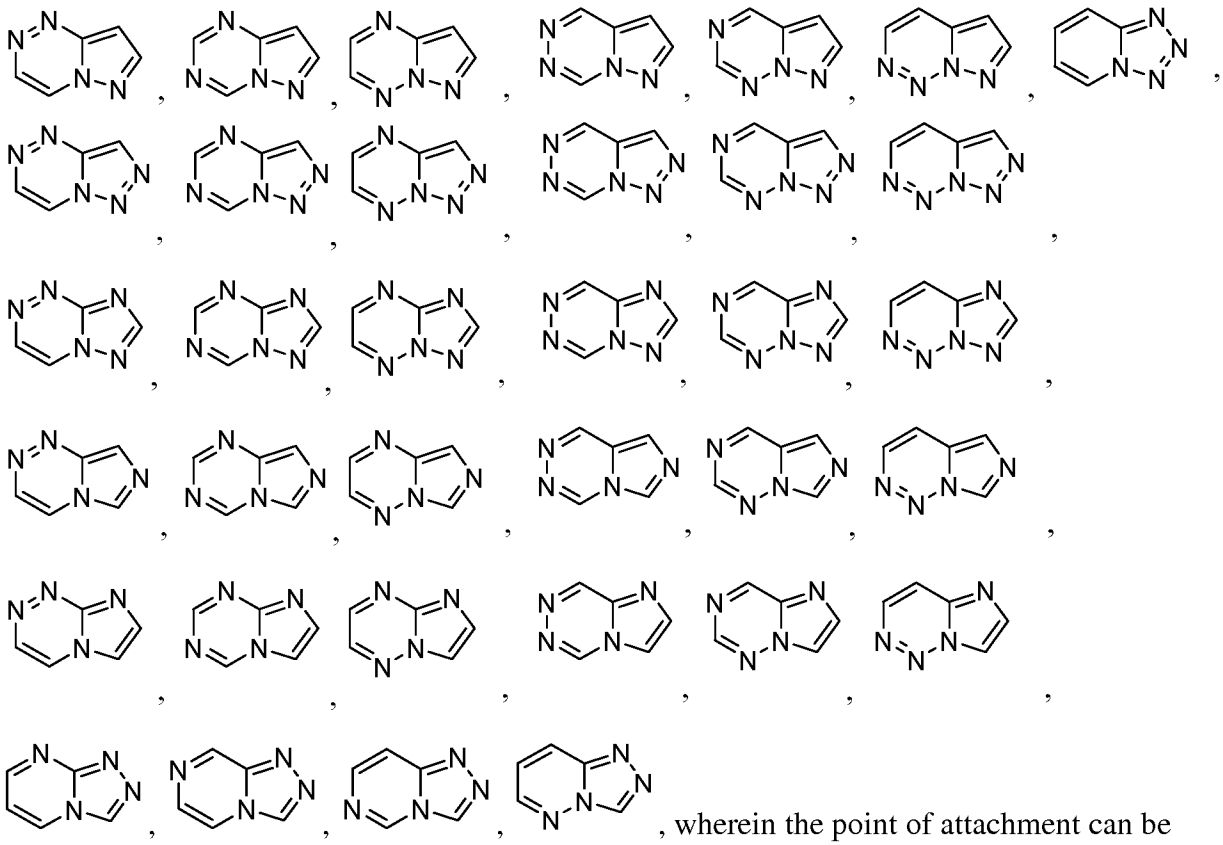
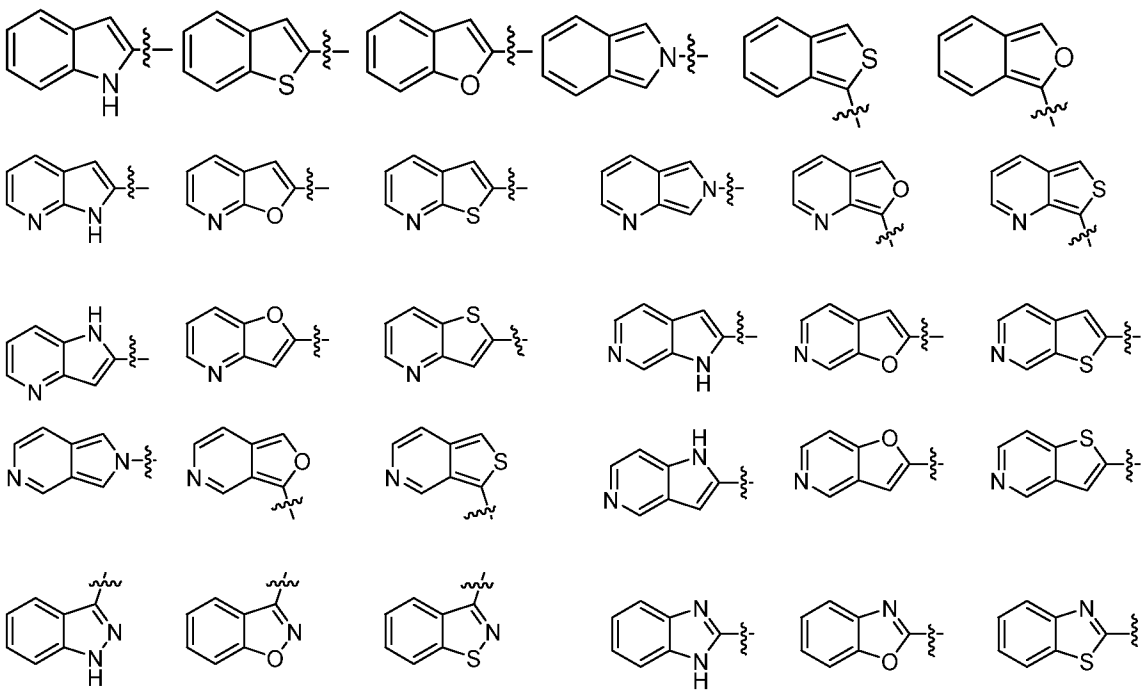
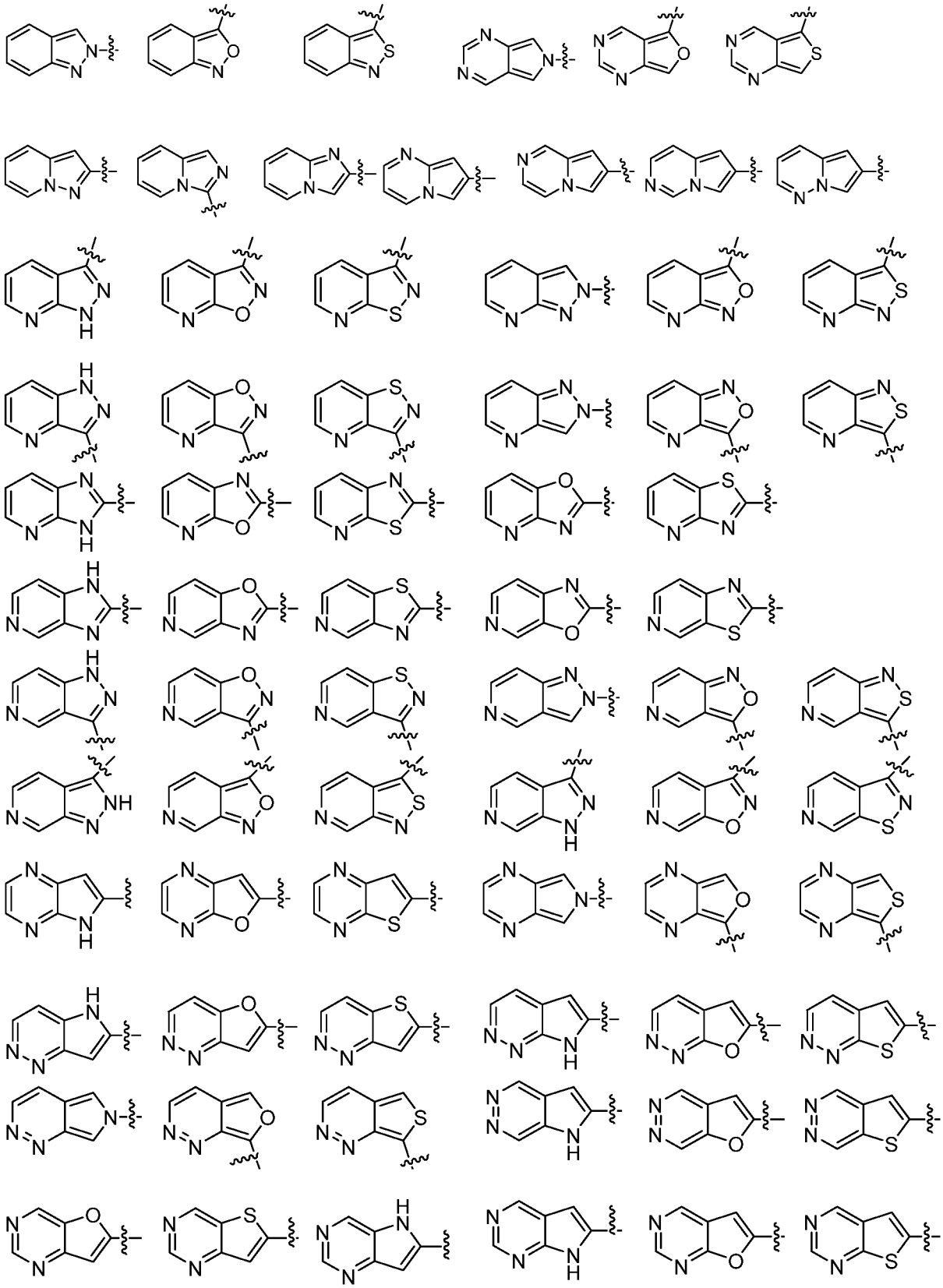
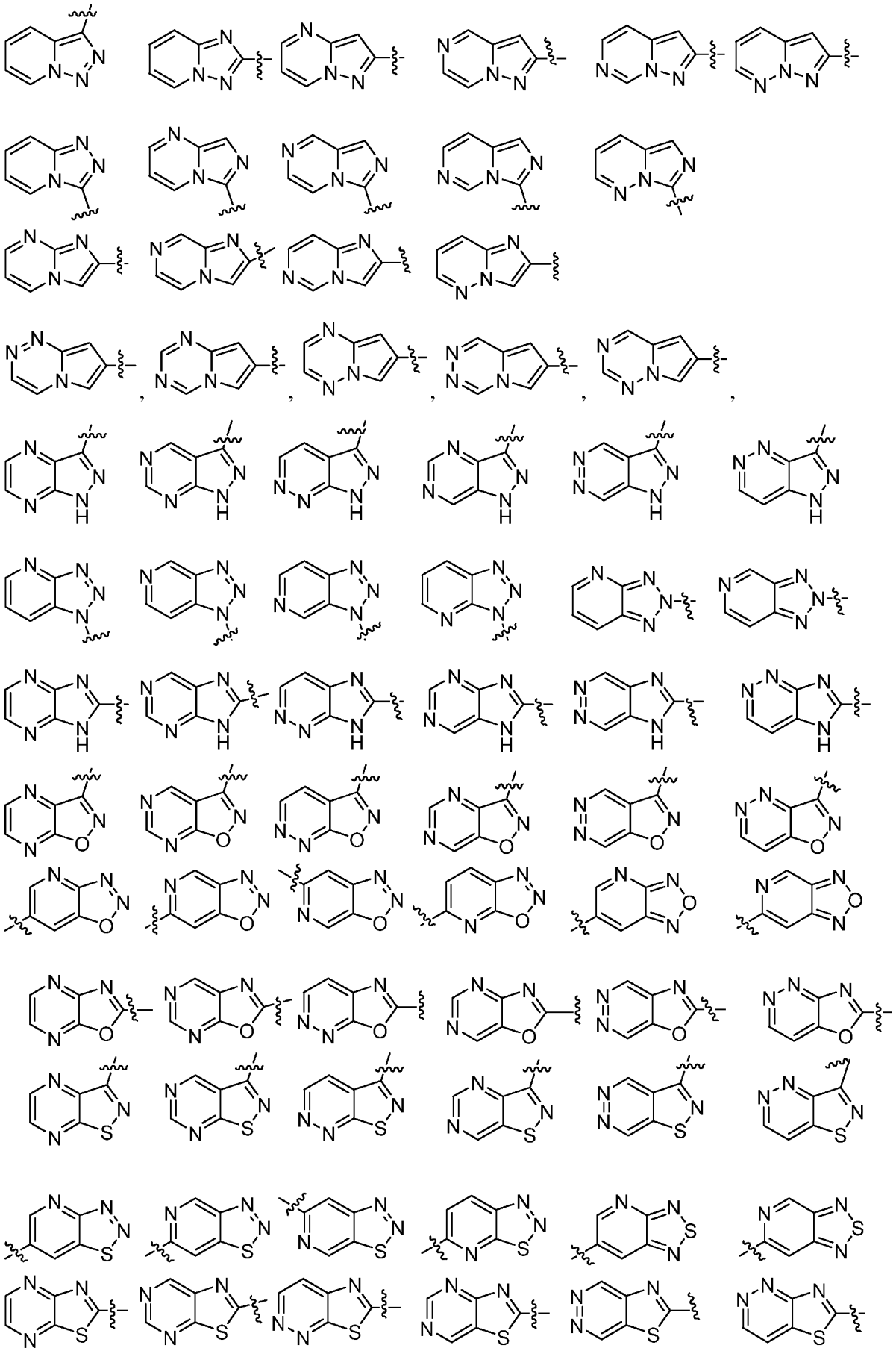


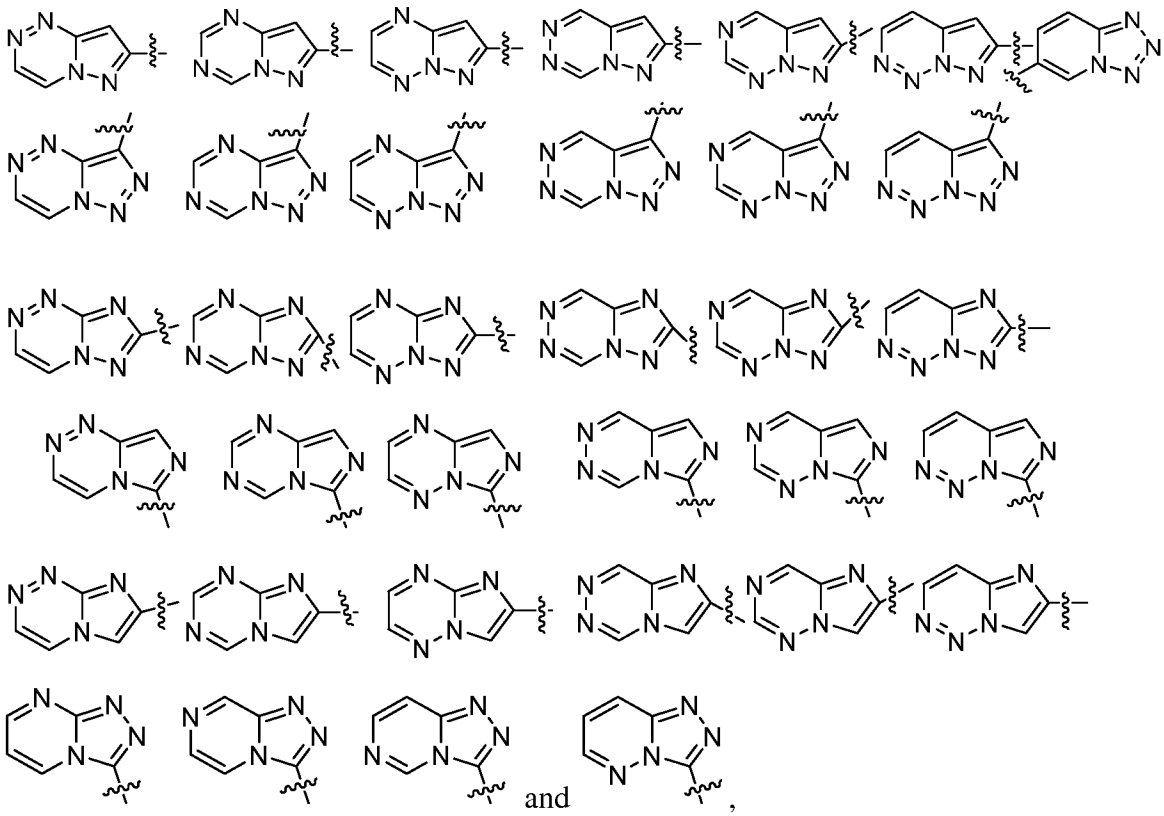
, wherein the point of attachment can be any carbon or nitrogen atom, as valency permits, and the ring may be substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits.

[00160] In certain embodiments, Ring Z, *e.g.*, Ar, Cy^A, Ring A, and the like, is selected from the group consisting of:





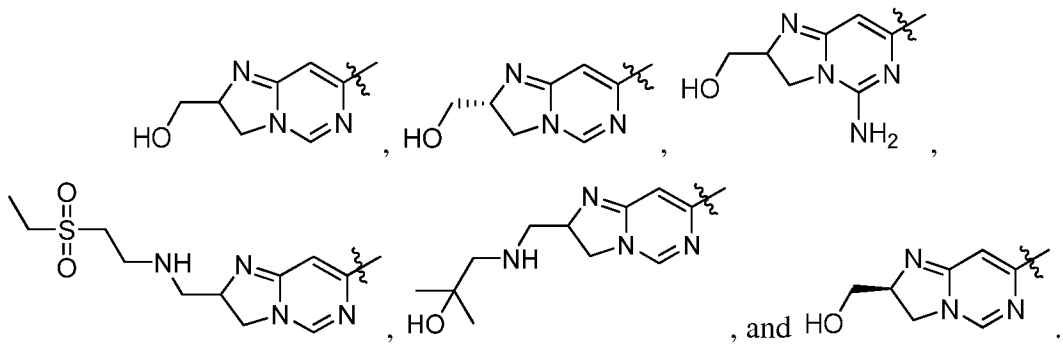




and

each of which may be optionally substituted with 1, 2, 3, 4, or 5 R^y groups as valency permits.

[00161] In certain embodiments, Ring Z, *e.g.*, Cy^A, Ring A, and the like, is an optionally substituted heterocyclyl (*i.e.,* an optionally substituted dihydroimidazo pyrimidinyl) selected from the group consisting of:



[00162] As defined generally above, Cy^A is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is unsubstituted. In certain embodiments, Cy^A is substituted with one or two R^y groups. In certain embodiments, Cy^A is substituted with one R^y group. In certain embodiments, Cy^A is substituted with two R^y groups. In certain embodiments, Cy^A is substituted with three R^y groups. In certain embodiments, Cy^A is substituted with four R^y groups.

[00163] In certain embodiments, Cy^A is phenyl substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is phenyl substituted with one or two R^y groups. In certain embodiments, Cy^A is unsubstituted phenyl. In certain embodiments, Cy^A is phenyl substituted with one R^y group. In certain embodiments, Cy^A is phenyl substituted with two R^y groups. In certain embodiments, Cy^A is phenyl substituted with three R^y groups. In certain embodiments, Cy^A is phenyl substituted with four R^y groups.

[00164] In certain embodiments, Cy^A is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is an unsubstituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^A is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one or two R^y groups. In certain embodiments, Cy^A is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one R^y group. In certain embodiments, Cy^A is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl), and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is a 6-membered heteroaryl having 1-3 nitrogens (*e.g.*, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl), and is substituted with 0, 1, 2, 3, or 4 R^y groups.

[00165] In certain embodiments, Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is an 8- to 12-membered bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is an unsubstituted bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with one or two R^y groups. In certain embodiments, Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with one R^y group. In certain embodiments, Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, wherein Cy is substituted with two R^y groups. In certain embodiments, Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with three R^y groups. In certain embodiments, Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with four R^y groups.

[00166] In certain embodiments, Cy^A is an 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is a 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl), wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is a 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl), wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Cy^A is selected from the group consisting of quinoline, benzimidazole, benzopyrazole, quinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, naphthalene, tetrahydronaphthalene, 2,3-dihydrobenzo[*b*][1,4]dioxine, isoindole, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, and quinoxalin-2(1*H*)-one, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups.

[00167] As defined generally above, each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$, wherein R^A and R^B are described herein.

[00168] In some embodiments, at least one R^y is halo. In certain embodiments, at least one R^y is fluoro. In certain embodiments, at least one R^y is chloro. In some embodiments, at least one R^y is –CN.

[00169] In some embodiments, at least one R^y is optionally substituted aliphatic. In certain embodiments, at least one R^y is substituted aliphatic. In certain embodiments, at least one R^y is unsubstituted aliphatic. In some embodiments, at least one R^y is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methyl, ethyl, or propyl. In certain embodiments, at least one R^y is methyl. In certain embodiments, at least one R^y is $–CF_3$, CHF_2, or CH_2F. In certain embodiments, at least one R^y is C_{1-6} alkyl substituted with aryl, heteroaryl, or heterocyclyl. In certain embodiments, at least one R^y is benzyl. In certain embodiments, at least one R^y is $–(C_{1-6}$ alkyl)-heteroaryl. In certain embodiments, at least one R^y is $–(C_{1-6}$ alkyl)-heterocyclyl. In certain embodiments, at least one R^y is $–CH_2$-heteroaryl. In certain embodiments, at least one R^y is $–CH_2$-heterocyclyl.

[00170] In some embodiments, at least one R^y is $–C(O)N(R^B)_2$. In certain embodiments, at least one R^y is $–C(O)NHR^B$. In certain embodiments, at least one R^y is $–C(O)NH_2$. In certain embodiments, at least one R^y is $–C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $–C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted morpholinyl.

[00171] In some embodiments, at least one R^y is $–SO_2N(R^B)_2$. In certain embodiments, at least one R^y is $–SO_2NHR^B$. In certain embodiments, at least one R^y is $–SO_2NH_2$. In certain embodiments, at least one R^y is $–SO_2N(R^B)_2$, wherein neither R^B is hydrogen. In certain embodiments, at least one R^y is $–SO_2NH(C_{1-6}$ alkyl) or $–SO_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one R^y is $–SO_2N(CH_3)_2$. In certain embodiments, at least one R^y is $–SO_2N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $–SO_2$-morpholinyl. In certain embodiments, at least one R^y is $–SO_2$-piperidinyl, $-SO_2$-piperazinyl, or $–SO_2$-piperidinyl.

[00172] In some embodiments, at least one R^y is $–SO_2R^A$. In some embodiments, at least one R^y is $–SO_2R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $–SO_2(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $–SO_2CH_3$. In some embodiments, at least one R^y is $–C(O)R^A$. In some embodiments, at least one R^y is $–C(O)R^A$,

wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is –C(O)(C_{1-6} alkyl). In some embodiments, at least one R^y is –$C(O)CH_3$.

[00173] In some embodiments, at least one R^y is –$N(R^B)C(O)R^A$. In certain embodiments, at least one R^y is –$NHC(O)R^A$. In certain embodiments, at least one R^y is –NHC(O)(C_{1-6} alkyl). In certain embodiments, at least one R^y is –$NHC(O)CH_3$.

[00174] In some embodiments, at least one R^y is –$N(R^B)SO_2R^A$. In some embodiments, at least one R^y is –$NHSO_2R^A$. In some embodiments, at least one R^y is –N(C_{1-6} alkyl)SO_2R^A. In certain embodiments, at least one R^y is –$NHSO_2$(C_{1-6} alkyl) or –N(C_{1-6} alkyl)SO_2(C_{1-6} alkyl). In certain embodiments, at least one R^y is –$NHSO_2CH_3$. In certain embodiments, at least one R^y is –$N(CH_3)SO_2CH_3$.

[00175] In some embodiments, at least one R^y is optionally substituted heterocyclyl, optionally substituted carbocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one R^y is an optionally substituted 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted pyrrolidinyl. In certain embodiments, at least one R^y is pyrroldinyl, hydroxypyrrolidinyl, or methylpyrrolidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperdinyl, optionally substituted piperazinyl, or optionally substituted morpholinyl. In certain embodiments, at least one R^y is morpholinyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, piperazinyl, methylpiperazinyl, acetylpiperazinyl, methylsulfonylpiperazinyl, aziridinyl, or methylaziridinyl. In some embodiments, at least one R^y is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having one heteroatom selected

from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heteroaryl having 1-3 nitrogens. In certain embodiments, at least one R^y is an optionally substituted pyrazolyl. In certain embodiments, at least one R^y is an optionally substituted imidazolyl. In certain embodiments, at least one R^y is an optionally substituted pyridyl. In certain embodiments, at least one R^y is an optionally substituted pyrimidyl. In certain embodiments, at least one R^y is pyrazolyl, methylpyrazolyl, imidazolyl, or methylimidazolyl.

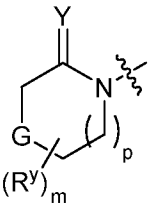
[00176] In some embodiments, at least one R^y is $-OR^A$. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted heterocyclyl. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted heteroaryl. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted cycloalkyl. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methoxy, ethoxy, or propoxy. In certain embodiments, at least one R^y is methoxy. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is $-OCH_2CH_2N(CH_3)_2$.

[00177] In some embodiments, at least one R^y is $-N(R^B)_2$. In some embodiments, at least one R^y is $-NHR^B$. In some embodiments, at least one R^y is $-N(C_{1-6}\text{ alkyl})_2$, $-NH(C_{1-6}\text{ alkyl})$, or $-NH_2$. In certain embodiments, at least one R^y is $-NH_2$. In certain embodiments, at least one R^y is $-NHCH_3$. In certain embodiments, at least one R^y is $-N(CH_3)_2$. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted heterocyclyl. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted heteroaryl. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted cycloalkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl. In some embodiments, at least one R^y is $-N(R^B)_2$, wherein each R^B is independently selected from hydrogen or C_{1-6} alkyl.

[00178] In some embodiments, for compounds of formula (**II^C**), (**II^{C}a**), (**II^C-b**), (**III^C**), (**III^C-a**), (**III^C-b**), (**IV^C**), (**IV^C-a**), (**IV^C-b**), (**V^C**), (**V^C-a**), (**V^C-b**), (**VI^C**), (**VI^C-a**), or (**VI^C-b**), two adjacent R^y groups may be taken together with their intervening atoms to form a

saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two adjacent R^y groups may be taken together with their intervening atoms to form a saturated carbocyclic ring. In some embodiments, two adjacent R^y groups may be taken together with their intervening atoms to form a partially unsaturated carbocyclic ring. In some embodiments, two adjacent R^y groups may be taken together with their intervening atoms to form a benzene ring. In some embodiments, two adjacent R^y groups may be taken together with their intervening atoms to form a saturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two adjacent R^y groups may be taken together with their intervening atoms to form a partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two adjacent R^y groups may be taken together with their intervening atoms to form an aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00179] As defined generally above, Ring C is an optionally substituted, 5- to 12-membered, monocyclic or bicyclic, heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. One of ordinary skill in the art will understand that Ring C comprises an amide or thioamide. In certain embodiments, Ring C is an optionally substituted, 5- to 6-membered, monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring C is an optionally substituted, 5- to 7-membered, monocyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring C is an optionally substituted, 8- to 10-membered, bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring C is an optionally substituted, 8- to 12-membered, bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring C is an optionally substituted piperdinone. In certain embodiments, Ring C is an optionally substituted pyridinone. In certain embodiments, Ring C is an optionally substituted piperazinone. In certain embodiments, Ring C is an optionally substituted isoindolinone. In certain embodiments, Ring C is an optionally substituted 2H-

benzo[b][1,4]oxazin-3(4H)-one. In some embodiments, Ring C is  , wherein G, R^y, m, and p are as described herein.

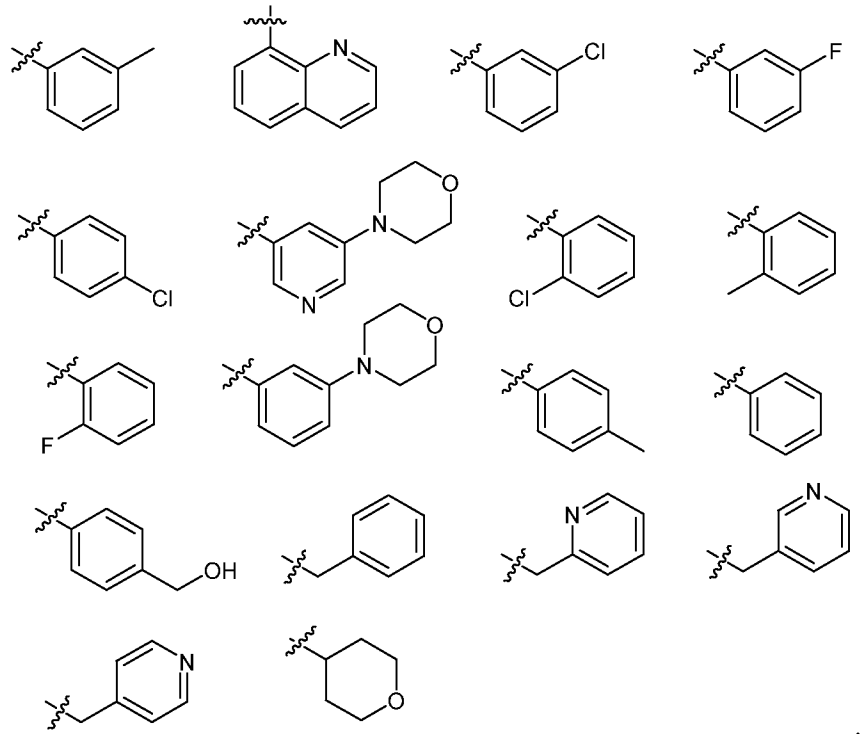
[00180] In certain embodiments, Y is O. In certain embodiments, Y is S.

[00181] As defined generally above, G is NR^{2C}, $CR^{3C}R^{4C}$, O or S. In certain embodiments, G is NR^{2C}. In certain embodiments, G is $CR^{3C}R^{4C}$. In certain embodiments, G is O. In certain embodiments, G is S.

[00182] As defined generally above, R^{2C} is selected from the group consisting of optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-S(=O)R^A$, $-SO_2R^A$, and $-SO_2N(R^B)_2$. In some embodiments, R^{2C} is optionally substituted aryl. In certain embodiments, R^{2C} is optionally substituted phenyl. In certain embodiments, R^{2C} is unsubstituted phenyl. In certain embodiments, R^{2C} is halophenyl. In certain embodiments, R^{2C} is fluorophenyl. In certain embodiments, R^{2C} is chlorophenyl. In some embodiments, R^{2C} is phenyl substituted with optionally substituted C_{1-6} alkyl. In some embodiments, R^{2C} is phenyl substituted with optionally substituted C_{1-3} alkyl. In certain embodiments, R^{2C} is phenyl substituted with methyl. In certain embodiments, R^{2C} is phenyl substituted with $-CH_2OH$. In some embodiments, R^{2C} is phenyl substituted with a heterocyclic ring. In certain embodiments, R^{2C} is phenyl substituted with morpholinyl. In certain embodiments, R^{2C} is phenyl substituted with tetrahydropyranyl. In some embodiments, R^{2C} is optionally substituted heteroaryl. In certain embodiments, R^{2C} is optionally substituted quinoline. In certain embodiments, R^{2C} is unsubstituted quinoline. In certain embodiments, R^{2C} is substituted quinoline. In certain embodiments, R^{2C} is optionally substituted pyridine. In certain embodiments, R^{2C} is pyridine substituted with a heterocyclic ring. In some embodiments, R^{2C} is optionally substituted aliphatic. In certain embodiments, R^{2C} is unsubstituted aliphatic. In certain embodiments, R^{2C} is $-CH_2$-aryl. In certain embodiments, R^{2C} is benzyl. In certain embodiments, R^{2C} is $-CH_2$-heteroaryl. In certain embodiments, R^{2C} is $-CH_2$-pyridyl. In some embodiments, R^{2C} is $-C(=O)R^A$. In certain embodiments, R^{2C} is $-C(=O)R^A$, wherein R^A is optionally substituted aliphatic. In certain embodiments, R^2 is

acetyl. In certain embodiments, R^{2C} is $-SO_2R^A$. In certain embodiments, R^{2C} is $-SO_2R^A$, wherein R^A is optionally substituted aliphatic. In certain embodiments, R^{2C} is $-SO_2CH_3$.

[00183] In certain embodiments, R^{2C} is selected from, but is not limited to, any one of the following aryl groups:



[00184] As defined generally above, R^{3C} is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$. In certain embodiments, R^{3C} is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-OC(O)R^A$, $-NR^BC(=O)R^A$, $-NR^BC(=O)N(R^B)_2$, $-SC(=O)R^A$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(=O)R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$.

[00185] In certain embodiments, R^{3C} is hydrogen. In some embodiments, R^{3C} is not hydrogen. In some embodiments, R^{3C} is halo. In certain embodiments, R^{3C} is fluoro. In

some embodiments, R^{3C} is optionally substituted aliphatic. In certain embodiments, R^{3C} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{3C} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{3C} is substituted C_{1-6} alkyl. In certain embodiments, R^{3C} is $-CF_3$, $-CHF_2$, or $-CH_2F$. In certain embodiments, R^{3C} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{3C} is methyl, ethyl, or propyl. In some embodiments, R^{3C} is –CN or $-NO_2$. In some embodiments, R^{3C} is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^{3C} is $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-OC(O)R^A$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$. In some embodiments, R^{3C} is optionally substituted aryl. In certain embodiments, R^{3C} is optionally substituted phenyl. In certain embodiments, R^{3C} is unsubstituted phenyl. In certain embodiments, R^{3C} is halophenyl. In certain embodiments, R^{3C} is fluorophenyl. In certain embodiments, R^{3C} is chlorophenyl. In some embodiments, R^{3C} is phenyl substituted with optionally substituted C_{1-6} alkyl. In some embodiments, R^{3C} is phenyl substituted with optionally substituted C_{1-3} alkyl. In certain embodiments, R^{3C} is phenyl substituted with methyl. In certain embodiments, R^{3C} is phenyl substituted with $-CH_2OH$. In some embodiments, R^{3C} is phenyl substituted with a heterocyclic ring. In certain embodiments, R^{3C} is phenyl substituted with morpholinyl. In certain embodiments, R^{3C} is phenyl substituted with tetrahydropyranyl. In some embodiments, R^{3C} is optionally substituted heteroaryl. In certain embodiments, R^{3C} is optionally substituted quinoline. In certain embodiments, R^{3C} is unsubstituted quinoline. In certain embodiments, R^{3C} is substituted quinoline. In certain embodiments, R^{3C} is optionally substituted pyridine. In certain embodiments, R^{3C} is pyridine substituted with a heterocyclic ring. In some embodiments, R^{3C} is optionally substituted aliphatic. In certain embodiments, R^{3C} is unsubstituted aliphatic. In certain embodiments, R^{3C} is $-CH_2$-aryl. In certain embodiments, R^{3C} is benzyl. In certain embodiments, R^{3C} is $-CH_2$-heteroaryl. In certain embodiments, R^{3C} is $-CH_2$-pyridyl.

[00186] As defined generally above, R^{4C} is selected from the group consisting of hydrogen, halo, and optionally substituted aliphatic. In certain embodiments, R^{4C} is hydrogen. In some embodiments, R^{4C} is not hydrogen. In some embodiments, R^{4C} is halo. In certain embodiments, R^{4C} is fluoro. In some embodiments, R^{4C} is optionally substituted aliphatic. In certain embodiments, R^{4C} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{4C} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{4C} is substituted C_{1-6} alkyl.

In certain embodiments, R^{4C} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{4C} is methyl, ethyl, or propyl.

[00187] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2.

[00188] As defined generally above, L_D is the linker L_B as defined herein, or L_D is –O–, –N(R)–,–C(R^{2A})(R^{3A})–, -O-C$R^{2A}R^{3A}$, -N(R)-C$R^{2A}R^{3A}$-, -O-C$R^{2A}R^{3A}$-O-, -N(R)-C$R^{2A}R^{3A}$-O, -N(R)-C$R^{2A}R^{3A}$-N(R)-, -O-C$R^{2A}R^{3A}$-N(R)-, -C$R^{2A}R^{3A}$-O-, -C$R^{2A}R^{3A}$-N(R)-, -O-C$R^{2A}R^{3A}$-C$R^{9}R^{10}$-, -N(R)-C$R^{2A}R^{3A}$-C$R^{9}R^{10}$-, -C$R^{2A}R^{3A}$-C$R^{9}R^{10}$-O-, -C$R^{2A}R^{3A}$-C$R^{9}R^{10}$-N(R)-, or –C$R^{2A}R^{3A}$-C$R^{9}R^{10}$-. In certain embodiments, L_D is –O–, –N(R)–, or –C$R^{2A}R^{3A}$–, wherein R, R^{2A}, and R^{3A} are as described herein. In certain embodiments, L_D is –O–. In some embodiments, L_D is –N(R)–. In certain embodiments, L_D is –NH-. In certain embodiments, L_D is –N(R)–, wherein R is optionally substituted C_{1-6} aliphatic. In certain embodiments, L_D is –N(R)–, wherein R is optionally substituted C_{1-6} alkyl. In certain embodiments, L_D is –N(R)–, wherein R is unsubstituted C_{1-6} alkyl. In certain embodiments, L_D is –N(R)–, wherein R is acetyl. In certain embodiments, L_D is –C$R^{2A}R^{3A}$-O-. In certain embodiments, L_D is –CH_2-O-. In certain embodiments, L_D is –C$R^{2A}R^{3A}$-N(R)-. In certain embodiments, L_D is –CH_2-NH-.

[00189] As defined generally above, Ring A is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is aromatic. In certain embodiments, Ring A is saturated. In certain embodiments, Ring A is partially unsaturated. In certain embodiments, Ring A is monocyclic. In certain embodiments, Ring A is bicyclic.

[00190] In certain embodiments, Ring A is phenyl. In certain embodiments, Ring A is a monocyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl). In certain embodiments, Ring A is a 6-membered heteroaryl having 1-3 nitrogens (*e.g.*, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl). In certain embodiments, Ring A is pyridyl. In certain embodiments, Ring A is pyrimidyl. In certain embodiments, Ring A is pyridazinyl. In some embodiments, Ring A is a carbocyclic ring. In some embodiments, Ring A is a 3- to 8-membered saturated carbocyclic ring. In some embodiments, Ring A is a

3- to 8-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00191] In certain embodiments, Ring A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is an 8- to 12-membered bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is an 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is a 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl). In certain embodiments, Ring A is a 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl). In certain embodiments, Ring A is selected from the group consisting of quinoline, benzimidazole, benzopyrazole, quinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, naphthalene, tetrahydronaphthalene, 2,3-dihydrobenzo[*b*][1,4]dioxine, isoindole, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, and quinoxalin-2(1*H*)-one.

[00192] In some embodiments, q is 0. In some embodiments, q is 1. In certain embodiments, q is 0 and m is 1. In certain embodiments, q is 0 and m is 2. In certain embodiments, q is 1 and m is 1. In certain embodiments, q is 1 and m is 2.

[00193] As defined generally above, L_1 is a bond, –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, –SO_2–, –SO_2N(R)–, –N(R)SO_2–, –OC(O)–, –C(O)O–, or an optionally substituted, straight or branched, C_{1-6} aliphatic chain wherein one, two, or three methylene units of L_1 are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, –SO_2–, –SO_2N(R)–, –N(R)SO_2–, –OC(O)–, or –C(O)O–. In some embodiments, L_1 is a bond. In some embodiments, L_1 is –O–, –S–, or –N(R)–. In some embodiments, L_1 is –C(O)–, –C(O)N(R)–, or –N(R)C(O)–. In some embodiments, L_1 is a C_{1-6} aliphatic chain wherein one, two, or three methylene units of L_1 are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, –SO_2–, –SO_2N(R)–, –

$N(R)SO_2$–, –OC(O)–, or –C(O)O–. In some embodiments, L_1 is a C_{1-3} aliphatic chain wherein one methylene unit of L_1 is optionally replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, $–SO_2–$, $–SO_2N(R)–$, $–N(R)SO_2–$, –OC(O)–, or –C(O)O–. In some embodiments, L_1 is –CHNH-.

[00194] As defined generally above, Cy^D is an optionally substituted, monocyclic, bicyclic or tricyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^D is aromatic. In certain embodiments, Cy^D is saturated. In certain embodiments, Cy^D is partially unsaturated. In certain embodiments, Cy^D is monocyclic. In certain embodiments, Cy^D is bicyclic. In certain embodiments, Cy^D is tricyclic.

[00195] In certain embodiments, Cy^D is optionally substituted phenyl. In certain embodiments, Cy^D is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^D is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl. In certain embodiments, Cy^D is an optionally substituted 6-membered heteroaryl having 1-3 nitrogens (*e.g.*, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl). In certain embodiments, Cy^D is optionally substituted pyrazole, optionally substituted pyridyl, or optionally substituted pyrimidyl. In some embodiments, Cy^D is an optionally substituted carbocyclic ring. In some embodiments, Cy^D is an optionally substituted 3- to 8-membered saturated carbocyclic ring. In some embodiments, Cy^D is an optionally substituted 3- to 8-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00196] In certain embodiments, Cy^D is an optionally substituted bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^D is an optionally substituted 8- to 12-membered bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^D is an optionally substituted 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^D is an optionally substituted 9- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Cy^D is an optionally substituted 9-membered bicyclic heteroaryl having 1-3

heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl). In certain embodiments, Cy^D is an optionally substituted 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl. In certain embodiments, Cy^D is optionally substituted indazole, optionally substituted quinoline, optionally substituted benzimidazole, optionally substituted benzothiazole, optionally substituted deazapurine, optionally substituted indole, optionally substituted purine, optionally substituted pyrazolopyridine, optionally substituted pyrrolopyridine, optionally substituted pyrroloprimidine, optionally substituted imidazopyridine, or optionally substituted imidazopyridine.

[00197] As defined generally above, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$; or R^9 and R^{10} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

[00198] In certain embodiments, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-OC(O)R^A$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$; or R^9 and R^{10} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

[00199] In certain embodiments, R^9 is hydrogen. In some embodiments, R^9 is not hydrogen. In some embodiments, R^9 is halo. In certain embodiments, R^9 is fluoro. In some embodiments, R^9 is optionally substituted aliphatic. In certain embodiments, R^9 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^9 is optionally substituted C_{1-6} alkyl. In

certain embodiments, R^9 is substituted C_{1-6} alkyl. In certain embodiments, R^9 is $-CF_3$, CHF_2, or CH_2F. In certain embodiments, R^9 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^9 is methyl, ethyl, or propyl. In some embodiments, R^9 is –CN or $-NO_2$. In some embodiments, R^9 is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^9 is $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-OC(O)R^A$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$. In certain embodiments, R^9 is $-N(R^B)_2$. In certain embodiments, R^9 is $-NHR^B$. In certain embodiments, R^9 is $-NH_2$. In certain embodimetns, R^9 is $-OR^A$. In certain embodiments, R^9 is –OH.

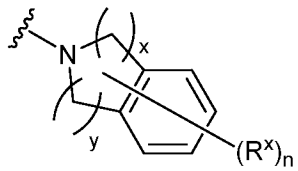
[00200] In certain embodiments, R^{10} is hydrogen. In some embodiments, R^{10} is not hydrogen. In some embodiments, R^{10} is halo. In certain embodiments, R^{10} is fluoro. In some embodiments, R^{10} is optionally substituted aliphatic. In certain embodiments, R^{10} is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{10} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{10} is substituted C_{1-6} alkyl. In certain embodiments, R^{10} is $-CF_3$, CHF_2, or CH_2F. In certain embodiments, R^{10} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{10} is methyl, ethyl, or propyl. In some embodiments, R^{10} is –CN or $-NO_2$. In some embodiments, R^{10} is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R^{10} is $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-OC(O)R^A$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$. In certain embodiments, R^{10} is $-N(R^B)_2$. In certain embodiments, R^{10} is $-NHR^B$. In certain embodiments, R^{10} is $-NH_2$. In certain embodiments, R^{10} is $-OR^A$. In certain embodiments, R^{10} is –OH.

[00201] In some embodiments, R^9 and R^{10} are the same. In some embodiments, R^9 and R^{10} are different. In some embodiments, R^9 and R^{10} are each hydrogen. In some embodiments, R^9 is hydrogen and R^{10} is not hydrogen. In some embodiments, R^9 is hydrogen and R^{10} is optionally substituted aliphatic. In some embodiments, R^9 is hydrogen and R^{10} is C_{1-6} alkyl. In some embodiments, R^9 is hydrogen and R^{10} is methyl. In some embodiments, R^9 is hydrogen and R^{10} is ethyl or propyl. In certain embodiments, R^9 and hydrogen and R^{10} is $-CF_3$, CHF_2, or CH_2F. In some embodiments, R^9 is hydrogen and R^{10} is $-N(R^B)_2$ or $-OR^A$. In some embodiments, R^9 is hydrogen and R^{10} is $-NH_2$. In some embodiments, R^9 is hydrogen

and R^{10} is –OH. In some embodiments, R^9 and R^{10} are not hydrogen. In some embodiments, R^9 and R^{10} are independently optionally substituted aliphatic. In some embodiments, R^9 and R^{10} are methyl. In some embodiments, R^9 and R^{10} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring.

[00202] As defined generally above, each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR'. In certain embodiments, at least one R^x is halo. In certain embodiments, at least one R^x is fluoro. In certain embodiments, at least one R^x is –CN. In certain embodiments, at least one R^x is optionally substituted aliphatic. In certain embodiments, at least one R^x is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^x is methyl. In certain embodiments, at least one R^x is $–CF_3$. In certain embodiments, at least one R^x is -OR'. In certain embodiments, R^x is not -OR'. In certain embodiments, at least one R^x is $–OCH_3$. In certain embodiments, R^x is not $–OCH_3$.

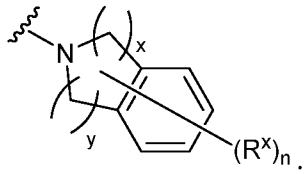
[00203] As is generally understood from the above disclosure, the ring system:



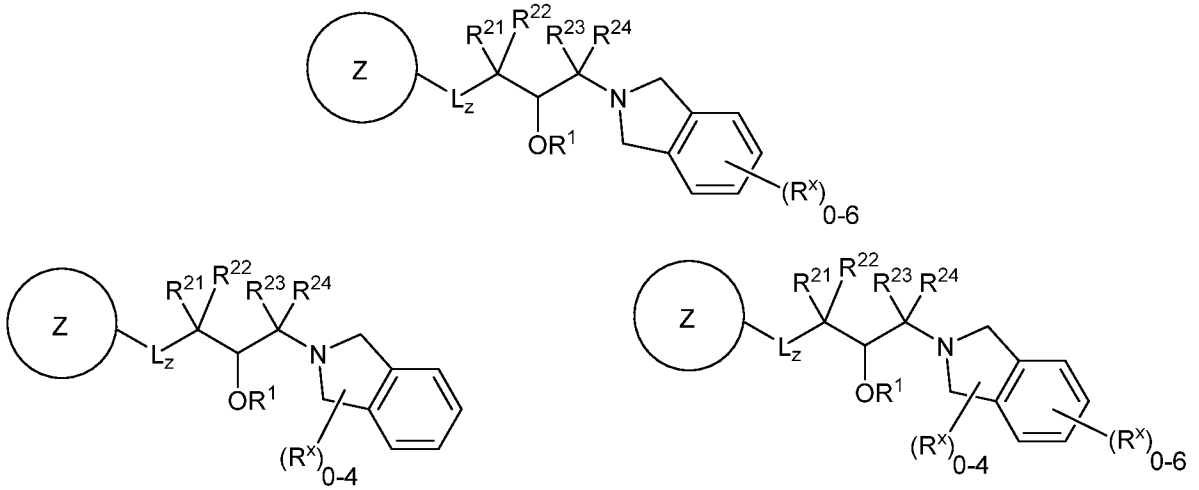
is a fused bicyclic ring system, *i.e.*, a phenyl ring fused to a nitrogen containing ring, wherein the point of attachment to the parent moiety is on the nitrogen, and wherein the fused bicyclic system is optionally substituted with $(R^x)_n$, wherein n and R^x are as defined above. As is generally understood, each of the phenyl ring and the nitrogen-containing ring can be independently optionally substituted with R^x, as valency permits.

[00204] In certain embodiments, the fused bicyclic ring system is optionally substituted with $(R^x)_n$, with the proviso that when the nitrogen-containing ring is substituted at one of the positions alpha to the nitrogen, R^x is not–$C(=O)R^{x1}$, wherein R^{x1} is optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, or $-SR^A$, wherein R^A and R^B are as generally defined herein. In certain embodiments, the nitrogen-containing ring does not comprise an R^x substituent. In certain embodiments, only the phenyl ring is optionally substituted with $(R^x)_n$.

[00205] Thus, one of ordinary skill in the art will appreciate that an R^x group can be attached anywhere on the ring system:



[00206] For example, when the ring system is an isoindoline ring, in certain embodiments, an R^x group is attached to the benzene portion of the isoindoline ring. In certain embodiments, an R^x group is attached to the dihydropyrrole portion of the isoindoline ring. In certain embodiments, R^x groups are attached to both the benzene portion and the dihydropyrrole portion of the isoindoline ring. See, for example, the structures shown below:



[00207] As defined generally above, n is 0, 1, 2, 3, 4, 5, 6, 7, or 8. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[00208] As defined generally above, k is 0, 1, 2, 3, or 4. In some embodiments, k is 0. In some embodiments, k is 1. In some embodiments, k is 2.

[00209] As defined generally above, X_1, X_2, X_3, and X_4 are independently selected from the group consisting of N, CH, and CR^y, provided that at least one of X_2, X_3, and X_4 is not N.

[00210] In certain embodiments, X_1 is N. In certain embodiments, X_1 is CH or CR^y. In certain embodiments, X_2 is N. In certain embodiments, X_2 is CH or CR^y. In certain embodiments, X_3 is N. In certain embodiments, X_3 is CH or CR^y. In certain embodiments, X_4 is N. In certain embodiments, X_4 is CH or CR^y.

[00211] In certain embodiments, each of X_1 and X_2 is N, and each of X_3 and X_4 is independently CH or CR^y. In certain embodiments, each of X_1 and X_3 is N, and each of X_2 and X_4 is independently CH or CR^y. In certain embodiments, each of X_1 and X_4 is N, and each of X_2 and X_3 is independently CH or CR^y. In certain embodiments, each of X_2 and X_4 is N, and each of X_1 and X_3 is independently CH or CR^y. In certain embodiments, each of X_2

and X_3 is N, and each of X_1 and X_4 is independently CH or CR^y. In certain embodiments, each of X_3 and X_4 is N, and each of X_1 and X_2 is independently CH or CR^y.

[00212] As generally defined above, R^{A1} and R^{A2} are independently hydrogen, substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group. In some embodiments, R^{A1} is hydrogen. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A1} is substituted C_{1-3} alkyl. In some embodiments, R^{A1} is $–CF_3$, $-CHF_2$, $-CH_2F$, or $–CH(CF_3)CH_3$. In some embodiments, R^{A1} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is acetyl. In some embodiments, R^{A1} is a nitrogen protecting group. In some embodiments, R^{A1} is $CH_3SO_2–$. In some embodiments, R^{A2} is hydrogen. In some embodiments, R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A2} is unsubstituted C_{1-3} alkyl. In some embodiments, R^{A2} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A2} is substituted C_{1-3} alkyl. In some embodiments, R^{A2} is $–CF_3$, $-CHF_2$, $-CH_2F$, or $–CH(CF_3)CH_3$. In some embodiments, R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A2} is acetyl. In some embodiments, R^{A2} is a nitrogen protecting group. In some embodiments, R^{A2} is $CH_3SO_2–$. In some embodiments, R^{A1} is hydrogen, and R^{A2} is hydrogen. In some embodiments, R^{A1} is hydrogen, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is $–CF_3$, $-CHF_2$, $-CH_2F$, or $–CH(CF_3)CH_3$. In some embodiments, R^{A1} is hydrogen, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is acetyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is hydrogen and R^{A2} is $CH_3SO_2–$. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is methyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is methyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is methyl, and R^{A2} is methyl. In some embodiments, R^{A1} is methyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is

methyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is methyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is methyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is methyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is ethyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is methyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is n-propyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is methyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is n-propyl and R^{A2} is isopropyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is n-propyl and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is isopropyl and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is isopropyl and R^{A2} is methyl. In some embodiments, R^{A1} is isopropyl and R^{A2} is ethyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is substituted or unsubstituted acyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is a nitrogen protecting group and R^{A2} is methyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is ethyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is n-propyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is isopropyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is a nitrogen protecting group.

[00213] As generally defined above, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted 3-6 membered heterocyclic ring. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted azetidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted pyrrolidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted piperidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a

substituted or unsubstituted piperazine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted morpholine.

[00214] In some embodiments, *e.g.* for Formula (**A**), Formula (**I**), or any subgenera thereof, the provided compound is of a free base form. In some embodiments, *e.g.* for Formula (**A**), Formula (**I**), or any subgenera thereof, the provided compound is in the form of a pharmaceutically acceptable salt as generally defined herein. In some embodiments, the provided compound is a hydrochloride salt thereof. In some embodiments, the provided compound is a tartrate salt thereof. In some embodiments, the provided compound is a monotartrate salt thereof. In some embodiments, the provided compound is a bitartrate salt thereof.

[00215] In certain embodiments, a provided compound is a compound listed in Table 1A, or a pharmaceutically acceptable salt thereof.

Table 1A. Exemplary Compounds

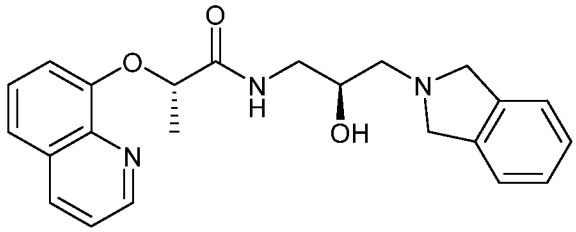
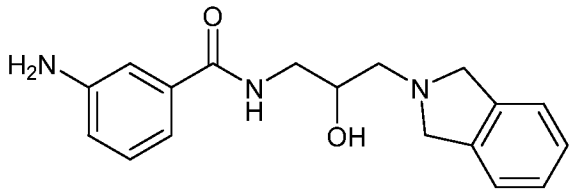
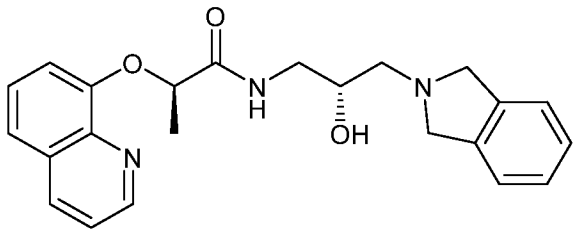
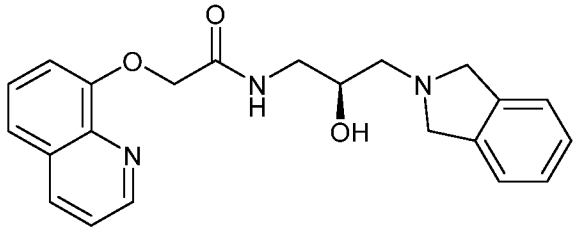
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
1		391.1896	392.1
2		311.1634	312.2
3		391.1896	392.1
4		377.1739	378.1

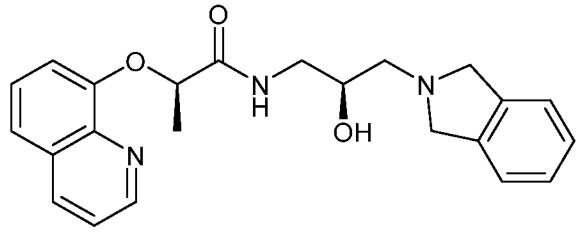
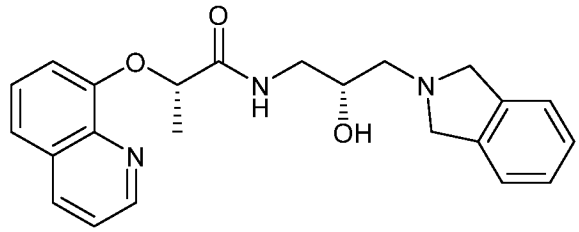
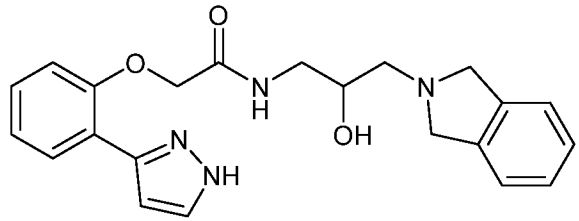
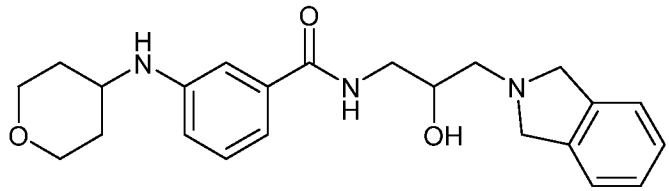
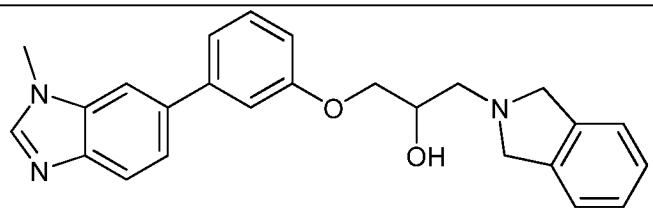
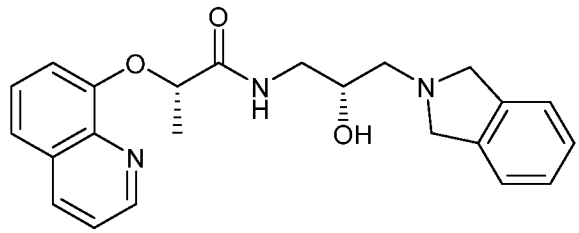
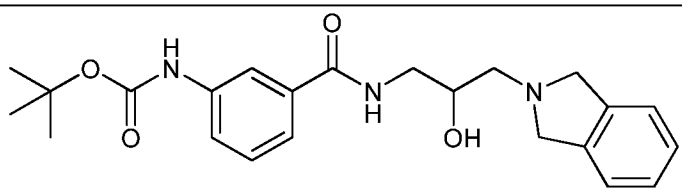
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
5		391.1896	392.1
6		391.1896	392.1
7		392.1848	393.2
8		395.2209	396.2
9		399.1947	400.2
10		397.2002	398.2
11		411.2158	412.2

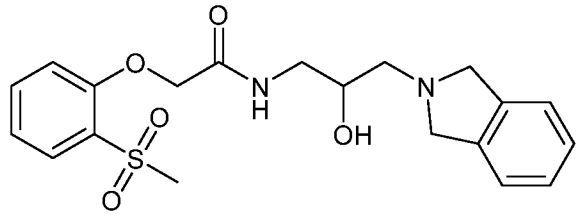
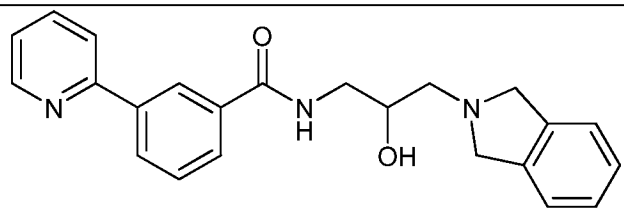
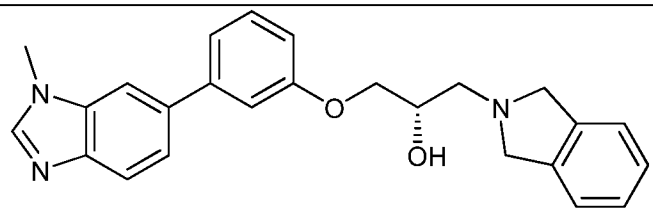
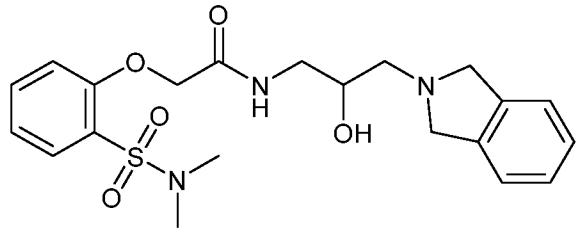
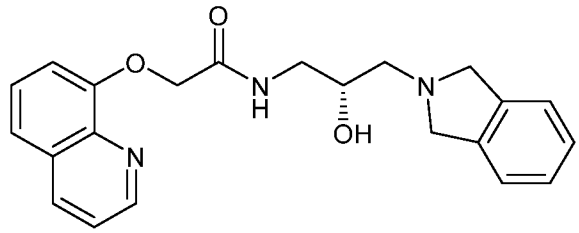
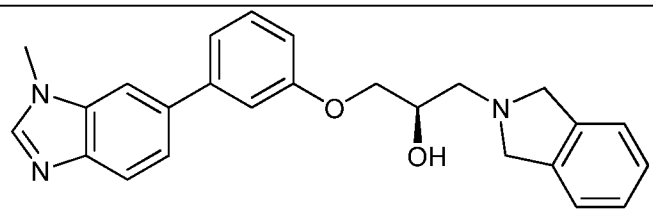
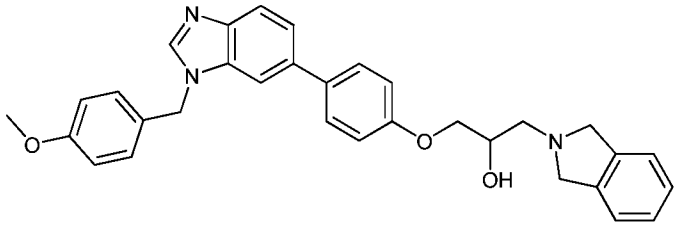
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
12		404.1406	405.2
13		373.179	374.2
14		399.1947	400.2
15		433.1671	434.1
16		377.1739	378.1
17		399.1947	400.2
18		505.2365	506.2

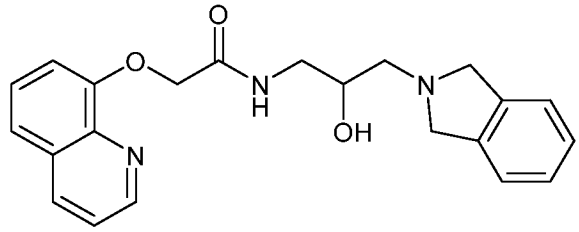
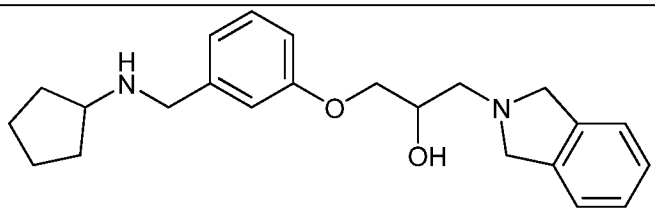
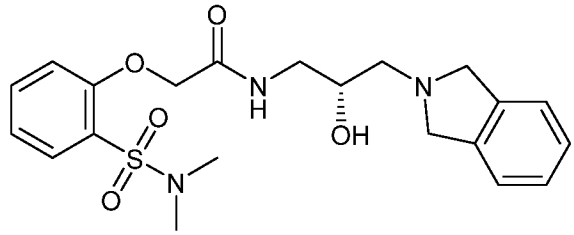
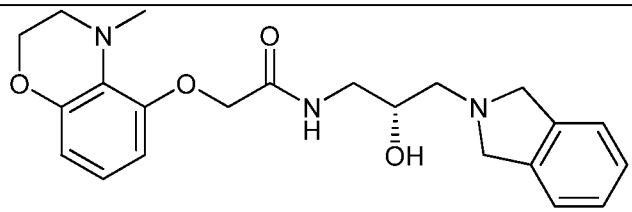
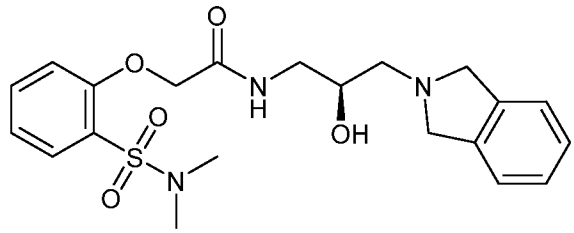
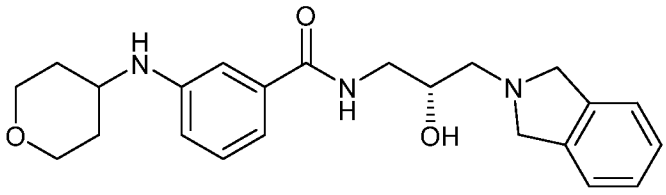
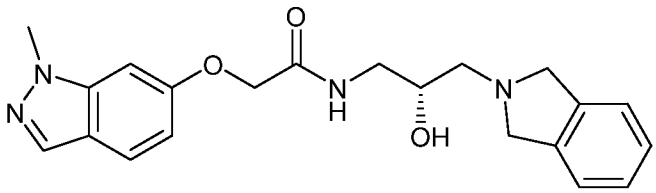
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
19		377.1739	378.1
20		366.2307	367.2
21		433.1671	434.2
22		397.2002	398.1
23		433.1671	
24		395.2209	396.2
25		380.1848	

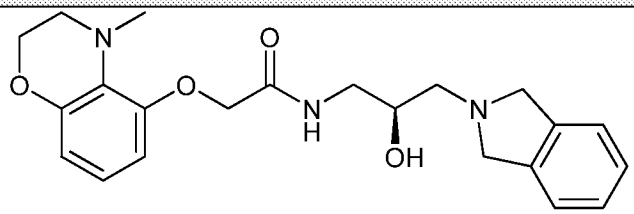
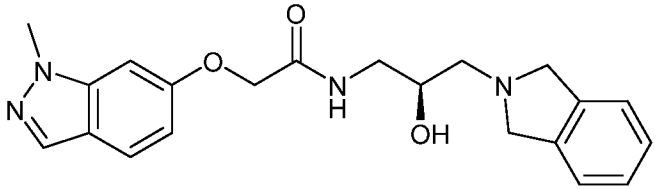
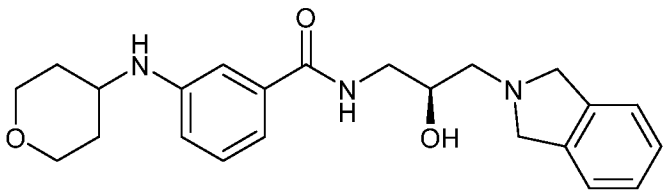
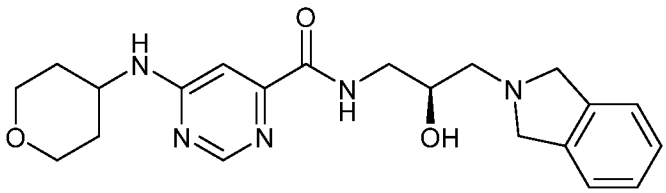
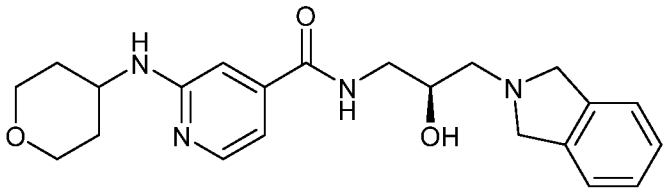
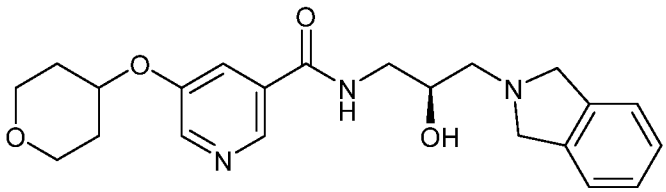
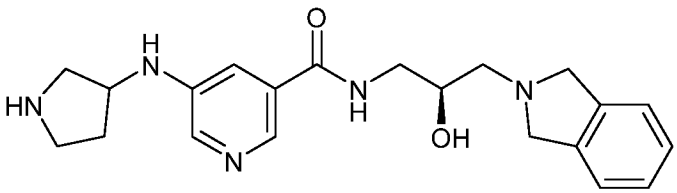
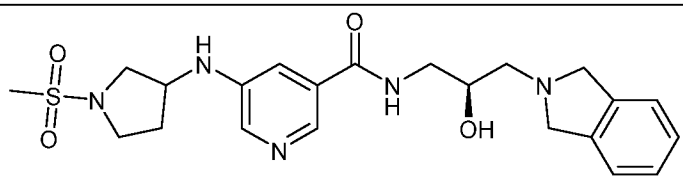
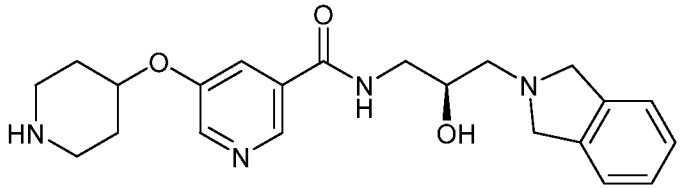
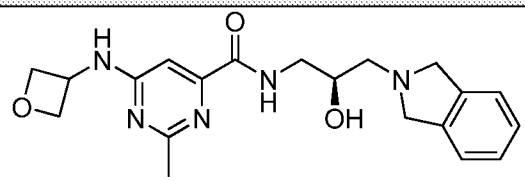
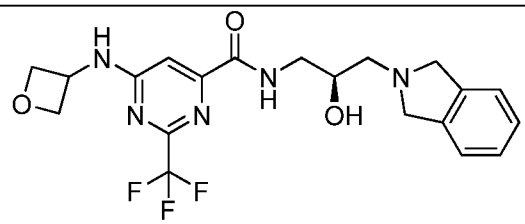
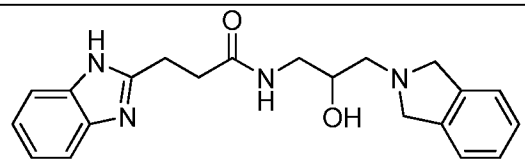
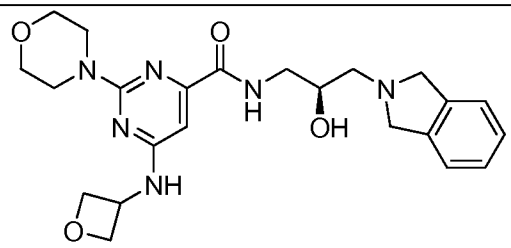
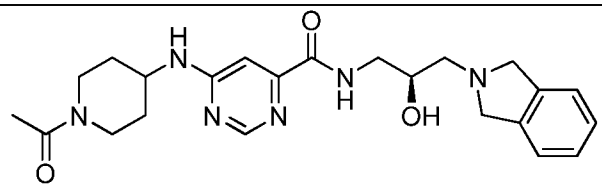
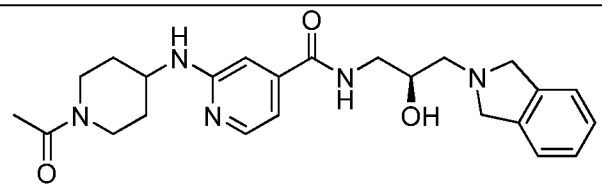
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
26		397.2002	398.2
27		380.1848	381.1
28		395.2209	396.2
29		397.2114	398.1
30		396.2161	
31		397.2002	398.2
32		381.2165	382.1
33		459.194	460.3

Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
34		396.2161	

[00216] In certain embodiments, a provided compound is a compound listed in Table 1B, or a pharmaceutically acceptable salt thereof.

Table 1B. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
35		383.1957	384.1
36		437.1675	438.1
37		364.1899	365.1
38		454.2329	455.1
39		438.2379	439.1
40		437.2427	438.1

[00217] In certain embodiments, a provided compound is a compound listed in Table 1C, or a pharmaceutically acceptable salt thereof.

Table 1C. Exemplary Compounds

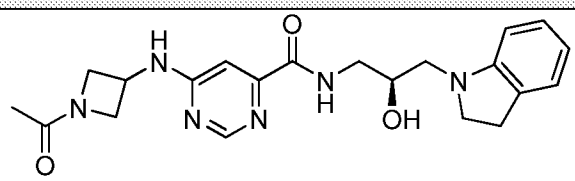
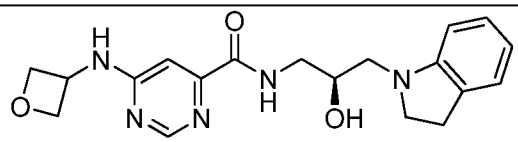
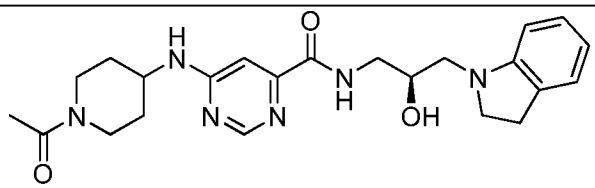
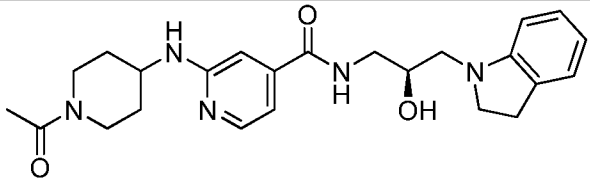
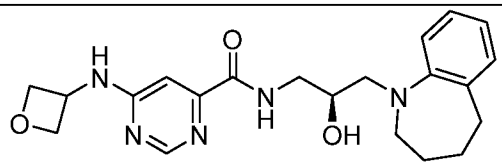
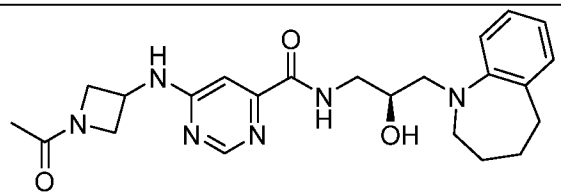
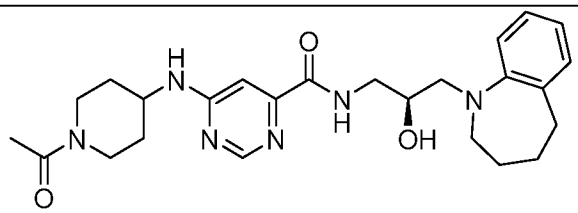
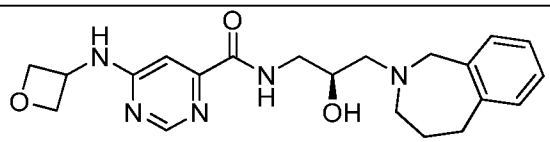
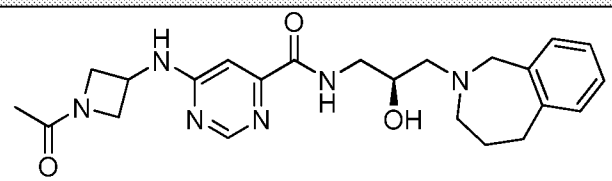
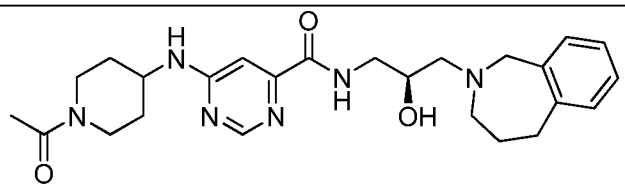
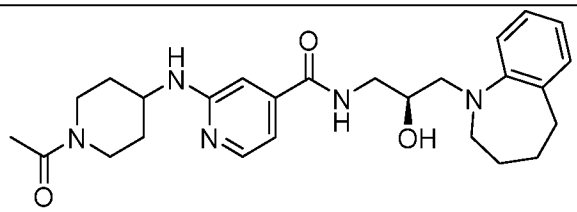
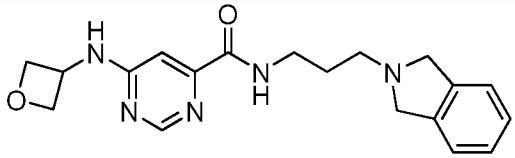
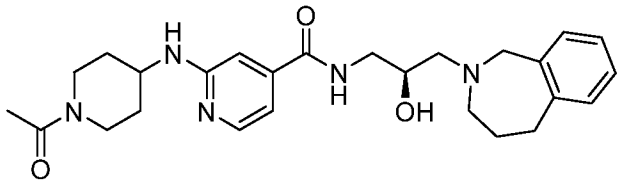
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
41		410.2066	411.2
42		369.1801	370.2
43		438.2379	439.2
44		437.2427	438.2
45		397.2114	398.2
46		438.2379	439.2
47		466.2692	467.3
48		397.2114	398.2

Table 1C. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
49		438.2379	439.2
50		466.2692	467.3
51		465.274	466.3

[00218] In certain embodiments, a provided compound is a compound listed in Table 1D, or a pharmaceutically acceptable salt thereof.

Table 1D. Exemplary Compound			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
52		353.1852	354.1
53		465.274	466.3

[00219] In certain embodiments, a provided compound is a compound listed in Table 1E, or a pharmaceutically acceptable salt thereof.

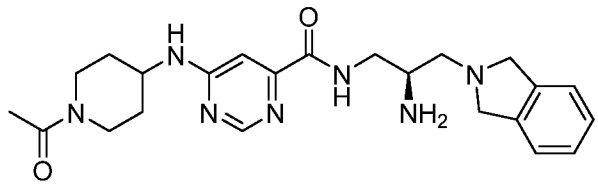
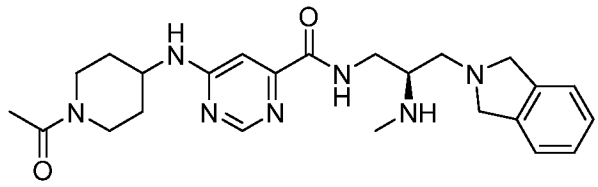
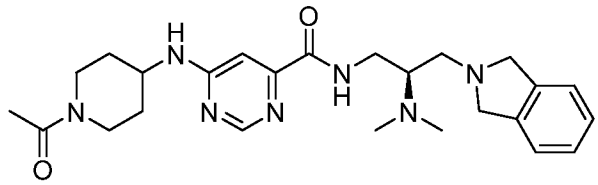
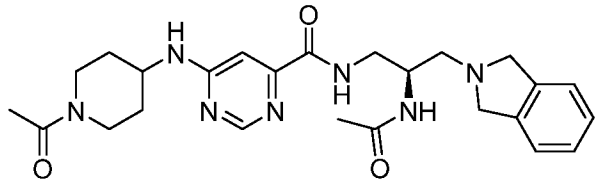
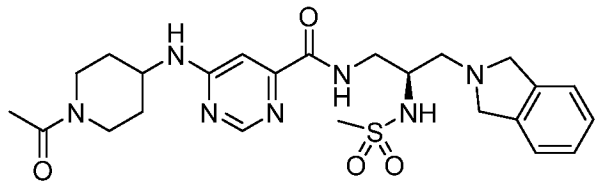
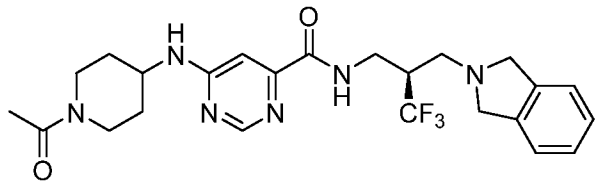
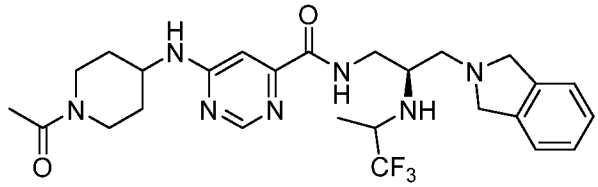
Table 1E. Exemplary Compounds			
Cmpd No	**Structure**	**Exact mass**	**LC-MS m/z (M+H)**
54		437.2539	--
55		451.2696	--
56		465.2852	--
57		479.2645	--
58		515.2315	--
59		490.2304	--
60		533.2726	--

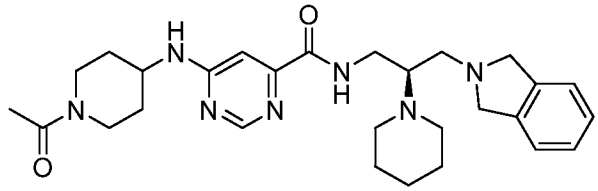
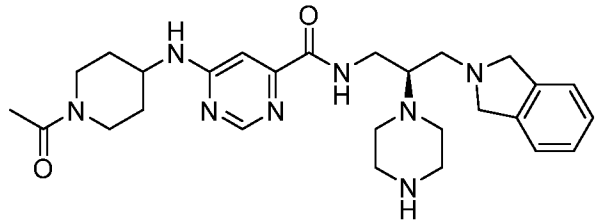
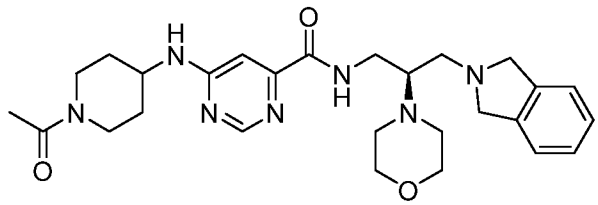
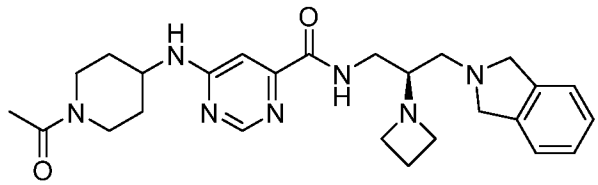
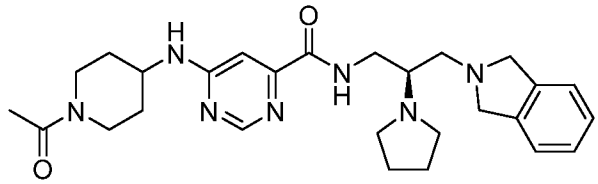
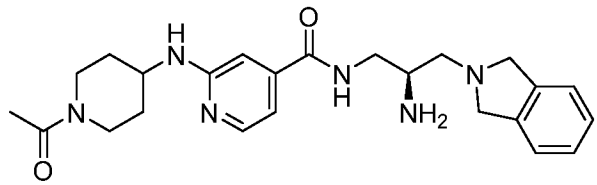
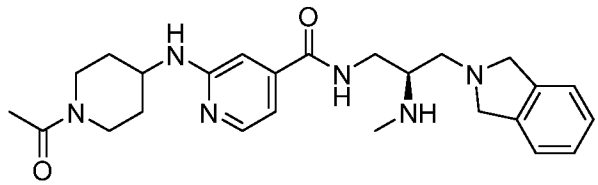
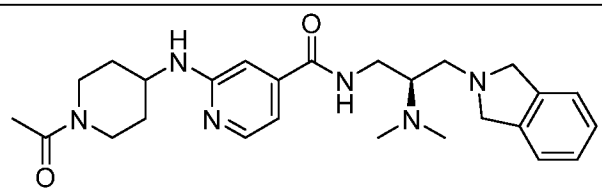
Table 1E. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
61		505.3165	--
62		506.3118	--
63		507.2958	--
64		477.2852	--
65		491.3009	--
66		436.2587	--
67		450.2743	--
68		464.2900	--

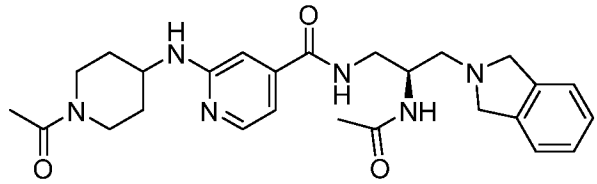
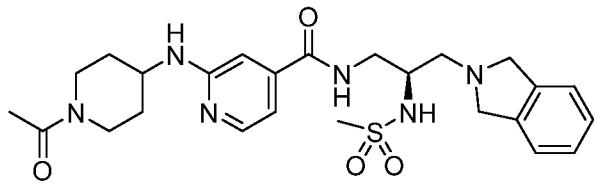
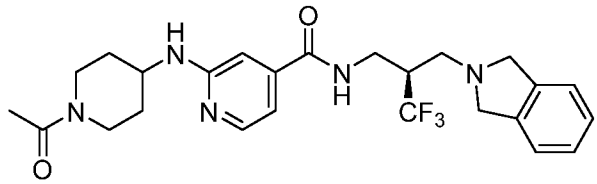
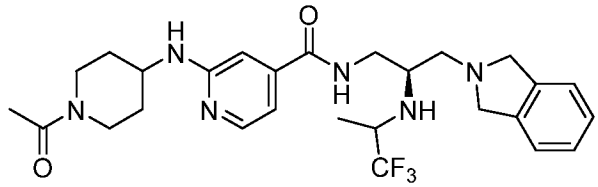
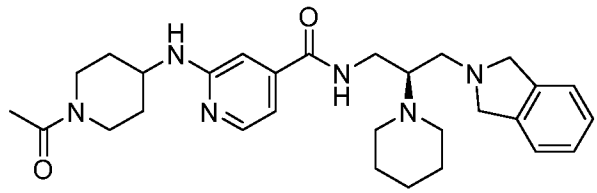
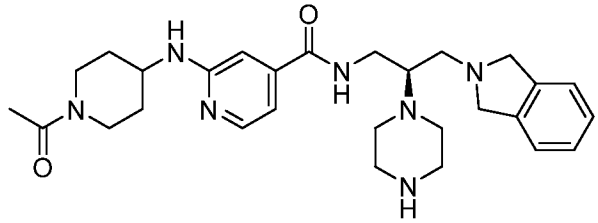
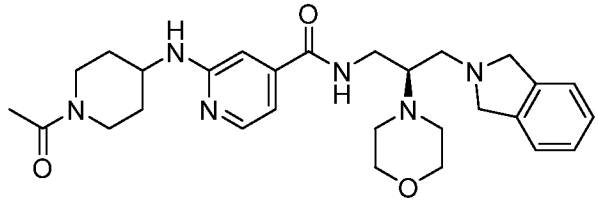
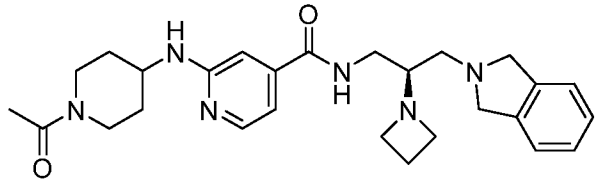
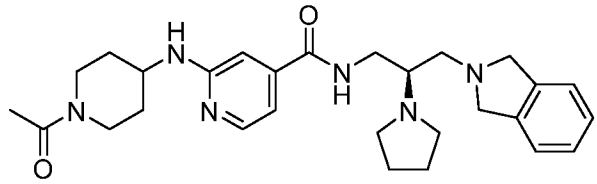
Table 1E. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
69		478.2692	--
70		514.2362	--
71		489.2352	--
72		532.2774	--
73		504.3213	--
74		505.3165	--
75		506.3005	--
76		476.2900	--

Table 1E. Exemplary Compounds			
Cmpd No	Structure	Exact mass	LC-MS m/z (M+H)
77		490.3056	--

[00220] In certain embodiments, a provided compound inhibits PRMT5. In certain embodiments, a provided compound inhibits wild-type PRMT5. In certain embodiments, a provided compound inhibits a mutant PRMT5. In certain embodiments, a provided compound inhibits PRMT5, *e.g.*, as measured in an assay described herein. In certain embodiments, the PRMT5 is from a human. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 0.1 μM. In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective for PRMT5 relative to one or more other methyltransferases.

[00221] It will be understood by one of ordinary skill in the art that the PRMT5 can be wild-type PRMT5, or any mutant or variant of PRMT5.

[00222] In some embodiments embodiment, the mutant or variant of PRMT5 contains one or more mutations (e.g., conservative substitutions). In some embodiments, provided herein is a PRMT5 point mutant. In some embodiments, the PRMT point mutant has an amino acid sequence that a degree of homology to the amino acid sequence of SEQ ID NO: 1 of at least

about 80%, e.g., at least about 85%, at least about 90%, at least about 95% , or at least about 97%. Further provided is a protein that has a degree of homology to the amino acid sequence of SEQ ID NO: 2 of at least about 80%, e.g., at least about 85%, at least about 90%, at least about 95% , or at least about 97%.

[00223] In certain embodiments, the PRMT5 is isoform A (GenBank accession no. NP006100) (SEQ ID NO.:1):

MAAMAVGGAG GSRVSSGRDL NCVPEIADTL GAVAKQGFDF LCMPVFHPRF
KREFIQEPAK NRPGPQTRSD LLLSGRDWNT LIVGKLSPWI RPDSKVEKIR
RNSEAAMLQE LNFGAYLGLP AFLLPLNQED NTNLARVLTN HIHTGHHSSM
FWMRVPLVAP EDLRDDIIEN APTTHTEEYS GEEKTWMWWH NFRTLCDYSK
RIAVALEIGA DLPSNHVIDR WLGEPIKAAI LPTSIFLTNK KGFPVLSKMH
QRLIFRLLKL EVQFIITGTN HHSEKEFCSY LQYLEYLSQN RPPPNAYELF
AKGYEDYLQS PLQPLMDNLE SQTYEVFEKD PIKYSQYQQA IYKCLLDRVP
EEEKDTNVQV LMVLGAGRGP LVNASLRAAK QADRRIKLYA VEKNPNAVVT
LENWQFEEWG SQVTVVSSDM REWVAPEKAD IIVSELLGSF ADNELSPECL
DGAQHFLKDD GVSIPGEYTS FLAPISSSKL YNEVRACREK DRDPEAQFEM
PYVVRLHNFH QLSAPQPCFT FSHPNRDPMI DNNRYCTLEF PVEVNTVLHG
FAGYFETVLY QDITLSIRPE THSPGMFSWF PILFPIKQPI TVREGQTICV
RFWRCSNSKK VWYEWAVTAP VCSAIHNPTG RSYTIGL

[00224] In certain embodiments, the PRMT5 is isoform B (GenBank accession no. NP001034708) (SEQ ID NO.:2)

MRGPNSGTEK GRLVIPEKQG FDFLCMPVFH PRFKREFIQE PAKNRPGPQT
RSDLLLSGRD WNTLIVGKLS PWIRPDSKVE KIRRNSEAAM LQELNFGAYL
GLPAFLLPLN QEDNTNLARV LTNHIHTGHH SSMFWMRVPL VAPEDLRDDI
IENAPTTHTE EYSGEEKTWM WWHNFRTLCD YSKRIAVALE IGADLPSNHV
IDRWLGEPIK AAILPTSIFL TNKKGFPVLS KMHQRLIFRL LKLEVQFIIT
GTNHHSEKEF CSYLQYLEYL SQNRPPPNAY ELFAKGYEDY LQSPLQPLMD
NLESQTYEVF EKDPIKYSQY QQAIYKCLLD RVPEEEKDTN VQVLMVLGAG
RGPLVNASLR AAKQADRRIK LYAVEKNPNA VVTLENWQFE EWGSQVTVVS
SDMREWVAPE KADIIVSELL GSFADNELSP ECLDGAQHFL KDDGVSIPGE
YTSFLAPISS SKLYNEVRAC REKDRDPEAQ FEMPYVVRLH NFHQLSAPQP
CFTFSHPNRD PMIDNNRYCT LEFPVEVNTV LHGFAGYFET VLYQDITLSI
RPETHSPGMF SWFPILFPIK QPITVREGQT ICVRFWRCSN SKKVWYEWAV
TAPVCSAIHN PTGRSYTIGL

[00225] In certain embodiments, the PRMT5 is transcript variant 1 (GenBank accession no. NM_006109).

[00226] Provided is pharmaceutical compositions comprising a compound described herein, *e.g.*, a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof, as described herein, and optionally a pharmaceutically acceptable excipient. It will be understood by one of ordinary skill in the art that the compounds described herein, or salts thereof, may be present in various forms, such as hydrates, solvates, or polymorphs. In certain embodiments, a provided composition comprises two or more compounds described herein. In certain embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is an amount effective for inhibiting PRMT5. In certain embodiments, the effective amount is an amount effective for treating a PRMT5-mediated disorder. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective to prevent a PRMT5-mediated disorder.

[00227] In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein, *e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**), or any subgenera thereof, and optionally a pharmaceutically acceptable excipient, wherein the compound is of a free base form. In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein, *e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**), or any subgenera thereof, and optionally a pharmaceutically acceptable excipient, wherein the compound is in the form of a pharmaceutically acceptable salt as generally defined herein. In certain embodiments, the provided pharmaceutical compositions comprise a hydrochloride salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a tartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a monotartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a bitartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a monotartrate salt and a bitartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the

provided pharmaceutical compositions comprise a compound described herein in a form of free base, and a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[00228] Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00229] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing a compound described herein (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

[00230] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

[00231] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the present disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00232] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00233] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00234] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00235] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.,* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.,* bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.,* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.,* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.,* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.,* polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60], sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.,* polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.,* Cremophor™), polyoxyethylene ethers, (*e.g.,* polyoxyethylene lauryl ether (Brij 30)), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00236] Exemplary binding agents include starch (*e.g.,* cornstarch and starch paste), gelatin, sugars (*e.g.,* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.,* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00237] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00238] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00239] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00240] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00241] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00242] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00243] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00244] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00245] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00246] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the compounds described herein are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00247] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00248] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00249] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00250] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the compounds described herein with suitable non–irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00251] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00252] Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00253] The active ingredient can be in micro–encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as

sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00254] Dosage forms for topical and/or transdermal administration of a provided compound may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any desired preservatives and/or buffers as can be required. Additionally, the present disclosure encompasses the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00255] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00256] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00257] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low–boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00258] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non–ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00259] Pharmaceutical compositions formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may

further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00260] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00261] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00262] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically–administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this disclosure.

[00263] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00264] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of provided compositions will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00265] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra–arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[00266] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode

of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00267] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[00268] In certain embodiments, a compound described herein may be administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00269] In some embodiments, a compound described herein is administered one or more times per day, for multiple days. In some embodiments, the dosing regimen is continued for days, weeks, months, or years.

[00270] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00271] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. In certain embodiments, a compound or composition provided herein is administered in combination with one or more additional therapeutically active agents that improve its bioavailability, reduce and/or modify its metabolism, inhibit its excretion, and/or modify its distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[00272] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In certain embodiments,

the additional therapeutically active agent is a compound of Formula (A), *e.g.*, Formula (I). In certain embodiments, the additional therapeutically active agent is not a compound of Formula (A), *e.g.*, Formula (I). In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of a provided compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00273] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[00274] Also encompassed by the present discosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a provided pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a provided pharmaceutical composition or compound. In some embodiments, a provided pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form. In some embodiments, a provided kits further includes instructions for use.

[00275] Compounds and compositions described herein are generally useful for the inhibition of PRMT5. In some embodiments, methods of treating PRMT5-mediated disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof), to a subject in need of treatment. In certain embodiments, the

effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the subject is suffering from a PRMT5-mediated disorder. In certain embodiments, the subject is susceptible to a PRMT5-mediated disorder.

[00276] As used herein, the term "PRMT5-mediated disorder" means any disease, disorder, or other pathological condition in which PRMT5 is known to play a role. Accordingly, in some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which PRMT5 is known to play a role.

[00277] In some embodiments, the present disclosure provides a method of inhibiting PRMT5 comprising contacting PRMT5with an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or subject. Thus, such methods encompass both inhibition of *in vitro* and *in vivo* PRMT5 activity. In certain embodiments, the method is an *in vitro* method, *e.g.,* such as an assay method. It will be understood by one of ordinary skill in the art that inhibition of PRMT5 does not necessarily require that all of the PRMT5 be occupied by an inhibitor at once. Exemplary levels of inhibition of PRMT5 include at least 10% inhibition, about 10% to about 25% inhibition, about 25% to about 50% inhibition, about 50% to about 75% inhibition, at least 50% inhibition, at least 75% inhibition, about 80% inhibition, about 90% inhibition, and greater than 90% inhibition.

[00278] In some embodiments, provided is a method of inhibiting PRMT5 activity in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00279] In certain embodiments, provided is a method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00280] In certain embodiments, provided is a method of altering transcription in a cell which comprises contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00281] In certain embodiments, a method is provided of selecting a therapy for a subject having a disease associated with PRMT5-mediated disorder or mutation comprising the steps of determining the presence of PRMT5-mediated disorder or gene mutation in the PRMT5 gene or and selecting, based on the presence of PRMT5-mediated disorder a gene mutation in the PRMT5 gene a therapy that includes the administration of a provided compound. In certain embodiments, the disease is cancer.

[00282] In certain embodiments, a method of treatment is provided for a subject in need thereof comprising the steps of determining the presence of PRMT5-mediated disorder or a gene mutation in the PRMT5 gene and treating the subject in need thereof, based on the presence of a PRMT5-mediated disorder or gene mutation in the PRMT5 gene with a therapy that includes the administration of a provided compound. In certain embodiments, the subject is a cancer patient.

[00283] In some embodiments, a provided compound is useful in treating a proliferative disorder, such as cancer, a benign neoplasm, an autoimmune disease, or an inflammatory disease. For example, while not being bound to any particular mechanism, PRMT5 has been shown to be involved in cyclin D1 dysregulated cancers. Increased PRMT5 activity mediates key events associated with cyclin D1-dependent neoplastic growth including CUL4 repression, CDT1 overexpression, and DNA re-replication. Further, human cancers harboring mutations in Fbx4, the cyclin D1 E3 ligase, exhibit nuclear cyclin D1 accumulation and increased PRMT5 activity. See, *e.g.*, Aggarwal *et al., Cancer Cell.* (2010) 18(4):329-40. Additionally, PRMT5 has also been implicated in accelerating cell cycle progression through G1 phase and modulating regulators of G1; for example, PRMT5 may upregulate cyclin-dependent kinase (CDK) 4, CDK6, and cyclins D1, D2 and E1. Moreover, PRMT5 may activate phosphoinositide 3-kinase (PI3K)/AKT signaling. See, *e.g.*, Wei *et al.*, *Cancer Sci.* (2012) 103(9):1640-50. PRMT5 has been reported to play a role in apoptosis through methylation of E2F-1. See, *e.g.*, Cho *et al.*, *EMBO J.* (2012) 31:1785-1797; Zheng *et al.*, *Mol. Cell.* (2013) 52:37-51. PRMT5 has been reported to be an essential regulator of splicing and affect the alternative splicing of 'sensor' mRNAs that can then lead to defects in downstream events such as apoptosis. See, *e.g.*, Bezzi *et al.*, *Genes Dev.* (2013) 27:1903-1916. PRMT5 has been reported to play a role in the RAS-ERK pathway. See, *e.g.*, Andrew-Perez *et al.*, *Sci Signal.* (2011) Sep 13;4(190)ra58 doi: 10.1126/scisignal.2001936. PRMT5 has been reported to affect C/EBPb target genes through interaction with the Mediator complex and hence affect cellular differentiation and inflammatory response. See, *e.g.*,Tsutsui *et al.*, *J. Biol. Chem.* (2013) 288:20955-20965. PRMT5 has been shown to methylate HOXA9 essential for

ELAM expression during the EC inflammatory response. See, *e.g.*, Bandyopadhyay *et al.*, *Mol. Cell. Biol.* (2012) 32:1202-1203. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating the following non-limiting list of cancers: breast cancer, esophageal cancer, bladder cancer, lung cancer, hematopoietic cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, pancreatic cancer, liver cancer, adenoid cystic carcinoma, lung adenocarcinoma, head and neck squamous cell carcinoma, brain tumors, hepatocellular carcinoma, renal cell carcinoma, melanoma, oligodendroglioma, ovarian clear cell carcinoma, and ovarian serous cystadenocarcinoma. See, *e.g.*, Pal *et al.*, *EMBO J.* (2007) 26:3558-3569 (mantle cell lymphoma); Wang *et al.*, *Mol. Cell Biol.* (2008) 28:6262-77 (chronic lymphocytic leukemia (CLL)); and Tae *et al.*, *Nucleic Acids Res.* (2011) 39:5424-5438.

[00284] In some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating prostate cancer and lung cancer, in which PRMT5 has been shown to play a role. See, *e.g.,* Gu *et al.*, *PLoS One* 2012;7(8):e44033; Gu *et al.*, *Biochem. J.* (2012) 446:235–241. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of cancer. In some embodiments, a provided compound is administered in combination with other compounds, drugs, or therapeutics to treat cancer.

[00285] In some embodiments, compounds described herein are useful for treating a cancer including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (*e.g.,* lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (*e.g.,* cholangiocarcinoma), bladder cancer, breast cancer (*e.g.,* adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (*e.g.,* meningioma; glioma, *e.g.,* astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (*e.g.,* cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (*e.g.,* colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (*e.g.,* Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma), esophageal cancer (*e.g.,* adenocarcinoma of the esophagus, Barrett's adenocarinoma), Ewing sarcoma, eye cancer (*e.g.,* intraocular melanoma, retinoblastoma), familiar hypereosinophilia, gall bladder cancer, gastric cancer (*e.g.,* stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (*e.g.,* head and neck squamous cell carcinoma, oral cancer (*e.g.,* oral

squamous cell carcinoma (OSCC), throat cancer (*e.g.,* laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), hematopoietic cancers (*e.g.,* leukemia such as acute lymphocytic leukemia (ALL) (*e.g.,* B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.,* B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.,* B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.,* B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (*e.g.,* B-cell HL, T-cell HL) and non–Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.,* diffuse large B–cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.,* mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.,* "Waldenström's macroglobulinemia"), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.,* cutaneous T-cell lymphoma (CTCL) (*e.g.,* mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (*e.g.,* nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma), liver cancer (*e.g.,* hepatocellular cancer (HCC), malignant hepatoma), lung cancer (*e.g.,* bronchogenic carcinoma, small cell lung cancer (SCLC), non–small cell lung cancer (NSCLC), adenocarcinoma of the lung), leiomyosarcoma (LMS), mastocytosis (*e.g.,* systemic mastocytosis), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (*e.g.,* polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (*e.g.,* neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (*e.g.,* gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (*e.g.,* cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic

cancer (*e.g.,* pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (*e.g.,* Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (*e.g.,* prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (*e.g.,* squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (*e.g.,* appendix cancer), soft tissue sarcoma (*e.g.,* malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (*e.g.,* seminoma, testicular embryonal carcinoma), thyroid cancer (*e.g.,* papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer, and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[00286] In some embodiments, a provided compound is useful in treating a metabolic disorder, such as diabetes or obesity. For example, while not being bound to any particular mechanism, a role for PRMT5 has been recognized in adipogenesis. Inhibition of PRMT5 expression in multiple cell culture models for adipogenesis prevented the activation of adipogenic genes, while overexpression of PRMT5 enhanced adipogenic gene expression and differentiation. See, *e.g.*, LeBlanc *et al.*, *Mol Endocrinol.* (2012) 26:583-597. Additionally, it has been shown that adipogenesis plays a pivotal role in the etiology and progression of diabetes and obesity. See, *e.g.*, Camp *et al.*, *Trends Mol Med.* (2002) 8:442-447. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating diabetes and/or obesity.

[00287] In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, diabetes. In some embodiments, the diabetes is Type 1 diabetes. In some embodiments, the diabetes is Type 2 diabetes. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, obesity. In some embodiments, a provided compound is useful to help a subject lose weight. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, such as metformin and insulin, to treat diabetes and/or obesity.

[00288] In some embodiments, a provided compound is useful in treating a blood disorder, *e.g.*, a hemoglobinopathy, such as sickle cell disease or β-thalassemia. For example, while not being bound to any particular mechanism, PRMT5 is a known repressor of γ-globin gene expression, and increased fetal γ-globin (HbF) levels in adulthood are associated with

symptomatic amelioration in sickle cell disease and β-thalassemia. See, *e.g.,* Xu *et al., Haematologica.* (2012) 97:1632-1640; Rank *et al. Blood.* (2010) 116:1585-1592. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating a blood disorder, such as a hemoglobinopathy such as sickle cell disease or β-thalassemia.

[00289] In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, sickle cell disease. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, β-thalassemia. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, to treat a hemoglobinopathy such as sickle cell disease or β-thalassemia.

[00290] In some embodiments, a provided compound is useful in treating inflammatory and autoimmune disease. PRMT5 is reported to activate NFkB signaling pathway through the methylation of p65. PRMT5 is reported to interact with Death receptor 4 and Death receptor 5 contributing to TRAIL-induced activation of inhibitor or kB kinase (IKK) and nuclear factor-kB (NF-kB). See, *e.g.,* Tanaka *et al., Mol. Cancer. Res.* (2009) 7:557-569.; Wei *et al., Proc. Nat'l. Acad. Sci. USA* (2013) 110:13516-21.

[00291] The term "inflammatory disease" refers to those diseases, disorders or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent. Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing,

seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[00292] Exemplary inflammatory diseases include, but are not limited to, inflammation associated with acne, anemia (*e.g.,* aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.,* polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.,* crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions,

atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis.

[00293] In certain embodiments, the inflammatory disease is an acute inflammatory disease (*e.g.*, for example, inflammation resulting from infection). In certain embodiments, the inflammatory disease is a chronic inflammatory disease (*e.g.*, conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds may also be useful in treating inflammation associated with cancer.

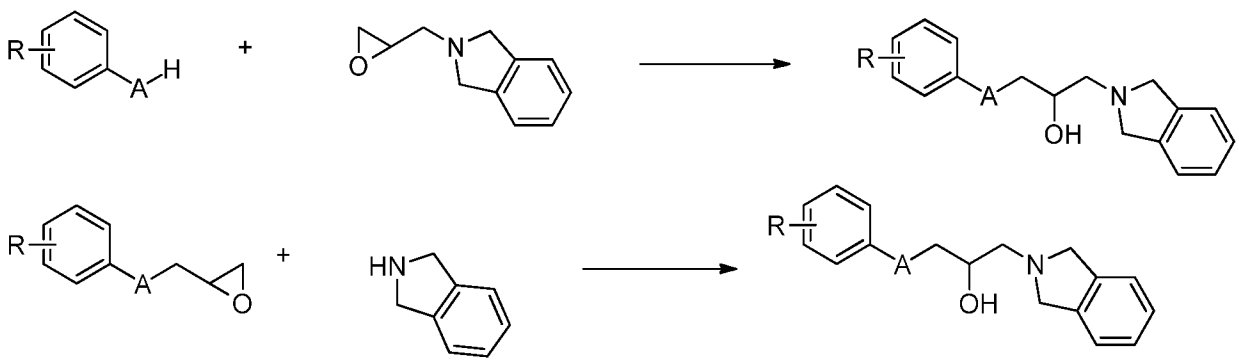
[00294] Exemplary autoimmune diseases, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic,

and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

[00295] In some embodiments, a provided compound is useful in somatic cell reprogramming, such as reprogramming somatic cells into stem cells. See, *e.g.,* Nagamatsu *et al., J Biol Chem.* (2011) 286:10641-10648. In some embodiments, a provided compound is useful in germ cell development, and are thus envisioned useful in the areas of reproductive technology and regenerative medicine. See, *e.g.,* Ancelin *et al., Nat. Cell. Biol.* (2006) 8:623-630.

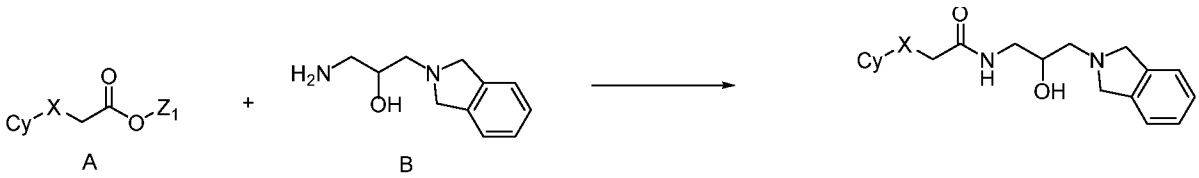
[00296] In some embodiments, compounds described herein can prepared using methods shown in general Scheme 1 ring opening of a chiral or racemic epoxide group to form an amino alcohol moiety. A ring opening step can be performed in either direction as shown in Scheme 1. Further substitution of the tetrahydroisoquinoline ring and/or the phenyl ring can be carried out before or after the coupling reaction.

Scheme 1



[00297] In some embodiments, compounds described herein can prepared using methods shown in general Scheme 2. Compound B can be prepared via ring opening of a chiral or racemic epoxide group. This amino alcohol intermediate can be coupled to form an amide via normal amide coupling methodology using a carboxylic acid A wherein Z_1 is hydrogen or via amination of an ester of intermediate A when Z_1 is an optionally substituted aliphatic group.

Scheme 2

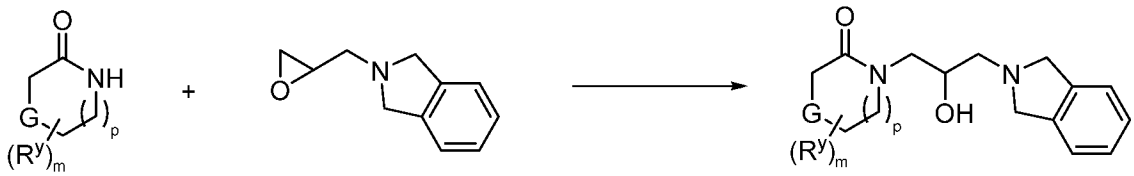


[00298] In some embodiments, compounds described herein can prepared using methods shown in general Scheme 3. Compound B can be prepared via ring opening of a chiral or racemic epoxide group. This amino alcohol intermediate can be coupled to form an amide via normal amide coupling methodology using a carboxylic acid A wherein Z_1 is hydrogen or via amination of an ester of intermediate A when Z_1 is an optionally substituted aliphatic group.

Scheme 3

[00299] In some embodiments, compounds described herein can prepared using methods shown in general Scheme 4, which describes ring opening of a chiral or racemic epoxide group to form the amino alcohol moiety linker.

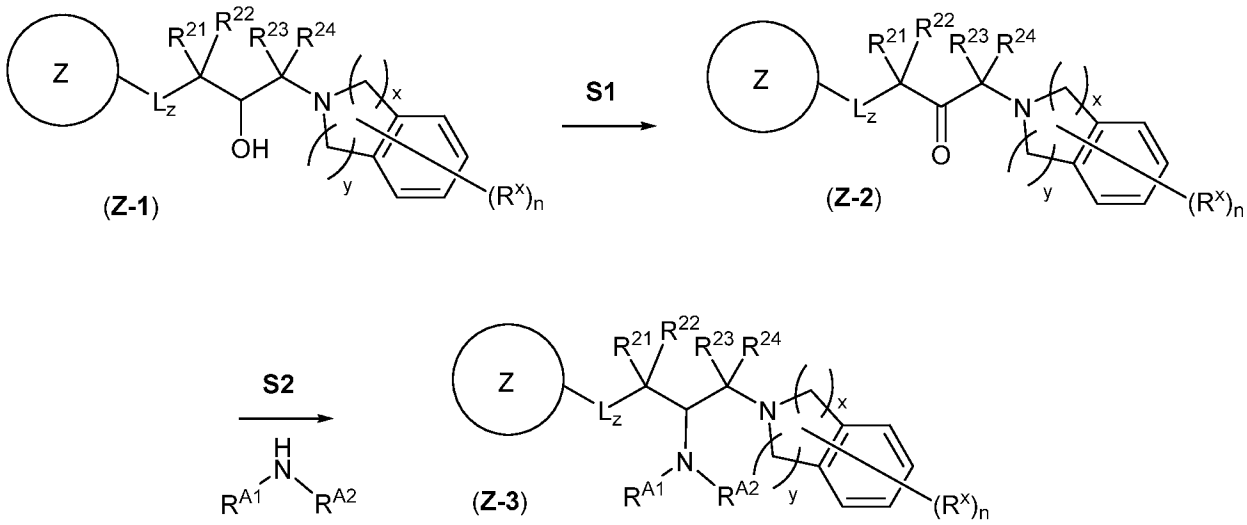
Scheme 4



[00300] In some embodiments of the compounds described herein, R^{12} or R^{13} is an amine. A non-limiting example of the synthetic sequence used to prepare such analogs is provided herein (see Scheme 5). In this example, an alcohol of Formula (**Z-1**) is oxidized under suitable conditions **S1** to affect transformation into an intermediate ketone of Formula (**Z-2**). A ketone of Formula (**Z-2**) can be contacted with a primary or secondary amine under

suitable conditions **S2** to affect a reductive amination which can afford an amino compound of Formula (**Z-3**).

Scheme 5



[00301] In some embodiments, the oxidation reaction **S1** is carried out directly with a stoichiometeric oxidant. In some embodiments, the stoichiometric oxidant is pyridinium chlorochromate. In some embodiments, the stoichiometric oxidant is pyridinium dichromate. In some embodiments, the stoichiometric oxidant is Dess-Martin periodinane. In some embodiments, the stoichiometric oxidant is prepared *in situ*. In some embodiments, the stoichiometric oxidant is prepared *in situ* using sulfur trioxide pyridine complex and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using oxallyl chloride and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using a carbodiimide and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using *N*-chlorosuccinimide and dimethylsulfide. In some embodiments, the oxidation reaction **S1** is catalyzed. In some embodiments, the catalyst is (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl. In some embodiments, the catalyst is a ruthenium complex. In some embodiments, the catalyst is a palladium complex. In some embodiments, the catalyst is a copper complex. For examples of standard methods and conditions for alcohol oxidation, see Epstein *et al.*, *Chem. Rev.* (1967) 67(3):247-260 and B.M. Trost ed. "Comprehensive Organic Synthesis", (1991), Vol. 7, p 281-305.

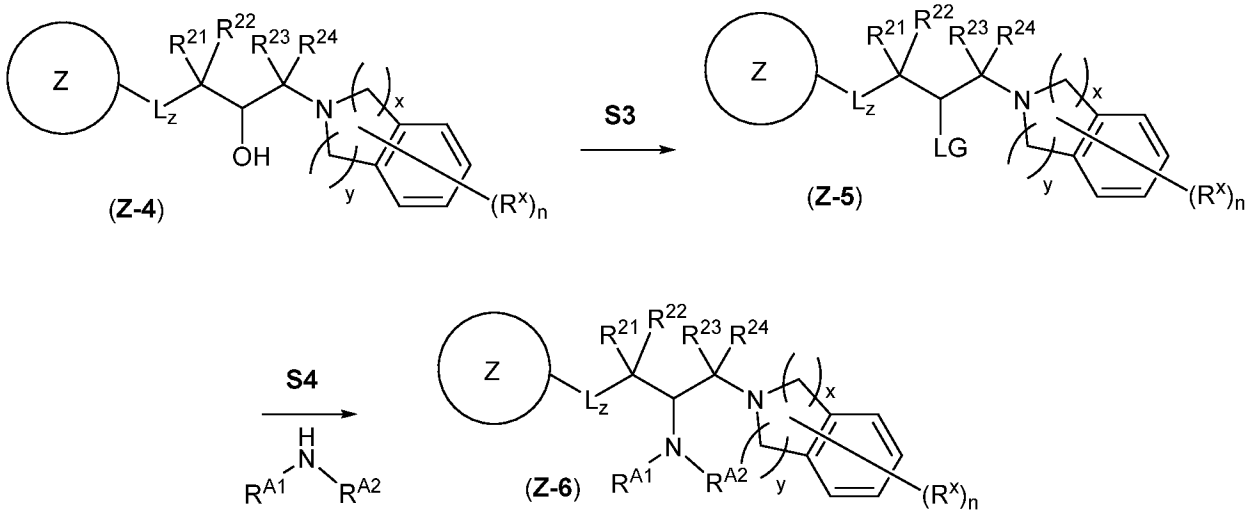
[00302] In some embodiments, both the oxidation step **S1** and reductive amination step **S2** occur in one pot. In some embodiments, both the oxidation step **S1** and the reductive amination step **S2** are carried out using the same catalyst. In some embodiments, the catalyst

is a rhodium complex. In some embodiments, the catalyst is a ruthenium complex. In some embodiments, the catalyst is an iridium complex.

[00303] In some embodiments, the reductive amination reaction **S2** is carried out using a borohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium borohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium cyanoborohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium triacetoxyborohydride. In some embodiments, the reductive amination reaction **S2** is carried out using a borane. In some embodiments, the reductive amination reaction **S2** is carried out using a silyl hydride. In some embodiments, the reductive amination reaction **S2** is carried out using hydrogen. In some embodiments, the reductive amination reaction **S2** is carried out in two steps, by first contacting a ketone of (**Z-2**) with an amine to form an intermediate imine, and then reducing the intermediate imine under sufficient conditions to afford a compound of Formula (**Z-3**). In some embodiments, the reaction conditions **S2** comprise addition of a protic acid. In some embodiments, the reaction conditions **S2** comprise addition of an aprotic acid. In some embodiments, the reaction conditions **S2** comprise *in situ* formation of the reducing agent. In some embodiments, the reaction conditions **S2** comprise a catalyst. In some embodiments, the reaction conditions **S2** comprise a transition metal catalyst. In some embodiments, the reaction conditions **S2** comprise a palladium or nickel catalyst. In some embodiments, the reductive amination reaction **S2** is stereoselective. In some embodiments, the stereoselective reductive amination reaction **S2** is carried out in the presence of a chiral catalyst. For examples of standard methods and conditions for reductive aminations, see Gomez *et al.*, *Adv. Synth. Catal.* (2002) 344(10):1037-1057 and Abdel-Magid *et al.*, *J. Org. Chem.* (1996), 61:3849.

[00304] An alterantive non-limiting synthetic sequence leading to the aforementioned amine analogs is described herein (see Scheme 6). The hydroxyl moiety of a compound of Formula (**Z-4**) can be transformed into a leaving group under sufficient conditions **S3** to afford a compound of Formula (**Z-5**). The leaving group of a compound of Formula (**Z-5**) can be displaced with an amine under suitable conditions **S4** to produce an amino compound of Formula (**Z-6**).

Scheme 6



[00305] In some embodiments, LG of Formula (**Z-5**) is a halide. In some embodiments, LG of Formula (**Z-5**) is bromine. In some embodiments, LG of Formula (**Z-5**) is iodine. In some embodiments, LG of Formula (**Z-5**) is a substituted or unsubstituted alkyl sulfonate. In some embodiments, LG of Formula (**Z-5**) is a substituted or unsubstituted aryl sulfonate. In some embodiments, LG of Formula (**Z-5**) is methyl sulfonate. In some embodiments, LG of Formula (**A-5**) is trifluoromethane sulfonate. In some embodiments, LG of Formula (**Z-5**) is a toluene sulfonate. In some embodiments, LG of Formula (**Z-5**) is a nitrobenzene sulfonate. In some embodiments, when LG of Formula (**Z-5**) is halide, conditions **S3** comprise a phosphoryl halide. In some embodiments, when LG of Formula (**Z-5**) is halide, conditions **S3** comprise a sulfuryl halide. In some embodiments, when LG of Formula (**Z-5**) is sulfonate, conditions **S3** comprise a sulfonyl halide. In some embodiments, when LG of Formula (**Z-5**) is sulfonate, conditions **S3** comprise a sulfonyl anhydride. For examples of standard methods and conditions for organohalide or sulfonate ester synthesis, see Lautens *et al.*, *Synthesis* (2011) 2:342-346 or Marcotullio *et al.*, *Synthesis* (2006) 16:2760-2766.

[00306] In some embodiments, conditions **S4** are neutral. In some embodiments, conditions **S4** comprise addition of a base. In certain embodiments of conditions **S4**, the base is either inorganic or organic. In certain embodiments of conditions **S4**, the base is inorganic. In certain embodiments of conditions **S4**, the base is organic. In certain embodiments of conditions **S4**, the base is a metal acetate, alkoxide, amide, amidine, carbonate, hydroxide, phenoxide, or phosphate. In certain embodiments of conditions **S4**, the base is sodium, potassium, or caesium carbonate. In certain embodiments of conditions **S4**, the base is sodium, potassium, or caesium bicarbonate. In certain embodiments of conditions **S4**, the

base is 1,1,3,3-tetramethylguanidine, 1,4-diazabicyclo[2.2.2]octane, 1,8-bis(dimethylamino)naphthalene, 1,8-diazabicycloundec-7-ene, ammonia, diisopropylamine, imidazole, N,N-diisopropylethylamine, piperidine, pyridine, pyrrolidine, or triethylamine. In some embodiments of conditions **S4**, the solvent is a polar protic solvent. In some embodiments of conditions **S4**, the solvent is a polar aprotic solvent. In some embodiments of conditions **S4**, the reaction is performed in the absence of solvent. In some embodiments, conditions **S4** comprise a catalyst. In some embodiments of conditions **S4**, the catalyst is an iodide salt. In some embodiments, both step **S3** and the displacement step **S4** occur in one pot. In some embodiments, the hydroxyl moiety of a compound of Formula (**Z-4**) is converted into a leaving group *in situ*. In some embodiments, the hydroxyl moiety of a compound of Formula (**Z-4**) is converted into a leaving group *in situ* using an azodicarboxylate and an aryl or alkyl phosphine. For examples of standard methods and conditions for amine syntheses through alkylation reactions, see Salvatore *et. al*, *Tetrahedron* (2001) 57:7785-7811.

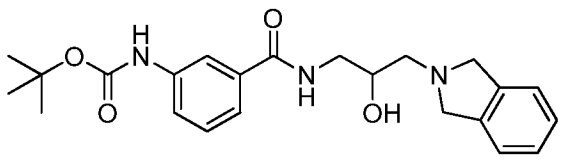
Examples

[00307] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Synthetic Methods

Compound 2

***tert*-butyl (3-((2-hydroxy-3-(isoindolin-2-yl)propyl)carbamoyl)phenyl)carbamate**

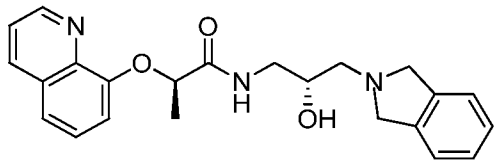


[00308] To a solution of 3-((*tert*-butoxycarbonyl)amino)benzoic acid (300 mg, 1.3 mmol) in DCM (8 mL) was added EDCI (383 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol), Et_3N (263 mg, 2.6 mmol), 1-amino-3-(isoindolin-2-yl)propan-2-ol (499 mg, 2.6 mmol), and the mixture was stirred at 25 °C for 16 h. The crude reaction mixture was washed with water and extracted with DCM. The combined organic layers were concentrated, and the residue was purified by column chromatography to yield the desired product (DCM: MeOH=10:1). (260 mg, yield 49%) MS (ESI^+) e/z: 412.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.87 (s,

1H), 7.58-7.50 (m, 1H), 7.45-7.38 (m, 1H), 7.34-7.28 (m, 1H), 7.25-7.14 (m, 4H), 4.08-3.96 (m, 5H), 3.63-3.53 (m, 1H), 3.45-3.37 (m, 1H), 2.94-2.80 (m, 2H), 1.53 (s, 9H).

Compound 3

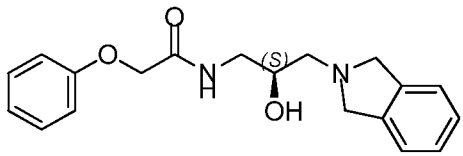
(*R*)-N-((*R*)-2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)propanamide



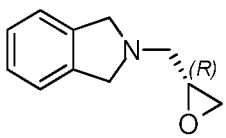
[00309] To a solution of (*R*)-methyl 2-(quinolin-8-yloxy)propanoate (100 mg, 0.433 mmol) in EtOH (1mL) was added (*R*)-1-amino-3-(isoindolin-2-yl)propan-2-ol (83 mg, 0.433 mmol). The reaction mixture was heated under microwave conditions at 120 ℃ for 0.5 h, concentrated, and purified by preparative TLC first and then by preparative HPLC purification. (19 mg, yield 11%) MS (ESI^+) e/z: 392.1 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.90 (d, *J*=2.76 Hz, 1H), 8.34 (d, *J*=8.28 Hz, 1 H), 7.64-7.48 (m, 3H), 7.34-7.24 (m, 1H), 7.23-7.08 (m, 4H), 5.07 (q, *J*=6.53 Hz, 1H), 3.97-3.71 (m, 5H), 3.49 (dd, *J*=13.55, 5.27 Hz, 1H), 3.29 (d, *J*=6.27 Hz, 1H), 2.71 (d, *J*=6.02 Hz, 2H), 1.72 (d, *J*=6.53 Hz, 3H).

Compound 4

(*S*)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-phenoxyacetamide

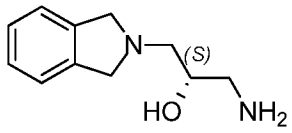


Step 1: (*R*)-2-(oxiran-2-ylmethyl)isoindoline



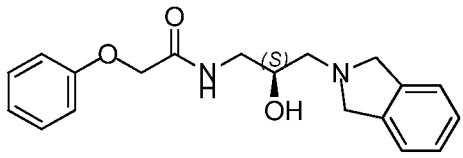
[00310] To a solution of isoindoline (500 mg, 4.20 mmol) and (*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfo nate (1.27 g, 5.04 mmol) in THF (100 mL) was added KF (580 mg, 10 mmol) at 0 °C. The reaction mixture was warmed to 25 °C, stirred for 16 h, filtered and concentrated. The crude product was used in the next step without further purification. (600 mg, yield 68%) MS (ESI^+) e/z: 176.1 $[M+1]^+$.

Step 2: (*S*)-1-amino-3-(isoindolin-2-yl)propan-2-ol



[00311] EtOH (50 mL) was cooled to -78 °C and ammonia gas was bubbled through the solution. To the solution was added (*R*)-2-(oxiran-2-ylmethyl)isoindoline (280 mg, 1.6 mmol), the reaction vessel was sealed and heated at 80 °C for 4 h. The reaction mixture was cooled, concentrated and the crude product was used in the next step without further purification. (600 mg, yield 91%) MS (ESI^+) e/z: 1193.1 $[M+1]^+$.

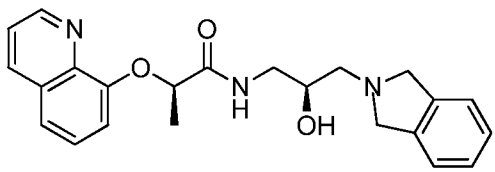
Step 3: (*S*)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-phenoxyacetamide



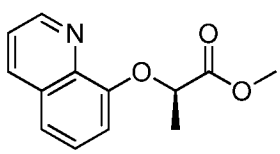
[00312] A solution of (*S*)-1-amino-3-(isoindolin-2-yl)propan-2-ol (100 mg, 0.52 mmol), ethyl 2-(quinolin-8-yloxy)acetate (120 mg, 0.52 mmol) in EtOH (1 mL) was heated under microwave conditions at 120 °C for 0.5 h. The reaction mixture was concentrated and purified by preparative HPLC purification. (60 mg, yield 31%) MS (ESI^+) e/z: 378.1 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.93-8.88 (m, 1H), 8.44-8.38 (m, 1H), 7.66-7.57 (m, 3H), 7.34-7.29 (m, 1H), 7.24-7.14 (m, 4H), 4.82-4.79 (m, 2H), 4.08-4.03 (m, 1H), 3.99 (s, 4H), 3.60-3.55 (m, 1H), 3.46-3.40 (m, 1H), 2.91-2.85 (m, 1H), 2.8 -2.78 (m, 1H).

Compound 5

(*R*)-N-((*S*)-2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)propanamide

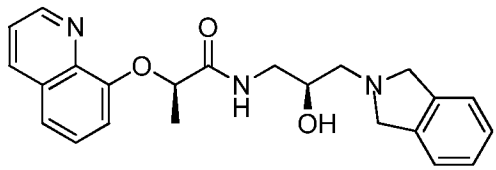


Step 1: (*R*)-methyl 2-(quinolin-8-yloxy)propanoate



[00313] To a solution of quinolin-8-ol (300 mg, 2.07 mmol) in THF (5 mL) was added (*S*)-methyl 2-hydroxypropanoate (215 mg, 2.07 mmol), PPh_3 (647 mg, 2.47 mmol), DEAD (430 mg, 2.47 mmol) and the resulting mixture was stirred at 25 °C for 16 h. Aqueous HCl (1M, 10 mL) was added, the mixture separated, and the aqueous layer extracted with ethyl acetate. The aqueous portion was basified by addition of saturated aqueous $NaHCO_3$ (20 mL) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography. (300 mg, yield 63%) MS (ESI^+) e/z: 232.1 $[M+1]^+$.

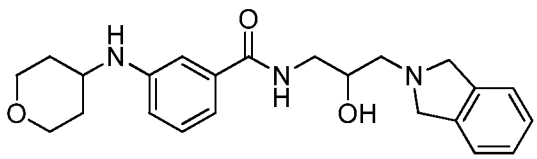
(*R*)-N-((S)-2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)propanamide



[00314] To a solution of (*R*)-methyl 2-(quinolin-8-yloxy)propanoate (100 mg, 0.433 mmol) in EtOH (1mL) was added (*S*)-1-amino-3-(isoindolin-2-yl)propan-2-ol (83 mg, 0.433 mmol). The reaction mixture was heated under microwave conditions at 120 °C for 0.5 h. The mixture was concentrated and purified by preparative HPLC purification. (15 mg, yield 8.8%) MS (ESI^+) e/z: 392.1 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: ^1H NMR (400 MHz, METHANOL-d_4) δ 8.90 (dd, *J*=4.27, 1.76 Hz, 1H) 8.33 (dd, *J*=8.41, 1.63 Hz, 1H) 7.51-7.64 (m, 3H) 7.29 (dd, *J*=6.15, 2.64 Hz, 1H) 7.08-7.22 (m, 4H) 5.08 (q, *J*=6.78 Hz, 1H) 3.75-3.93 (m, 5H) 3.36-3.43 (m, 2H) 2.55-2.66 (m, 2H) 1.73 (d, *J*=6.78 Hz, 3H).

Compound 6

N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-3-((tetrahydro-2H-pyran-4-yl)amino)benzamide

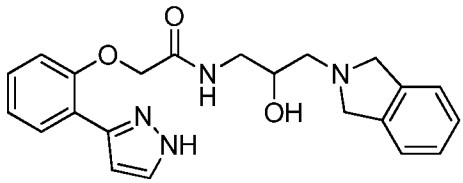


[00315] To a solution of 3-amino-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)benzamide (120 mg, 0.39 mmol) in MeOH (10 mL) was added dihydro-2H-pyran-4(3H)-one (78 mg, 0.78 mmol) and AcOH (0.05 mL). The mixture was stirred at 25 °C for 2 h. $NaBH_3CN$ (123 mg, 1.95 mmol) was added, and the resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated, and the residue was dissolved in water, extracted with ethyl

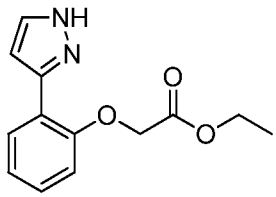
acetate, dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC purification. (22 mg, yield 14%) MS (ESI^+) e/z: 396.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.62-7.53 (m, 2H), 7.53-7.36 (m, 5H), 7.30-7.21 (m, 1H), 4.76-4.57 (m, 2H), 4.34-4.24 (m, 1H), 4.08-3.96 (m, 2H), 3.74-3.65 (m, 1H), 3.65-3.57 (m, 2H), 3.57-3.43 (m, 4H), 3.36-3.32 (m, 2H), 2.03-1.91 (m, 2H), 1.72-1.57 (m, 2H).

Compound 8

2-(2-(1H-pyrazol-3-yl)phenoxy)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)acetamide

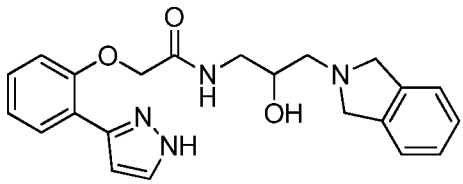


Step 1:ethyl 2-(2-(1H-pyrazol-3-yl)phenoxy)acetate



[00316] To a solution of 2-(1H-pyrazol-3-yl) phenol (400mg, 2.5 mmol) and K_2CO_3 (518 mg, 3.75 mmol) in CH_3CN (10 mL) was added ethyl 2-bromoacetate (418 g, 2.5 mmol). The mixture was stirred at room temperature for 2 h, diluted with water, extracted with ethyl acetate and concentrated. The crude material was purified by column chromatography. (129 mg, yield 21%) MS (ESI^+) e/z: 247.2 $[M+1]^+$.

Step 2: 2-(2-(1H-pyrazol-3-yl)phenoxy)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)acetamide

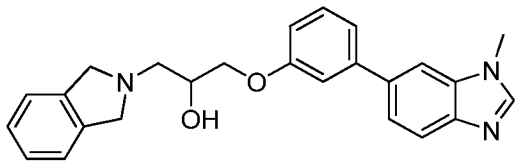


[00317] Ethyl 2-(2-(1H-pyrazol-3-yl)phenoxy)acetate (129 mg, 0.52 mmol) and 1-amino-3-(isoindolin-2-yl)propan-2-ol (100mg, 0.52mmol) were dissolved in EtOH (1 mL) and heated under microwave conditions at 120°C for 1 h. The reaction mixture was concentrated and

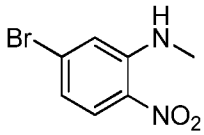
purified by preparative HPLC purification. (16.2 mg, yield 8%) MS (ESI^+) e/z: 393.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.70 (d, J=7.53 Hz, 2H), 7.39-7.32 (m, 1H), 7.26-7.14 (m, 4H), 7.14-7.05 (m, 2H), 6.74 (d, J=1.76 Hz, 1H), 4.70 (br. s., 2H), 3.97 (s, 5H), 3.54 (dd, J=13.55, 4.77 Hz, 1H), 3.38 (d, J=8.53 Hz, 1H), 2.81 (d, J=4.27 Hz, 2H).

Compound 9

1-(isoindolin-2-yl)-3-(3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenoxy)propan-2-ol

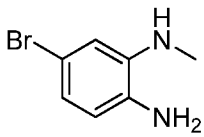


Step 1: 5-bromo-N-methyl-2-nitroaniline



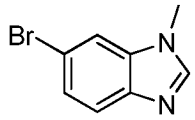
[00318] To a solution of 4-bromo-2-fluoro-1-nitrobenzene (10 g, 45.7 mmol) in DMSO (50 mL) was added TEA (18.47 g, 183 mmol), methylamine hydrochloride (6.1 g, 91.4 mmol) and the reaction mixture was heated under microwave conditions at 120 °C for 3 h. The mixture was cooled, extracted with ethyl acetate; the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The crude product was used in next step without further purification. (10.5 g, yield 98%) MS (ESI^+) e/z: 231.1.

Step 2: 5-bromo-N1-methylbenzene-1,2-diamine



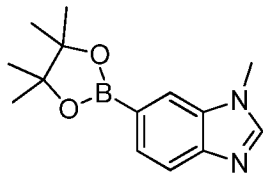
[00319] To a solution of 5-bromo-N-methyl-2-nitroaniline (10 g, 43.5 mmol) in $EtOH/H_2O$ (700 mL) was added Fe (14.6 g, 261 mmol), ammonium chloride (14 g, 261 mmol) and the reaction mixture was heated at 60 °C for 4 h. The crude reaction mixture was filtered, concentrated, dissolved in ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was used in next reaction without further purification. (7.9 g, yield 90%) MS (ESI^+) e/z: 202.1.

Step 3: 6-bromo-1-methyl-1H-benzo[d]imidazole



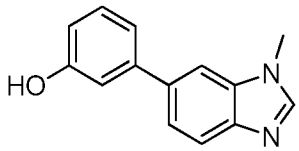
[00320] To a solution of 5-bromo-N1-methylbenzene-1,2-diamine (7.4 g, 37 mmol) in trimethyl orthoformate (100 mL) was added p-toluenesulfonic acid (0.36g, 1.9 mmol). The reaction mixture was heated at 100 °C for 4 h, cooled, concentrated, dissolved in ethyl acetate, washed with brine, dried over sodium sulfate and concentrated. The crude product was used in next step without further purification. (7.3 g, yield 93%) MS (ESI^+) e/z: 212.1.

Step 4: 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole



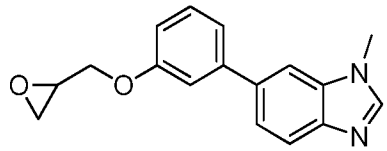
[00321] To a solution of 6-bromo-1-methyl-1H-benzo[d]imidazole (5 g, 23.8 mmol) in dioxane (60 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (9.1 g, 35.7 mmol), $Pd(dppf)Cl_2$ (0.5 g) and potassium acetate (4.67 g, 47.6 mmol). The reaction mixture was heated at 100 °C for 3 h, cooled and concentrated. The crude reaction mixture was purified by column chromatography. (6 g, yield 98%) MS (ESI^+) e/z: 259.1.

Step 5: 3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenol



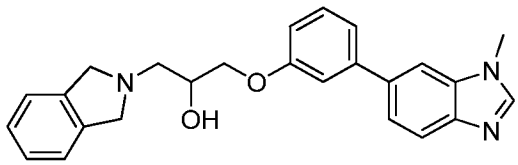
[00322] To a solution of 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo [d]imidazole (6 g, 23.1 mmol) in dioxane/water (50 mL) was added 3-bromophenol (4.8 g, 27.7 mmol), $Pd(dppf)Cl_2$ (0.3g) and Cs_2CO_3 (15g, 46.2 mmol). The reaction mixture was heated at 100 °C for 3 h, cooled and concentrated. The crude reaction mixture was purified by column chromatography. (4.8 g, yield 92%) MS (ESI^+) e/z: 225.1.

Step 6: 1-methyl-6-(3-(oxiran-2-ylmethoxy)phenyl)-1H-benzo[d]imidazole



[00323] To a solution of NaH (161 mg, 6.69 mmol) in DMF (5 mL) was added 3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenol (500 mg, 2.23 mmol) at 27 °C. After 0.5 h, 2-(chloromethyl)oxirane (246 mg, 2.68 mmol) was added and the reaction mixture was stirred 16 h, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was used in next step without further purification. (500 mg, yield 80%).

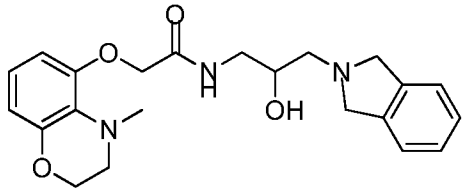
Step 7: 1-(isoindolin-2-yl)-3-(3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenoxy)propan-2-ol



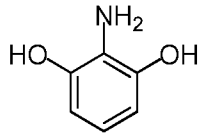
[00324] To a solution of 1-methyl-6-(3-(oxiran-2-ylmethoxy)phenyl)-1H-benzo[d]imidazole (500 mg, 1.78 mmol) in MeOH (5 mL) was added isoindoline (213 mg, 1.78 mmol) at 25 °C, and the mixture was heated to reflux and stirred for 16 h. The reaction mixture was cooled, concentrated and purified by preparative HPLC purification. (80 mg, yield 11%) MS (ESI^+) e/z: 400.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.22 (s, 1 H), 7.87 (s, 1H), 7.71 (d, J=8.4 Hz, 1H), 7.53 (d, J=8.4 Hz, 1H), 7.41-7.19 (m, 7H) , 6.97-6.95(m, 1H) , 4.16 - 4.04 (m, 7H), 3.89 (s, 3 H), 3.04-2.87 (m, 2H).

Compound 10

N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)oxy)acetamide

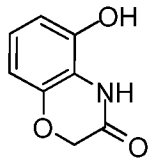


Step 1: 2-aminobenzene-1,3-diol



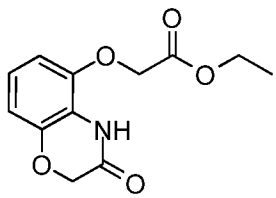
[00325] To a solution of 2-nitrobenzene-1,3-diol (5.00 g, 32.2 mmol) in MeOH (100 mL) was added Pd/C (200 mg). The mixture was stirred under a H_2 atmosphere at 25 °C for 16 h, filtered, and concentrated. The crude product was used in the next step without further purification. (3.00 g, yield 75%).

Step 2: 5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one



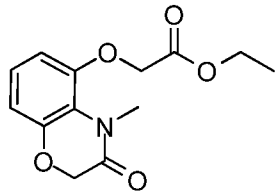
[00326] To a solution of 2-aminobenzene-1,3-diol (2.00 g, 16.0 mmol) and TEA (1.94 g, 19.2 mmol) in anhydrous DMF (30 mL) was added 2-chloroacetyl chloride (1.81 g, 16.0 mmol). After 16 h, K_2CO_3 (2.65 g, 19.2 mmol) was added and the reaction mixture was stirred for another 16 h. The mixture was diluted with water and extracted with DCM. The combined organic extracts were washed with water, brine, the combined organic extracts dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography. (1.7 g, yield 65%).

Step 3: ethyl 2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy)acetate



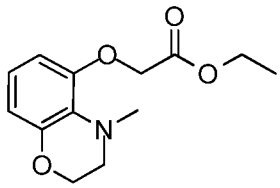
[00327] A solution of 5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one (100 mg, 0.604 mmol) and K_2CO_3 (167 mg, 1.21 mmol) in anhydrous DMF (5 mL) was stirred at 27 °C for 5 minutes, then ethyl 2-bromoacetate (121 mg, 0.727 mmol) was added. The reaction mixture was stirred at 27 °C for 16 h and concentrated. MS (ESI^+) e/z: 238.0 $[M+1]^+$.

Step 4:ethyl 2-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy)acetate



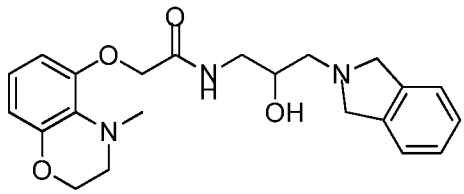
[00328] To the solution of ethyl 2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yloxy) acetate (72 mg, 0.287 mmol) and K_2CO_3 (39.6 mg, 0.287 mmol) in DMF (5 mL) was added MeI (40.7 mg, 0.287 mmol). The mixture was stirred at 25 °C for 16 h, partitioned between water (50 mL) and DCM (100 mL), the organic portion was washed with water, brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by preparative TLC. (43 mg, yield 57%). ^{1}H NMR (MeOD, 400 MHz), δ ppm: 6.99 (t, J=8.3 Hz, 1H), 6.74 (d, J=7.5 Hz, 1H), 6.55 (d, J=8.3 Hz, 1H), 4.69 (s, 2H), 4.51 (s, 2H), 4.30 (q, J=7.2 Hz, 2H), 3.56 (s, 3H), 1.34-1.33 (m, 1H), 1.33 (t, J=7.2 Hz, 3H).

Step 5: ethyl 2-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)oxy)acetate



[00329] A solution of ethyl 2-((4-methyl-3-oxo-3,4-dihydro-2H-benzo [b][1,4]oxazin -5-yl)oxy)acetate (100 mg, 0.377 mmol) in anhydrous THF (3 mL) was cooled to 0 °C and BH_3-Me_2S (0.1 mL) added. The solution was stirred at 27 °C for 6 h, diluted with methanol and concentrated. The residue was partitioned between ethyl acetate (30 mL) and water (20 mL), the organic layer washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by preparative TLC. (72 mg, yield 76%) MS (ESI^+) e/z: 252.2 $[M+1]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz), δ ppm: 6.87-6.76 (m, 1H), 6.62-6.52 (m, 1H), 6.40-6.28 (m, 1H), 4.70 (s, 2H), 4.34-4.22 (m, 2H), 4.18-4.06 (m, 2H), 3.21-3.07 (m, 2H), 2.99-2.85 (m, 3H), 1.33-1.25 (m, 3H).

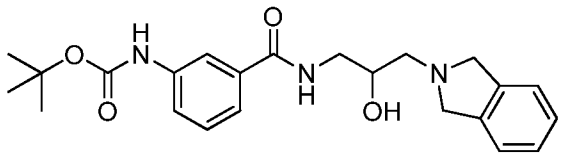
Step 6: N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)oxy)acetamide



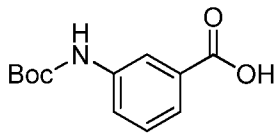
[00330] A solution of ethyl 2-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)oxy) acetate (72 mg, 0.287 mmol), 1-amino-3-(isoindolin-2-yl) ropan -2-ol (55 mg, 0.755 mmol) in EtOH (0.1 mL) was heated under microwave conditions at 120 °C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC purification. (17.4 mg, yield 15%). MS (ESI^+) e/z: 398.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.27-7.13 (m, 4H), 6.91 (t, *J*=8.3 Hz, 1H), 6.66-6.50 (m, 2H), 4.66-4.59 (m, 2H), 4.23-4.09 (m, 2H), 4.02-3.86 (m, 5H), 3.49 (dd, *J*=4.9, 13.7 Hz, 1H), 3.32-3.27 (m, 1H), 3.21-3.11 (m, 2H), 2.92-2.81 (m, 3H), 2.80-2.70 (m, 2H).

Compound 11

***tert*-butyl (3-((2-hydroxy-3-(isoindolin-2-yl)propyl)carbamoyl)phenyl)carbamate**

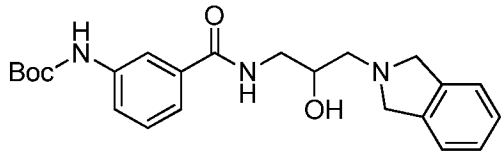


Step 1: 3-((*tert*-butoxycarbonyl)amino)benzoic acid



[00331] To a solution of 3-aminobenzoic acid (1.37 g, 10 mmol) in THF (20 mL) and H_2O (2 mL) was added Boc_2O (2.18 g, 10 mmol) and Et_3N (1.52 g, 15 mmol). The reaction mixture was stirred at 25 °C for 16 h, concentrated, dissolved in water and extracted with ethyl acetate. The combined extracts were concentrated and the crude product was used in the next step without further purification. (2.5 g, yield 96%) MS (ESI^+) e/z: 260.0 $[M+1]^+$.

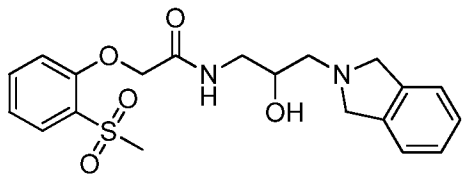
Step 2: *tert*-butyl (3-((2-hydroxy-3-(isoindolin-2-yl)propyl)carbamoyl)phenyl)carbamate



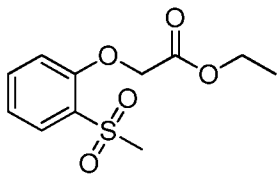
[00332] To a solution of 3-((*tert*-butoxycarbonyl)amino)benzoic acid (300 mg, 1.3 mmol) in DCM (8 mL) was added EDCI (383 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol), Et_3N (263 mg, 2.6 mmol), 1-amino-3-(isoindolin-2-yl)propan-2-ol (499 mg, 2.6 mmol), and the mixture was stirred at 25 °C for 16 h. The crude reaction mixture was washed with water and extracted with DCM. The combined organic layers were concentrated, and the residue was purified by column chromatography (DCM: MeOH=10:1). (260 mg, yield 49%) MS (ESI^+) e/z: 412.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.87 (s, 1H), 7.58-7.50 (m, 1H), 7.45-7.38 (m, 1H), 7.34-7.28 (m, 1H), 7.25-7.14 (m, 4H), 4.08-3.96 (m, 5H), 3.63-3.53 (m, 1H), 3.45-3.37 (m, 1H), 2.94-2.80 (m, 2H), 1.53 (s, 9H).

Compound 12

N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(2-(methylsulfonyl)phenoxy)acetamide

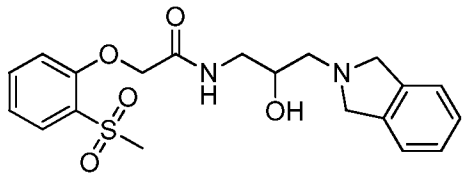


Step 1: ethyl 2-(2-(methylsulfonyl)phenoxy)acetate



[00333] To a solution of 2-(methylsulfonyl)phenol (100 mg, 0.58 mmol) and K_2CO_3 (276 mg, 2 mmol) in CH_3CN (10 mL) was added ethyl 2-bromoacetate (115.2 mg, 0.69 mmol) at 25 °C. The mixture was heated at 80 °C for 4 h, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude product was used in the next step without further purification. (140 mg, yield 94%).

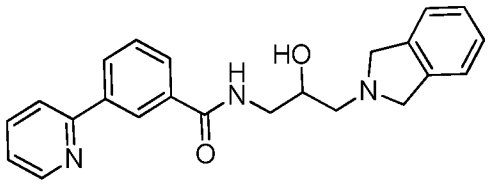
Step 2: N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(2-(methylsulfonyl)phenoxy)acetamide



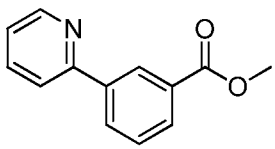
[00334] Ethyl 2-(2-(methylsulfonyl)phenoxy)acetate (50 mg, 0.19 mmol) and 1-amino-3-(isoindolin-2-yl)propan-2-ol (36 mg, 0.19 mmol) were dissolved in EtOH (1 mL) and heated under microwave conditions at 120 °C 0.5 h. The reaction mixture was concentrated and purified by preparative HPLC purification. (11 mg, yield 14%) MS (ESI^+) e/z: 405.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.98-7.91 (m, 1H), 7.76-7.69 (m, 1H), 7.33-7.24 (m, 2H), 7.21 (d, J=2.76 Hz, 4H), 4.86-4.80 (m, 2H), 4.01-3.97 (m, 4H), 3.97-3.91 (m, 1H), 3.57-3.50 (m, 1H), 3.39-3.35 (m, 1H), 3.30 (s, 3H), 2.86-2.81 (m, 1H), 2.81-2.74 (m, 1H).

Compound 13

N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-3-(pyridin-2-yl)benzamide

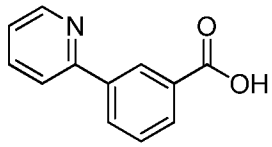


Step 1: methyl 3-(pyridin-2-yl)benzoate



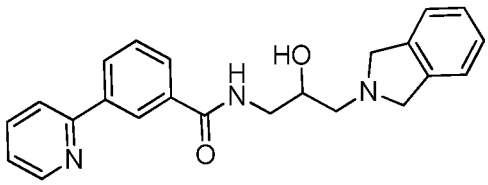
[00335] A solution (3-(methoxycarbonyl)phenyl)boronic acid (500 mg, 2.78 mmol), 2-bromopyridine (399 mg, 2.53 mmol), K_2CO_3 (1.0 g, 7.6 mmol) and $Pd(dppf)Cl_2$ (20 mg) in a mixture of dioxane (10 mL) and water (2.5 mL) was heated under microwave conditions at 120 °C for 0.5 h. The reaction mixture was filtered, concentrated, and the crude product was purified by column chromatography eluting with petroleum ether/ethyl acetate (5:1). (400 mg, yield 74%) MS (ESI^+) e/z: 214.1 $[M+1]^+$.

Step 2: 3-(pyridin-2-yl)benzoic acid



[00336] To a solution of methyl 3-(pyridin-2-yl)benzoate (400 mg, 1.88 mmol) in MeOH (3 mL) was added aqueous of NaOH (1 mL, 40 mol%). The reaction mixture was stirred at room temperature for 3 h and concentrated. The crude residue was dissolved in water and the pH was adjusted to 5~6 with 2N of HCl. The solution was extracted with ethyl acetate, brine, dried over sodium sulfate, filtered and concentrated. (350 mg, yield 93%) MS (ESI^+) e/z: 200.1 $[M+1]^+$.

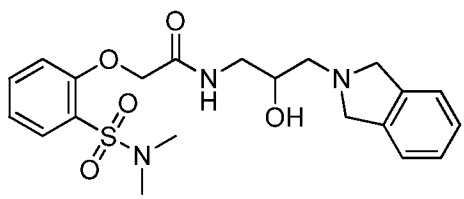
Step 3: N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-3-(pyridin-2-yl)benzamide



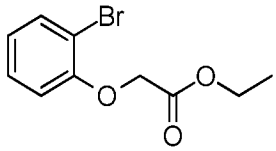
[00337] To a solution of 3-(pyridin-2-yl)benzoic acid (60 mg, 0.30 mmol) in DCM (8 mL) was added EDCI (86 mg, 0.45 mmol), HOBt (61 mg, 0.45 mmol), Et_3N (61 mg, 0.6 mmol) and 1-amino-3-(isoindolin-2-yl)propan-2-ol (86 mg, 0.45 mmol). The mixture was stirred at 25 °C for 16 h, washed with water and extracted with DCM. The combined organic extracts were concentrated, and the residue was purified by preparative HPLC purification. (30 mg, 27%) MS (ESI^+) e/z: 374.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.65 (d, J=4.8 Hz, 1H), 8.15 (d, J=8.0 Hz, 1H), 7.96-7.92 (m, 3H), 7.62 (dd, J=7.2 Hz, 1H), 7.40-7.35 (m, 6H), 4.70 (s, 4H), 4.29 (br.s, 1H), 3.63-3.30 (m, 4H).

Compound 15

2-(2-(N,N-dimethylsulfamoyl)phenoxy)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)acetamide

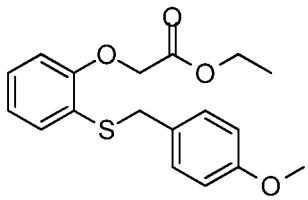


Step 1: ethyl 2-(2-bromophenoxy)acetate



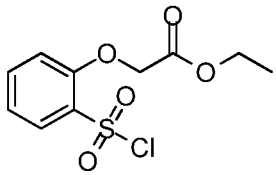
[00338] To a solution of 2-bromophenol (2 g, 0.0116 mol) in MeCN (10 mL) was added ethyl bromoacetate (2.12 g , 0.0128 mol) and K_2CO_3 (4.81 g, 0.035 mol). The mixture was stirred at 80 ℃ for 4 h, filtered and concentrated. The crude product was used in the next step without further purification.

Step 2: ethyl 2-(2-((4-methoxybenzyl)thio)phenoxy)acetate



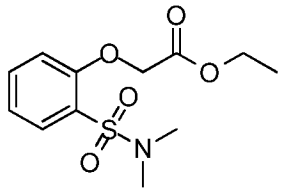
[00339] To a solution of ethyl 2-(2-bromophenoxy)acetate (3.0 g, 0.0116 mol) in dioxane (30 mL) was added (4-methoxyphenyl)methanethiol (2.14 g, 0.0139 mol), $Pd_2(dba)_3$ (20 mg), xantphos (20 mg) and DIEA (3 mL). The mixture was degassed 4 times (N_2) and heated at reflux for 3 h, concentrated, and the crude product was purified by column chromatography. (3 g, yield 79%) MS (ESI^+) e/z: 355.1 $[M+1]^+$.

Step 3: ethyl 2-(2-(chlorosulfonyl)phenoxy)acetate



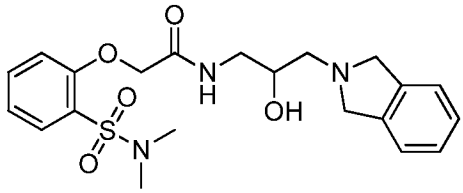
[00340] To a solution of ethyl 2-(2-((4-methoxybenzyl)thio)phenoxy)acetate (1.0g, 3.01 mmol) in MeCN:HOAC:H_2O (80:1:2, 10 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (1.19 g, 6.02 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 3 h and concentrated. The crude residue was extracted with DCM, aqueous $NaHCO_3$ that had been cooled to 10 ℃, the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude product was used in the next step without further purification.

Step 4: ethyl 2-(2-(N,N-dimethylsulfamoyl)phenoxy)acetate



[00341] To a solution of ethyl 2-(2-(chlorosulfonyl)phenoxy)acetate (300 mg, 1.08 mmol) in pyridine (5 mL) was added dimethylamine hydrochloride (105 mg, 1.30 mmol) at 0 °C. The mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was concentrated and the crude product was used in the next step without further purification. (250 mg, yield 81%) MS (ESI^+) e/z: 288.0 $[M+1]^+$.

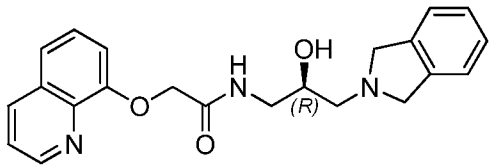
Step 5: 2-(2-(N,N-dimethylsulfamoyl)phenoxy)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)acetamide



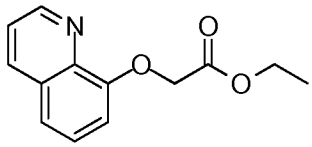
[00342] To a solution of ethyl 2-(2-(N,N-dimethylsulfamoyl)phenoxy)acetate (100 mg, 0.35 mmol) in EtOH (1mL) was added 1-amino-3-(isoindolin-2-yl)propan-2-ol (66.8 mg, 0.35 mmol). The reaction mixture was heated under microwave conditions at 120 °C for 0.5 h. The material was concentrated and purified by preparative HPLC purification. (20 mg, yield 13%) MS (ESI^+) e/z: 434.1 $[M+1]^+$.. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.85 (dd, J=7.78, 1.51 Hz, 1H), 7.70-7.61 (m, 1H), 7.27-7.16 (m, 6H), 4.75 (s, 2H), 4.05-3.91 (m, 5H), 3.55 (dd, J=13.68, 4.89 Hz, 1H), 3.40-3.35 (m, 1H), 2.92-2.77 (m, 8H).

Compound 16

(*R*)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)acetamide

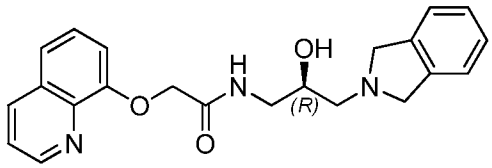


Step 1: ethyl 2-(quinolin-8-yloxy)acetate



[00343] To a solution of quinolin-8-ol (3 g, 0.0207 mol) in MeCN (10 mL) was added ethyl bromoacetate (4.12 g , 0.025 mol) and K_2CO_3 (5.75 g , 0.0414 mol). The mixture was stirred at 80 ºC for 12 h, filtered and concentrated. The crude residue was purified by column chromatography. (3.9 g, yield, 82%) MS (ESI^+) e/z: 232.1 $[M+1]^+$.

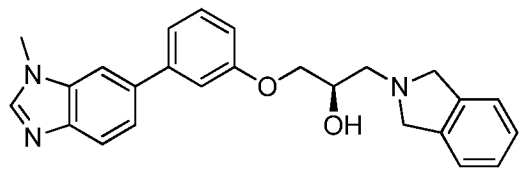
Step 2: (*R*)-N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)acetamide



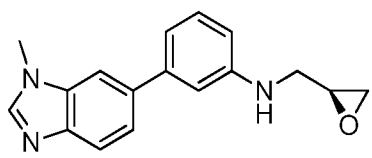
[00344] (*R*)-1-amino-3-(isoindolin-2-yl)propan-2-ol (100 mg, 0.52 mmol) and ethyl 2-(quinolin-8-yloxy)acetate (120 mg, 0.52 mmol) were dissolved in EtOH (1 mL) and heated under microwave conditions at 120 °C for 0.5 h. The reaction mixture was concentrated and purified by preparative HPLC purification. (100 mg, yield 51%) MS (ESI^+) e/z: 378.1 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.95-8.85 (m, 1 H), 8.44-8.34 (m, 1H), 7.69-7.54 (m, 3H), 7.33-7.27 (m, 1H), 7.18 (s, 4H), 4.79 (s, 2H), 4.09-4.03 (m, 1H), 3.99 (s, 4H), 3.61-3.53 (m, 1H), 3.47-3.38 (m, 1H), 2.91-2.85 (m, 1H), 2.84-2.77 (m, 1H).

Compound 17

(*R*)-1-(isoindolin-2-yl)-3-(3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenoxy)propan-2-ol

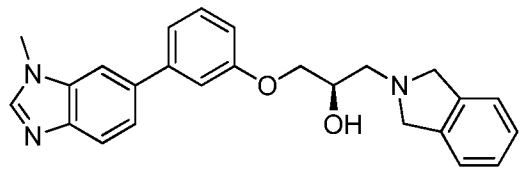


Step 1: (*S*)-3-(1-methyl-1H-benzo[d]imidazol-6-yl)-N-(oxiran-2-ylmethyl)aniline



[00345] To a solution of NaH (161 mg, 6.69 mmol) in DMF (5 mL) was added 3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenol (500 mg, 2.23 mmol) at 27 °C. After 0.5 h, (*S*)-2-(chloromethyl)oxirane (246 mg, 2.68 mmol) was added and the reaction mixture was stirred 16 h, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was used in next step without further purification. (480 mg, yield 77%).

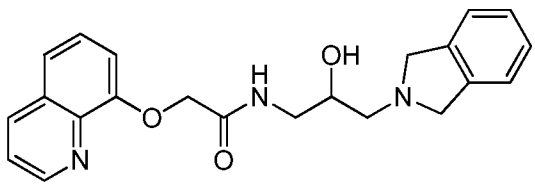
Step 2: (*R*)-1-(isoindolin-2-yl)-3-(3-(1-methyl-1H-benzo[d]imidazol-6-yl)phenoxy)propan-2-ol



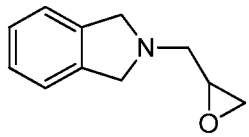
[00346] To a solution of (*S*)-3-(1-methyl-1H-benzo[d]imidazol-6-yl)-N-(oxiran-2-ylmethyl) aniline (480 mg, 1.71 mmol) in MeOH (5 mL) was added isoindoline (213 mg, 1.78 mmol) at 25 °C, and the mixture was heated to reflux and stirred for 16 h. The reaction mixture was cooled, concentrated and purified by preparative HPLC and SFC purification. (104.8 mg, yield 15%) MS (ESI^+) e/z: 400.2 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.44-8.26 (m, 1H), 8.17 (s, 1H), 7.82-7.66 (m, 2H), 7.63-7.52 (m, 1H), 7.44-7.37 (m, 5H), 7.36-7.28 (m, 2H), 6.99 (dd, *J*=8.03, 1.63 Hz, 1H), 4.78 (s, 4H), 4.47 (dd, *J*=8.97, 3.58 Hz, 1H), 4.23-4.10 (m, 2H), 3.94 (s, 3H), 3.74-3.58 (m, 2H).

Compound 19

N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)acetamide



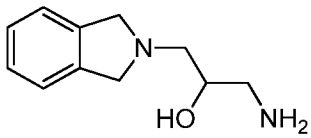
Step 1: 2-(oxiran-2-ylmethyl)isoindoline



[00347] To a solution of isoindoline（200 mg, 1.68 mmol) and 2-(bromomethyl)oxirane (272 mg, 2.0 mmol) in CH_3CN (10 mL) was added K_2CO_3 (690 mg, 5 mmol) and reaction

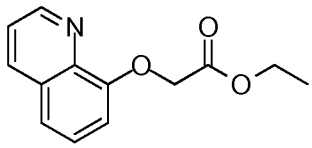
mixture was stirred at 25 °C for 16 h. The mixture was filtered, concentrated and the crude product was used in the next step without further purification. (280 mg, yield 95%) MS (ESI^+) e/z: 176.1 $[M+1]^+$.

Step 2: 1-amino-3-(isoindolin-2-yl)propan-2-ol



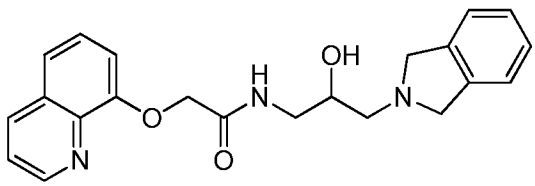
[00348] EtOH (50 mL) was cooled to -78 °C and ammonia gas was bubbled through the solution. To the solution was added 2-(oxiran-2-ylmethyl)isoindoline (280 mg, 1.6 mmol), the reaction vessel was sealed and heated at 80 °C for 4 h. The reaction mixture was cooled, concentrated and the crude product was used in the next step without further purification. (300 mg, yield 98%) MS (ESI^+) e/z: 193.1 $[M+1]^+$.

Step 3: ethyl 2-(quinolin-8-yloxy)acetate



[00349] To a solution of quinolin-8-ol (3 g, 0.0207 mol) in MeCN (10 mL) was added ethyl bromoacetate (4.12 g , 0.025 mol) and K_2CO_3 (5.75 g , 0.0414 mol). The mixture was stirred at 80 ℃ for 12 h, filtered and concentrated. The residue was purified by column chromatography. (3.9 g, yield 81%) MS (ESI^+) e/z: 232.1 $[M+1]^+$.

Step 4: N-(2-hydroxy-3-(isoindolin-2-yl)propyl)-2-(quinolin-8-yloxy)acetamide

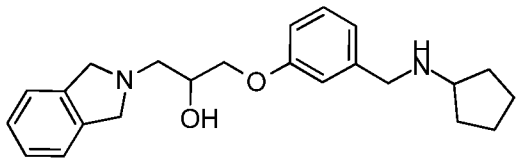


[00350] 1-amino-3-(isoindolin-2-yl)propan-2-ol(50 mg, 0.26 mmol) and ethyl 2-(quinolin-8-yloxy)acetate (60 mg, 0.26 mmol) were dissolved in EtOH (1 mL) and heated under microwave conditions at 120 °C for 0.5 h. The reaction mixture was concentrated and purified by preparative HPLC purification. (17.2 mg, yield 18%) MS (ESI^+) e/z: 378.1 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.95-8.87 (m, 1H), 8.45-8.36 (m, 1H), 7.67-7.56 (m, 3H), 7.35-7.25 (m, 1H), 7.24-7.12 (m, 4H), 4.83-4.76 (m, 2H), 4.09-4.03 (m, 1H),

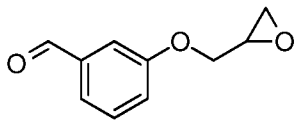
4.02-3.95 (m, 4H), 3.60-3.54 (m, 1H), 3.46-3.40 (m, 1H), 2.92-2.86 (m, 1H), 2.84-2.78 (m, 1H).

Compound 20

1-(3-((cyclopentylamino)methyl)phenoxy)-3-(isoindolin-2-yl)propan-2-ol

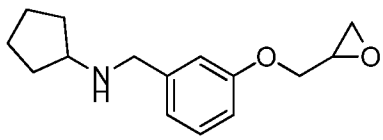


Step 1: 3-(oxiran-2-ylmethoxy)benzaldehyde



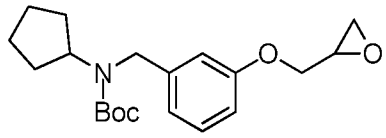
[00351] To a solution of 3-hydroxybenzaldehyde (2.0 g, 16.38 mmol) in DMF (30 mL) at 0 °C was added NaH (983 mg, 24.57 mmol) in portions. After 0.5 h, a solution of 2-(bromomethyl)oxirane (2.69 mg, 19.65 mmol) in DMF (5 mL) was added and the reaction mixture was warmed to room temperature for 5 h. The mixture was concentrated, dissolved in ethyl acetate and washed with water. The organic portion was dried over sodium sulfate, filtered and concentrated. The crude product was used in the next step without further purification. (2.1 g, yield 72%) MS (ESI^+) e/z: 179.1 $[M+1]^+$.

Step 2: N-(3-(oxiran-2-ylmethoxy)benzyl)cyclopentanamine



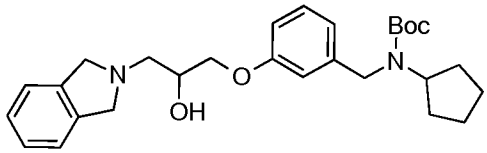
[00352] To a solution of 3-(oxiran-2-ylmethoxy)benzaldehyde (1.0 g, 5.61 mmol) in MeOH (15 mL) was added cyclopentanamine (502 mg, 5.89 mmol) at room temperature. After 4 h, sodium borohydride (318 mg, 8.42 mmol) was added in portions and the mixture was stirred for another 1 h. The reaction mixture was quenched by adding aquesous 1 N HCl until the pH was adjusted to 4-5. The resulting solution was diluted with ethyl acetate, washed with water, dried over sodium sulfate, filtered and concentrated. The crude product was used in the next step without further purification. (1.1 g, yield 79%) MS (ESI^+) e/z: 248.2 $[M+1]^+$.

Step 3: *tert*-butyl cyclopentyl(3-(oxiran-2-ylmethoxy)benzyl)carbamate



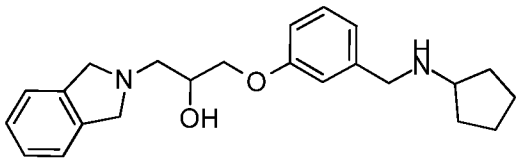
[00353] To a solution of N-(3-(oxiran-2-ylmethoxy)benzyl)cyclopentanamine (1.0 g, 4.04 mmol) in THF (30 mL) was added Boc_2O (1.32 g, 6.06 mmol) and TEA (614 mg, 6.06 mmol). The reaction mixture was stirred at room temperature for 12 h, concentrated, dissolved in ethyl acetate and washed with water. The organic extracts were dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography eluting with 10-30% of ethyl acetate in hexane. (1.2 g, yield 86%) MS (ESI^+) e/z: 348.2 $[M+1]^+$.

Step 4: *tert*-butyl cyclopentyl(3-(2-hydroxy-3-(isoindolin-2-yl)propoxy)benzyl)carbamate



[00354] To a solution of *tert*-butyl cyclopentyl(3-(oxiran-2-ylmethoxy)benzyl)carbamate (300 mg, 0.86 mmol) in EtOH (5 mL) was added isoindoline (113 mg, 0.95 mmol). The reaction mixture was heated under microwave conditions at 110 °C for 0.8 h. The mixture was concentrated and the crude product was used in the next step without further purification. (220 mg, yield 55%) MS (ESI^+) e/z: 467.3 $[M+1]^+$.

Step 5:1-(3-((cyclopentylamino)methyl)phenoxy)-3-(isoindolin-2-yl)propan-2-ol



[00355] To a solution of *tert*-butyl cyclopentyl(3-(2-hydroxy-3-(isoindolin-2-yl) propoxy) benzyl)carbamate (200 mg, 0.43 mmol) in ethyl acetate (10 mL) was added HCl/ethyl acetate (5 mL) at 0 °C. After 4 h, the reaction mixture was concentrated and purified by preparative HPLC purification. (90 mg, yield 57%) MS (ESI^+) e/z: 367.3 $[M+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.42-7.37 (m, 5H), 7.15-7.05 (m, 3H), 4.72-4.59 (m, 4H), 4.48-4.42 (m, 1H), 4.18 (s, 2H), 4.11-4.08 (m, 2H), 3.74-3.30 (m, 3H), 2.19-2.12 (m, 2H), 1.84-1.65 (m, 6H).

LC-MS conditions

Method A (LCMS-B (0-60AB_ELSD_2MIN))

[00356] Experiments performed on an Agilent 1200 HPLC (with a PDA detector and a ELSD detector) with Agilent 6100 MSD mass spectrometer using ESI as ionization source using an Xtimate TM-C18 30*2.1mm column and a 0.8ml/minute flow rate. Acquire Time: 2 min, Wavelength: UV220, Oven Temp.: 50 °C. The solvent system was a gradient starting with 100% water containing 0.038%TFA (solvent A) and 0% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 40% solvent A and 60% solvent B over the next 0.9 minutes . This was maintained for 0.6minutes before returning to 100% solvent A over the next 0.5 minute. Total run time was 2 min.

Method B (LCMS-C(10-80_AB))

[00357] Experiments performed on an SHIMADZU 20A HPLC (with a PDA detector) with SHIMADZU 2010EV MSD mass spectrometer using ESI as ionization source using an Xtimate TM-C18 30*2.1mm column and a 1.2ml/minute flow rate. The solvent system was a gradient starting with 90% water containing 0.038%TFA (solvent A) and 10% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 20% solvent A and 80% solvent B over the next 0.9 minutes . This was maintained for 0.6minutes before returning to 90% solvent A and 10% solvent B over the next 0.5 minute. Total run time was 2 min.

Method C (LCMS-E(5-95AB_220&254nm))

[00358] Experiments performed on an SHIMADZU 20A HPLC (with a PDA detector) with SHIMADZU 2010EV MSD mass spectrometer using ESI as ionization source using an Merk RP-18e 2*25mm column and a 1.5ml/minute flow rate. The solvent system was a gradient starting with 95% water containing 0.038%TFA (solvent A) and 5% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B over the next 0.7 minutes . This was maintained for 0.4minutes before returning to 95% solvent A and 5% solvent B over the next 0.4 minute. Total run time was 1.5 min.

Method D (LCMS-A(0-30_AB))

[00359] Experiments performed on an SHIMADZU 20A HPLC (with a PDA detector) with SHIMADZU 2010EV MSD mass spectrometer using ESI as ionization source using an

Xtimate TM-C18 30*2.1mm column and a 1.2ml/minute flow rate. The solvent system was a gradient starting with 100% water containing 0.038%TFA (solvent A) and 0% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 70% solvent A and 30% solvent B over the next 0.9 minutes . This was maintained for 0.6minutes before returning to 100% solvent A over the next 0.5 minute. Total run time was 2 min.

==========

General HPLC conditions (Acidic)

Mobile phase A: 4L H_2O\1.5ml TFA; Mobile phase B: 4L ACN\0.75ml TFA

Column: HPLC-D: Innovation C18 UPLC Column 2.1X30mm, 2.6um

HPLC-E: Xtimate C18 2.1*30mm*3um

HPLC-H: Innovation C18 UPLC Column 2.1X30mm, 2.6um

Column temperature: 50 °C; Wavelength: 220nm&254nm&215nm

General HPLC conditions (Basic)

Mobile phase A: 4L H_2O\2ml NH_4OH; Mobile phase B: Acetonitrile

Column: HPLC-B: XBridge C18 2.1*50mm,5um

HPLC-C: Xbridge shield RP18 2.1*50mm,5u

Column temperature: 30 °C; Wavelength：220nm&254nm&215nm

General HPLC conditions (Neutral)

Mobile phase A: H_2O; Mobile phase B: Acetonitrile

Column: HPLC-B: XBridge C18 2.1*50mm,5um

HPLC-C: Xbridge shield RP18 2.1*50mm, 5um

Column temperature: 30℃; Wavelength：220nm&254nm&215nm

Method A (0-30AB_6MIN)

Flow Rate: 0.8ml/min

Gradient：0%B to 30%B in 4.2min, holding 30%B for 1min, 30%B to 0%B in 0.01min, holding 0%B for 1.09min and then end.

Method B (0-60AB_6MIN)

Flow Rate: 0.8ml/min

Gradient : 0%B to 60%B in 4.2min, holding 60%B for 1min, 60%B to 0%B in 0.01min, holding 0%B for 1.09min and then end.

Method C (10-80AB_6MIN)

Flow Rate: 0.8ml/min

Gradient : 10%B to 80%B in 4.2min, holding 80%B for 1min, 80%B to 10%B in 0.01min, holding 10%B for 1.09min and then end.

Chiral HPLC conditions :

Method A (OJ-H) :

Column: Chiralcel OJ-H 250×4.6mm I.D., 5um

Mobile phase: A/B=90/10, A:Hexane with 0.1%DEA ,B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Method B (OD-H):

Column: Chiralcel OD-H 250×4.6mm I.D., 5um

Mobile phase: A/B=90/10, A: Hexane with 0.1%DEA ,B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Method C (AD-H):

Column: Chiralpak AD-H 250×4.6mm I.D., 5um

Mobile phase: A/B=90/10, A: Hexane with 0.1%DEA, B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Method D (AS-H):

Column: Chiralpak OJ-H 250×4.6mm I.D., 5um

Mobile phase: A/B=90/10, A: Hexane with 0.1%DEA, B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Biological Assays

PRMT5 Biochemical Assay

[00360] General Materials. S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, KCl, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ^{3}H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[00361] Substrates. Peptide representative of human histone H4 residues 1-15 was synthesized with a C-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was high high-perfomance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Ac-SGRGKGGKGLGKGGA[K-Biot]-amide (SEQ ID NO.:3).

[00362] Molecular Biology: Full-length human PRMT5 (NM_006109.3) transcript variant 1 clone was amplified from a fetal brain cDNA library, incorporating flanking 5' sequence encoding a FLAG tag (MDYKDDDDK) (SEQ ID NO.:4) fused directly to Ala 2 of PRMT5. Full-length human MEP50 (NM_024102) clone was amplified from a human testis cDNA library incorporating a 5' sequence encoding a 6-histidine tag (MHHHHHH) (SEQ ID NO.:5) fused directly to Arg 2 of MEP50. The amplified genes were sublconed into pENTR/D/TEV (Life Technologies) and subsequently transferred by Gateway^{TM} *att*L x *att*R recombination to pDEST8 baculvirus expression vector (Life Technologies).

[00363] Protein Expression. Recombinant baculovirus and Baculovirus-Infected Insect Cells (BIIC) were generated according to Bac-to-Bac kit instructions (Life Technologies) and Wasilko, 2006, respectively. Protein over-expression was accomplished by infecting exponentially growing *Spodoptera frugiperda* (SF9) cell culture at 1.2X10^{6}cell/ml with a 5000 fold dilution of BIIC stock. Infections were carried out at 27^{o}C for 72 hours, harvested by centrifugation, and stored at -80^{o}C for purification.

[00364] Protein Purification. Expressed full-length human Flag-PRMT5/6His-MeP50 protein complex was purified from cell paste by NiNTA agarose affinity chromatography

after a five hour equilibration of the resin with buffer containing 50mM Tris-HCL, pH 8.0, 25 mM NaCl, and 1mM TCEP at 4°C, to minimize the adsorption of tubulin impurity by the resin. Flag-PRMT5/6His-MeP50 was eluted with 300mM Imidazole in the same buffer. The purity of recovered protein was 87%. Reference: Wasilko, D.J. and S.E. Lee: "TIPS: titerless infected-cells preservation and scale-up" Bioprocess J., 5 (2006), pp. 29–32.

[00365] Predicted Translations:

Flag-PRMT5 (SEQ ID NO.:6)

MDYKDDDDKA AMAVGGAGGS RVSSGRDLNC VPEIADTLGA VAKQGFDFLC MPVFHPRFKR
EFIQEPAKNR PGPQTRSDLL LSGRDWNTLI VGKLSPWIRP DSKVEKIRRN SEAAMLQELN
FGAYLGLPAF LLPLNQEDNT NLARVLTNHI HTGHHSSMFW MRVPLVAPED LRDDIIENAP
TTHTEEYSGE EKTWMWWHNF RTLCDYSKRI AVALEIGADL PSNHVIDRWL GEPIKAAILP
TSIFLTNKKG FPVLSKMHQR LIFRLLKLEV QFIITGTNHH SEKEFCSYLQ YLEYLSQNRP
PPNAYELFAK GYEDYLQSPL QPLMDNLESQ TYEVFEKDPI KYSQYQQAIY KCLLDRVPEE
EKDTNVQVLM VLGAGRGPLV NASLRAAKQA DRRIKLYAVE KNPNAVVTLE NWQFEEWGSQ
VTVVSSDMRE WVAPEKADII VSELLGSFAD NELSPECLDG AQHFLKDDGV SIPGEYTSFL
APISSSKLYN EVRACREKDR DPEAQFEMPY VVRLHNFHQL SAPQPCFTFS HPNRDPMIDN
NRYCTLEFPV EVNTVLHGFA GYFETVLYQD ITLSIRPETH SPGMFSWFPI LFPIKQPITV
REGQTICVRF WRCSNSKKVW YEWAVTAPVC SAIHNPTGRS YTIG L

6His-MEP50 (SEQ ID NO.:7)

MHHHHHHRKE TPPPLVPPAA REWNLPPNAP ACMERQLEAA RYRSDGALLL GASSLSGRCW
AGSLWLFKDP CAAPNEGFCS AGVQTEAGVA DLTWVGERGI LVASDSGAVE LWELDENETL
IVSKFCKYEH DDIVSTVSVL SSGTQAVSGS KDICIKVWDL AQQVVLSSYR AHAAQVTCVA
ASPHKDSVFL SCSEDNRILL WDTRCPKPAS QIGCSAPGYL PTSLAWHPQQ SEVFVFGDEN
GTVSLVDTKS TSCVLSSAVH SQCVTGLVFS PHSVPFLASL SEDCSLAVLD SSLSELFRSQ
AHRDFVRDAT WSPLNHSLLT TVGWDHQVVH HVVPTEPLPA PGPASVTE

[00366] General Procedure for PRMT5/MEP50 Enzyme Assays on Peptide Substrates. The assays were all performed in a buffer consisting of 20mM Bicine (pH=7.6), 1mM TCEP, 0.005% BSG, and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platemate Plus outfitted with a 384-channel head (Thermo Scientific). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of PRMT5/MEP50, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the

PRMT5/MEP50 enzyme and the peptide was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT5/MEP50 for 30 min at 25 degrees Celsius, then a cocktail (10ul) containing ^{3}H-SAM was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: PRMT5/MEP50 was 4nM, ^{3}H-SAM was 75nM, peptide was 40nM, SAH in the minimum signal control wells was 100uM, and the DMSO concentration was 1%. The assays were stopped by the addition of non-radioactive SAM (10ul) to a final concentration of 600uM, which dilutes the ^{3}H-SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed three times with 0.1%Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^{3}H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\%\ inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}}\right) \times 100$$

Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{(1 + (\frac{X}{IC_{50}})^{Hill\ Coefficient}}$$

Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

Z-138 Methylation Assay

[00367] Z-138 suspension cells were purchased from ATCC (American Type Culture Collection, Manassas, VA). RPMI/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum, and D-PBS were purchased from Life Technologies, Grand Island, NY, USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, and Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, NE, USA. Symmetric di-methyl arginine antibody was purchased from EMD Millipore, Billerica, MA, USA. 16% Paraformaldehyde was purchased from Electron Microscopy Sciences, Hatfield, PA, USA.

[00368] Z-138 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37 °C under 5% CO_2.

[00369] Cell Treatment, In Cell Western (ICW) for detection of Symmetric di-Methyl Arginine and DNA content. Z-138 cells were seeded in assay medium at a concentration of 50,000 cells per mL to a 384-well cell culture plate with 50 µL per well. Compound (100 nL) from 384 well source plates was added directly to 384 well cell plate. Plates were incubated at 37°C, 5% CO_2 for 96 hours. After four days of incubation, 40 µL of cells from incubated plates were added to poly-D-lysine coated 384 well culture plates (BD Biosciences 356697). Plates were incubated at room temperature for 30 minutes then incubated at 37°C, 5% CO_2 for 5 hours. After the incubation, 40 µL per well of 8% paraformaldehyde in PBS (16% paraformaldahyde was diluted to 8% in PBS) was added to each plate and incubated for 30 minutes. Plates were transferred to a Biotek 405 plate washer and washed 5 times with 100 µL per well of wash buffer (1X PBS with 0.1% Triton X-100 (v/v)). Next 30 µL per well of Odyssey blocking buffer were added to each plate and incubated 1 hour at room temperature. Blocking buffer was removed and 20 µL per well of primary antibody was added (symmetric di-methyl arginine diluted 1:100 in Odyssey buffer with 0.1% Tween 20 (v/v)) and plates were incubated overnight (16 hours) at 4°C. Plates were washed 5 times with 100 µL per well of wash buffer. Next 20 µL per well of secondary antibody was added (1:200 800CW goat anti-rabbit IgG (H+L) antibody, 1:1000 DRAQ5 (Biostatus limited) in Odyssey buffer with 0.1% Tween 20 (v/v)) and incubated for 1 hour at room temperature. The plates were washed 5 times with 100 µL per well wash buffer then 1 time with 100 µL per well of water. Plates were allowed to dry at room temperature then imaged on the Licor Odyssey machine which measures integrated intensity at 700nm and 800nm wavelengths. Both 700 and 800 channels were scanned.

[00370] **Calculations:** First, the ratio for each well was determined by:

$$\left(\frac{\text{symmetric di-methyl Arginine 800nm value}}{\text{DRAQ5 700nm value}}\right)$$

[00371] Each plate included fourteen control wells of DMSO only treatment (minimum inhibition) as well as fourteen control wells for maximum inhibition treated with 3 μM of a reference compound (Background wells). The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Reference compound was serially diluted three-fold in DMSO for a total of nine test concentrations, beginning at 3 μM. Percent inhibition was determined and IC_{50} curves were generated using triplicate wells per concentration of compound.

Percent Inhibition = 100-

$$\left(\left(\frac{\text{(Individual Test Sample Ratio)}-\text{(Background Avg Ratio)}}{\text{(Minimum Inhibition Ratio)}-\text{(Background Average Ratio)}}\right)*100\right)$$

Z-138 Proliferation Assay

[00372] Z-138 suspension cells were purchased from ATCC (American Type Culture Collection, Manassas, VA). RPMI/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum were purchased from Life Technologies, Grand Island, NY, USA. V-bottom polypropylene 384-well plates were purchased from Greiner Bio-One, Monroe, NC, USA. Cell culture 384-well white opaque plates were purchased from Perkin Elmer, Waltham, MA, USA. Cell-Titer Glo® was purchased from Promega Corporation, Madison, WI, USA. SpectraMax M5 plate reader was purchased from Molecular Devices LLC, Sunnyvale, CA, USA.

[00373] Z-138 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and cultured at 37°C under 5% CO_2. Under assay conditions, cells were incubated in assay medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37°C under 5% CO_2.

[00374] For the assessment of the effect of compounds on the proliferation of the Z-138 cell line, exponentially growing cells were plated in 384-well white opaque plates at a density of 10,000 cells/ml in a final volume of 50 μl of assay medium. A compound source plate was prepared by performing triplicate nine-point 3-fold serial dilutions in DMSO, beginning at 10 mM (final top concentration of compound in the assay was 20 μM and the DMSO was 0.2%).

A 100 nL aliquot from the compound stock plate was added to its respective well in the cell plate. The 100% inhibition control consisted of cells treated with 200 nM final concentration of staurosporine and the 0% inhibition control consisted of DMSO treated cells. After addition of compounds, assay plates were incubated for 5 days at 37ºC, 5% CO_2, relative humidity > 90%.

Cell viability was measured by quantitation of ATP present in the cell cultures, adding 35 µl of Cell Titer Glo® reagent to the cell plates. Luminescence was read in the SpectraMax M5 microplate reader. The concentration of compound inhibiting cell viability by 50% was determined using a 4-parametric fit of the normalized dose response curves.

[00375] Results for certain compounds described herein are shown in **Table 2**.

Table 2. Biological Assay Results

Cmpd No	Biochemical IC_{50}	ICW EC_{50}	Proliferation EC_{50}
1	C	--	--
2	C	--	--
3	C	--	--
4	A	B	C
5	A	B	C
6	*	--	--
7	B	B	**
8	B	B	--
9	C	--	--
10	B	B	**
11	B	C	--
12	B	B	--
13	B	C	**
14	D	--	--
15	A	B	C
16	C	--	--
17	C	--	--
18	C	--	--
19	B	C	**
20	C	--	D

Table 2. Biological Assay Results			
Cmpd No	**Biochemical IC_{50}**	**ICW EC_{50}**	**Proliferation EC_{50}**
21	B	B	**
22	B	C	--
23	A	A	B
24	A	--	--
25	D	--	--
26	B	B	**
27	B	C	**
28	A	B	D
29	A	B	C
30	A	B	C
31	--	C	--
32	--	C	**
33	--	B	**
34	--	--	--
35	B	F	**
36	B	B	D
37	B	B	**
38	A	A	C
39	A	--	B
40	A	A	B
41	C	--	D
42	*	F	G
43	*	F	G
44	*	F	G
45	*	F	G
46	*	F	G
47	C	F	G
48	*	F	G
49	C	F	G
50	*	F	G

Table 2. Biological Assay Results			
Cmpd No	**Biochemical IC_{50}**	**ICW EC_{50}**	**Proliferation EC_{50}**
51	*	--	--
52	*	--	--
53	C	F	--

For **Table 2**, "A" indicates an IC_{50} or EC_{50} < 0.100 μM, "B" indicates an IC_{50} or EC_{50} of 0.101 – 1.000 μM, "C" indicates an IC_{50} or EC_{50} of 1.001 – 10.000 μM, "D" indicates an IC_{50} or EC_{50} of 10.001 – 50 μM, and "E" indicates an IC_{50} or EC_{50} > 50 μM, "--" indicates no data, "F" indicates an IC_{50} or EC_{50} > 1 μM, "G" indicates an IC_{50} or EC_{50} > 5 μM, "*" indicates an IC_{50} or EC_{50} > 10 μM, "**" indicates an IC_{50} or EC_{50} > 20 μM.

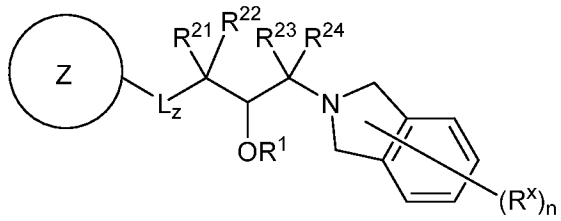
Other Embodiments

[00376] The foregoing has been a description of certain non–limiting embodiments of the invention. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

What is claimed is:

Claims

1. A compound of Formula (**I**):



I

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L_z is a linker;

Ring Z is an optionally substituted, monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{21}, R^{22}, R^{23}, and R^{24} are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

wherein, and unless otherwise specified,

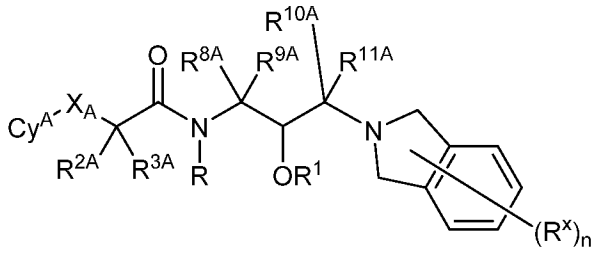
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

carbocyclyl or carbocyclic refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms in the non–aromatic ring system;

aryl refers to a radical of a monocyclic or polycyclic aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

2. The compound of claim 1 of Formula ($\mathbf{I^A}$):



$\mathbf{I^A}$

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

X_A is a bond, –O–, –N(R)–, $–CR^{4A}R^{5A}–$, $-O-CR^{4A}R^{5A}$, $-N(R)-CR^{4A}R^{5A}-$, $-O-CR^{4A}R^{5A}-O-$, $-N(R)-CR^{4A}R^{5A}-O$, $-N(R)-CR^{4A}R^{5A}-N(R)-$, $-O-CR^{4A}R^{5A}-N(R)-$, $-CR^{4A}R^{5A}-O-$, $-CR^{4A}R^{5A}-N(R)-$, $-O-CR^{4A}R^{5A}-CR^{6A}R^{7A}-$, $-N(R)-CR^{4A}R^{5A}-CR^{6A}R^{7A}-$, $-CR^{6A}R^{7A}-CR^{4A}R^{5A}-O-$, $-CR^{6A}R^{7A}-CR^{4A}R^{5A}-N(R)-$, or $–CR^{6A}R^{7A}-CR^{4A}R^{5A}–$;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

R^{2A} and R^{3A} are independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$; or R^{2A} and R^{3A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^{4A} and R^{5A} are independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$; or R^{4A} and R^{5A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

R^{6A} and R^{7A} are independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$; or R^{6A} and R^{7A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^{8A}, R^{9A}, R^{10A}, and R^{11A} are independently hydrogen, halo, or optionally substituted aliphatic;

Cy^A is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups;

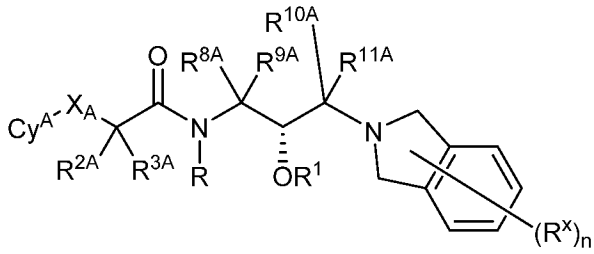
each R^y is independently selected from the group consisting of halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, or -$SO_2N(R^B)_2$;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

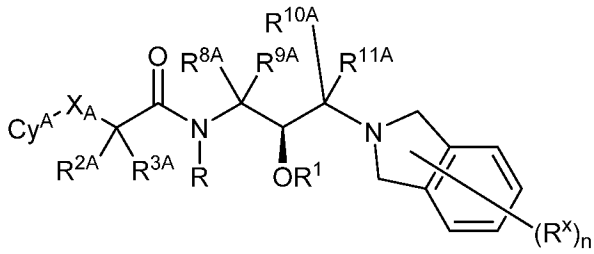
3. The compound of claim 2, wherein the compound is of Formula (**I^A-a**):



I^A-a

or a pharmaceutically acceptable salt thereof.

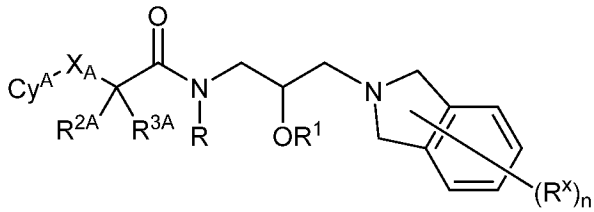
4. The compound of claim 2, wherein the compound is of Formula (**I^A-b**):



I^A-b

or a pharmaceutically acceptable salt thereof.

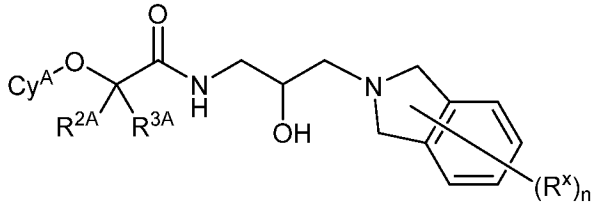
5. The compound of claim 2, wherein the compound is of Formula (**I^A-c**):



I^A-c

or a pharmaceutically acceptable salt thereof.

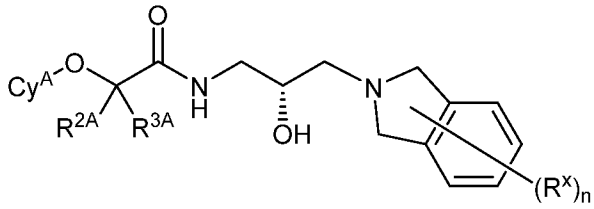
6. The compound of claim 2, wherein the compound is of Formula (**II^A**):



II^A

or a pharmaceutically acceptable salt thereof.

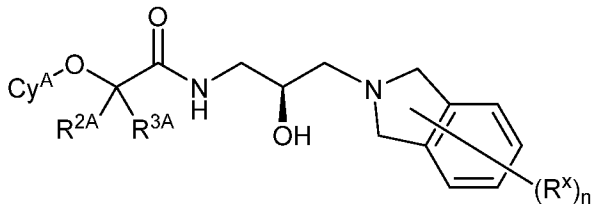
7. The compound of claim 6, wherein the compound is of Formula (**II^A-a**):



II^A-a

or a pharmaceutically acceptable salt thereof.

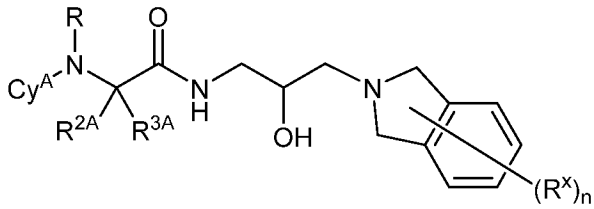
8. The compound of claim 6, wherein the compound is of Formula (**II^A-b**):



II^A-b

or a pharmaceutically acceptable salt thereof.

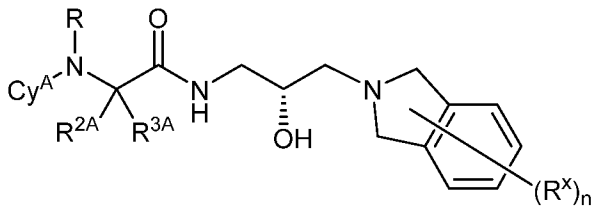
9. The compound of claim 2, wherein the compound is of Formula (**III^A**):



III^A

or a pharmaceutically acceptable salt thereof.

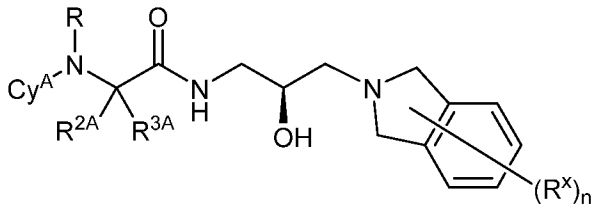
10. The compound of claim 9, wherein the compound is of Formula (**III^A-a**):



III^A-a

or a pharmaceutically acceptable salt thereof.

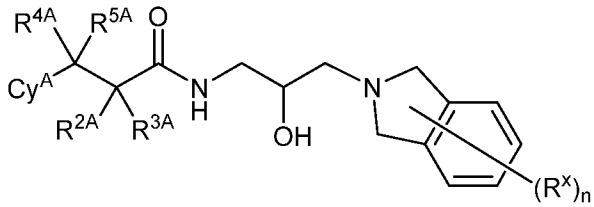
11. The compound of claim 9, wherein the compound is of Formula (**III^A-b**):



III^A-b

or a pharmaceutically acceptable salt thereof.

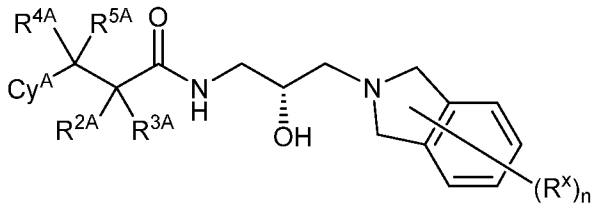
12. The compound of claim 2, wherein the compound is of Formula (**IV^A**):



IV^A

or a pharmaceutically acceptable salt thereof.

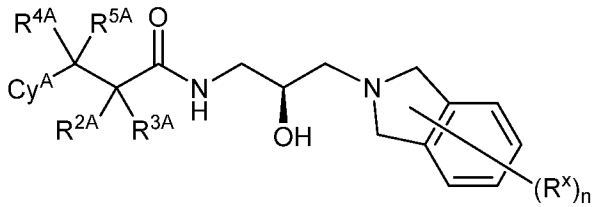
13. The compound of claim 12, wherein the compound is of Formula (**IV^A-a**):



IV^A-a

or a pharmaceutically acceptable salt thereof.

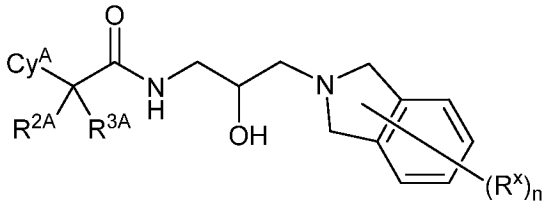
14. The compound of claim 12, wherein the compound is of Formula (**IV^A-b**):



IV^A-b

or a pharmaceutically acceptable salt thereof.

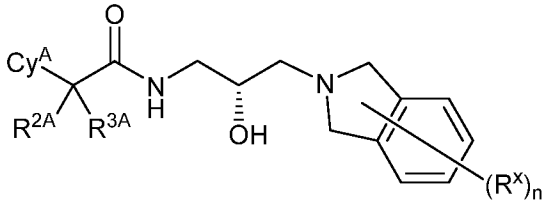
15. The compound of claim 2, wherein the compound is of Formula (**V^A**):



$\mathbf{V^A}$

or a pharmaceutically acceptable salt thereof.

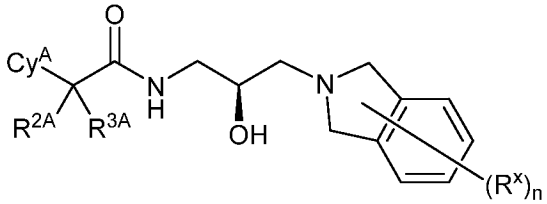
16. The compound of claim 15, wherein the compound is of Formula ($\mathbf{V^A}$-**a**):



$\mathbf{V^A}$-**a**

or a pharmaceutically acceptable salt thereof.

17. The compound of claim 15, wherein the compound is of Formula ($\mathbf{V^A}$-**b**):



$\mathbf{V^A}$-**b**

or a pharmaceutically acceptable salt thereof.

18. The compound of any one of claims 2-5, wherein R^1 is hydrogen.

19. The compound of any one of claims 2-18, wherein n is 0.

20. The compound of any one of claims 2-18, wherein n is 1.

21. The compound of any one of claims 2-18, wherein n is 2.

22. The compound of any one of claims 2-21, wherein R^{2A} and R^{3A} are each hydrogen.

23. The compound of any one of claims 2-21, wherein R^{2A} is hydrogen and R^{3A} is not hydrogen.

24. The compound of claim 23, wherein R^{3A} is optionally substituted aliphatic.

25. The compound of claim 24, wherein R^{3A} is C_{1-6} alkyl.

26. The compound of claim 25, wherein R^{3A} is methyl.

27. The compound of any one of claims 2-21, wherein R^{2A} and R^{3A} are not hydrogen.

28. The compound of claim 27, wherein R^{2A} and R^{3A} are optionally substituted aliphatic.

29. The compound of claim 28, wherein R^{2A} and R^{3A} are methyl.

30. The compound of any one of claims 2-5, wherein R is hydrogen.

31. The compound of any one of claims 12-14, wherein R^{4A} and R^{5A} are each hydrogen.

32. The compound of any one of claims 2-31, wherein Cy^A is phenyl substituted with 0, 1, 2, 3, or 4 R^y groups.

33. The compound of claim 32, wherein Cy^A is phenyl substituted with 1 or 2 R^y groups.

34. The compound of claim 33, wherein Cy^A is phenyl substituted with one R^y group.

35. The compound of any one of claims 2-31, wherein Cy^A is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with 0, 1, 2, 3, or 4 R^y groups.

36. The compound of claim 35, wherein Cy^A is unsubstituted.

37. The compound of claim 35, wherein Cy^A is substituted with 1 or 2 R^y groups.

38. The compound of claim 37, wherein Cy^A is substituted with one R^y group.

39. The compound of any one of claims 2-31, wherein Cy^A is a bicyclic saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups.

40. The compound of claim 39, wherein Cy^A is an 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups.

41. The compound of claim 40, wherein Cy^A is a 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups.

42. The compound of claim 40, wherein Cy^A is a 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups.

43. The compound of claim 39, wherein Cy^A is selected from the group consisting of quinoline, benzimidazole, benzopyrazole, quinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, naphthalene, tetrahydronaphthalene, 2,3-dihydrobenzo[*b*][1,4]dioxine, isoindole, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, and quinoxalin-2(1*H*)-one, wherein Cy^A is substituted with 0, 1, 2, 3, or 4 R^y groups.

44. The compound of any one of claims 39-43, wherein Cy^A is unsubstituted.

45. The compound of any one of claims 39-43, wherein Cy^A is substituted with 1 or 2 R^y groups.

46. The compound of claim 45, wherein Cy^A is substituted with one R^y group.

47. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is halo.

48. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is -CN.

49. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $-OR^A$.

50. The compound of claim 49, wherein at least one R^y is $–OCH_3$.

51. The compound of claim 49, wherein R^A is optionally substituted aliphatic.

52. The compound of claim 51, wherein at least one R^y is $–OCH_2CH_2N(CH_3)_2$.

53. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $–N(R^B)_2$.

54. The compound of claim 53, wherein at least one R^y is $–NHR^B$.

55. The compound of claim 53, wherein at least one R^y is $–N(CH_3)_2$.

56. The compound of claim 54, wherein at least one R^y is $–NHCH_3$.

57. The compound of claim 53, wherein at least one R^y is $–NH_2$.

58. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is optionally substituted aliphatic.

59. The compound of claim 58, wherein at least one R^y is C_{1-6} alkyl.

60. The compound of claim 59, wherein at least one R^y is methyl.

61. The compound of claim 58, wherein at least one R^y is $–CH_2$-heterocyclyl.

62. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $–C(O)N(R^B)_2$.

63. The compound of claim 62, wherein at least one R^y is $–C(O)NHR^B$.

64. The compound of claim 63, wherein at least one R^y is $–C(O)NH_2$.

65. The compound of claim 62, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl.

66. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $–SO_2R^A$.

67. The compound of claim 66, wherein at least one R^y is $–SO_2CH_3$.

68. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $–N(R^B)C(O)R^A$.

69. The compound of claim 68, wherein at least one R^y is $–NHC(O)R^A$.

70. The compound of claim 69, wherein at least one R^y is $–NHC(O)CH_3$.

71. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $–N(R^B)SO_2R^A$.

72. The compound of claim 71, wherein at least one R^y is $–NHSO_2R^A$.

73. The compound of claim 72, wherein at least one R^y is $–NHSO_2CH_3$.

74. The compound of claim 71, wherein at least one R^y is $–N(CH_3)SO_2R^A$.

75. The compound of claim 71, wherein at least one R^y is $–N(CH_3)SO_2CH_3$.

76. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is an optionally substituted 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

77. The compound of claim 76, wherein at least one R^y is an optionally substituted 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur.

78. The compound of claim 77, wherein at least one R^y is pyrroldinyl, hydroxypyrrolidinyl, or methylpyrrolidinyl.

79. The compound of claim 76, wherein at least one R^y is an optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

80. The compound of claim 76, wherein at least one R^y is morpholinyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, piperazinyl, methylpiperazinyl, acetylpiperazinyl, methylsulfonylpiperazinyl, aziridinyl, or methylaziridinyl.

81. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

82. The compound of claim 81, wherein at least one R^y is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

83. The compound of claim 82, wherein at least one R^y is pyrazolyl, methylpyrazolyl, imidazolyl, or methylimidazolyl.

84. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $-SO_2N(R^B)_2$.

85. The compound of claim 84, wherein at least one R^y is $-SO_2NHR^B$.

86. The compound of claim 84, wherein at least one R^y is $–SO_2NH_2$.

87. The compound of claim 84, wherein neither R^B is hydrogen.

88. The compound of claim 84, wherein at least one R^y is $–SO_2N(CH_3)_2$.

89. The compound of claim 84, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl.

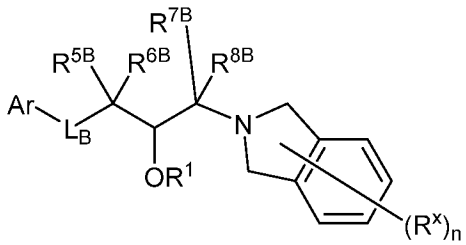
90. The compound any one of claims 32-35, 37-43, 45, and 46, wherein at least one R^y is $–C(O)R^A$.

91. The compound of claim 90, wherein R^A is optionally substituted aliphatic.

92. The compound of claim 91, wherein R^A is C_{1-6} alkyl.

93. The compound of claim 92, wherein at least one R^y is $–C(O)CH_3$.

94. The compound of claim 1 of Formula ($\mathbf{I^B}$):



$\mathbf{I^B}$

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is hydrogen, R^z, or $–C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L_B is $–N(R)C(O)–$, $–C(O)N(R)–$, $–N(R)C(O)N(R)–$,$–N(R)C(O)O–$, or $–OC(O)N(R)–$;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

Ar is a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits;

each R^y is independently selected from the group consisting of halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, or -$SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

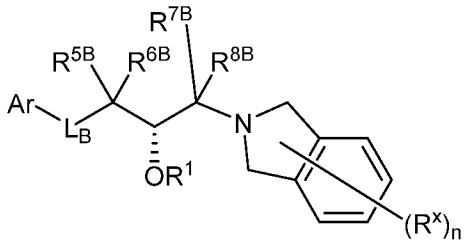
R^{5B}, R^{6B}, R^{7B}, and R^{8B} are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

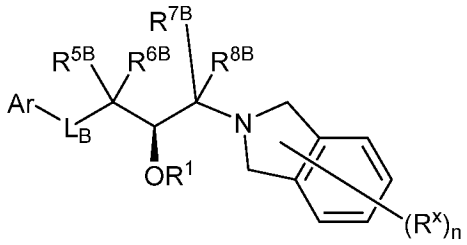
95. The compound of claim 94, wherein the compound is of Formula (**I^B-a**):



I^B-a

or a pharmaceutically acceptable salt thereof.

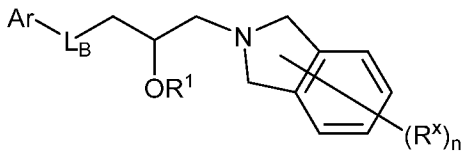
96. The compound of claim 94, wherein the compound is of Formula (**I^B-b**):



I^B-b

or a pharmaceutically acceptable salt thereof.

97. The compound of claim 94, wherein the compound is of Formula (**I^B-c**):



I^B-c

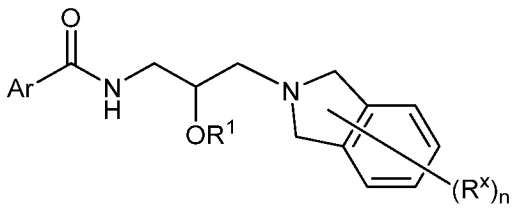
or a pharmaceutically acceptable salt thereof.

98. The compound of any one of claims 94-97, wherein L_B is –C(O)N(R)–.

99. The compound of any one of claims 94-97, wherein L_B is –NHC(O)NH-.

100. The compound of any one of claims 94-97, wherein L_B is –OC(O)NH-.

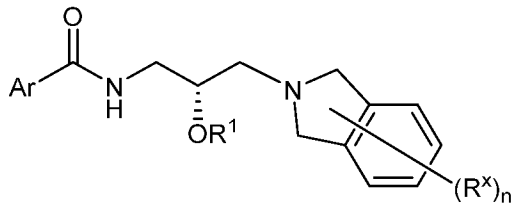
101. The compound of claim 94, wherein the compound is of Formula (**II^B**):



II^B

or a pharmaceutically acceptable salt thereof.

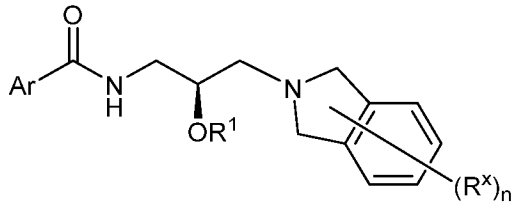
102. The compound of claim 101, wherein the compound is of Formula (**II^B-a**):



II^B-a

or a pharmaceutically acceptable salt thereof.

103. The compound of claim 101, wherein the compound is of Formula (**II^B-b**):



II^B-b

or a pharmaceutically acceptable salt thereof.

104. The compound of any one of claims 94-103, wherein R^1 is hydrogen.

105. The compound of any one of claims 94-103, wherein n is 0.

106. The compound of any one of claims 94-103, wherein n is 1.

107. The compound of any one of claims 94-103, wherein n is 2.

108. The compound of any one of claims 94-107, wherein Ar is phenyl.

109. The compound of any one of claims 94-107, wherein Ar is heteroaryl.

110. The compound of claim 109, wherein Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

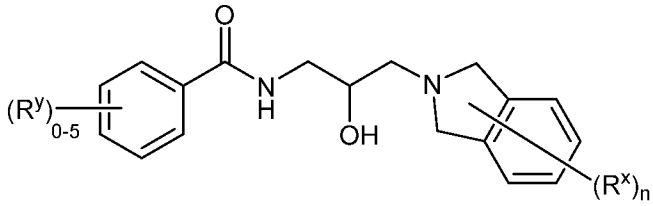
111. The compound of claim 110, wherein Ar is pyridyl.

112. The compound of any one of claims 94-111, wherein Ar is unsubstituted.

113. The compound of any one of claims 94-111, wherein Ar is substituted with 1 or 2 R^y groups.

114. The compound of claim 113, wherein Ar is substituted with one R^y group.

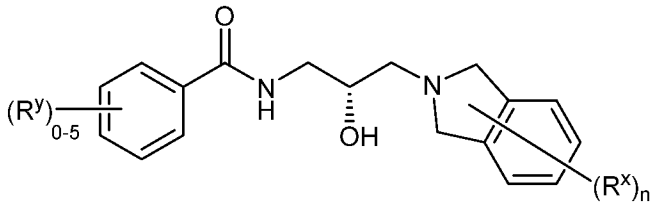
115. The compound of claim 94, wherein the compound is of Formula (**III^B**):



III^B

or a pharmaceutically acceptable salt thereof.

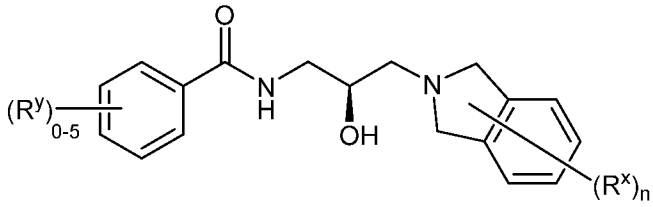
116. The compound of claim 115, wherein the compound is of Formula (**III^B-a**):



III^B-a

or a pharmaceutically acceptable salt thereof.

117. The compound of claim 115, wherein the compound is of Formula (**III^B-b**):



III^B-b

or a pharmaceutically acceptable salt thereof.

118. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is heteroaryl or heterocyclyl.

119. The compound of claim 118, wherein at least one R^y is 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

120. The compound of claim 119, wherein at least one R^y is a 6-membered heteroaryl having 1-3 nitrogens.

121. The compound of claim 119, wherein at least one R^y is pyridyl.

122. The compound of claim 118, wherein at least one R^y is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

123. The compound of claim 122, wherein at least one R^y is optionally substituted pyrazole.

124. The compound of claim 122, wherein at least one R^y is pyrrole.

125. The compound of claim 118, wherein at least one R^y is a 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

126. The compound of claim 125, wherein at least one R^y is a 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur.

127. The compound of claim 126, wherein at least one R^y is optionally substituted pyrrolidine.

128. The compound of claim 125, wherein at least one R^y is a 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

129. The compound of claim 128, wherein at least one R^y is optionally substituted piperazine.

130. The compound of claim 128, wherein at least one R^y is morpholine.

131. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is optionally substituted aliphatic.

132. The compound of claim 131, wherein at least one R^y is optionally substituted C_{1-6} alkyl.

133. The compound of claim 132, wherein at least one R^y is C_{1-6} alkyl substituted with an aryl, heteroaryl, or heterocyclyl.

134. The compound of claim 133, wherein at least one R^y is $–CH_2$-aryl, $-CH_2$-heteroaryl, or $–CH_2$-heterocyclyl.

135. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is $-N(R^B)_2$.

136. The compound of claim 135, wherein at least one R^y is $–NHR^B$.

137. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is $-SO_2N(R^B)_2$.

138. The compound of claim 137, wherein at least one R^y is $–SO_2NHR^B$.

139. The compound of claim 138, wherein at least one R^y is $–SO_2NH_2$.

140. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is $-C(O)N(R^B)_2$.

141. The compound of claim 140, wherein at least one R^y is $–C(O)NHR^B$.

142. The compound of claim 141, wherein at least one R^y is $–C(O)NH_2$.

143. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is $-NR^BC(O)R^A$.

144. The compound of claim 143, wherein at least one R^y is $–NHC(O)R^A$.

145. The compound of claim 144, wherein at least one R^y is $–NHC(O)CH_3$.

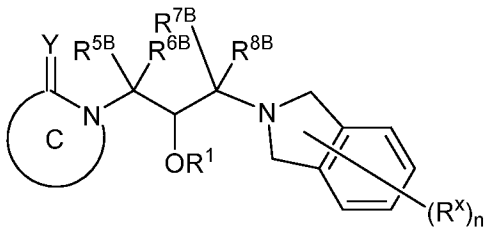
146. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is $-NR^BSO_2R^A$.

147. The compound of claim 146, wherein at least one R^y is $–NHSO_2R^A$.

148. The compound of claim 147, wherein at least one R^y is $–NHSO_2CH_3$.

149. The compound of any one of claims 94-111 and 113-117, wherein at least one R^y is $–OR^A$.

150. The compound of claim 1 of Formula ($\mathbf{I^C}$):



$\mathbf{I^C}$

or a pharmaceutically acceptable salt thereof,

wherein

Ring C is an optionally substituted, 5- to 12-membered, monocyclic or bicyclic, heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^1 is hydrogen, R^z, or $–C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

Y is O or S;

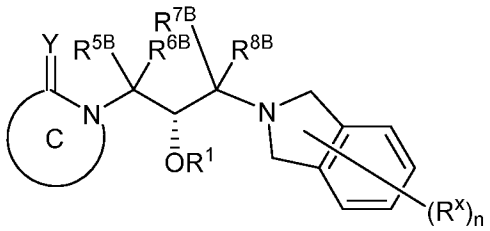
R^{5B}, R^{6B}, R^{7B}, and R^{8B} are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

R' is hydrogen or optionally substituted aliphatic; and

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

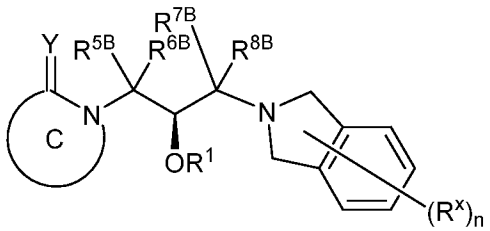
151. The compound of claim 150, wherein the compound is of Formula (I^C-a):



I^C-a

or a pharmaceutically acceptable salt thereof.

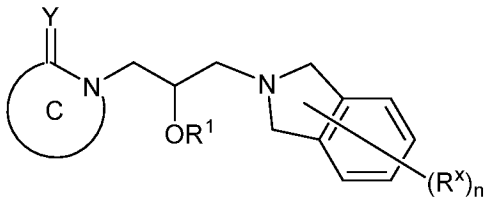
152. The compound of claim 150, wherein the compound is of Formula (I^C-b):



I^C-b

or a pharmaceutically acceptable salt thereof.

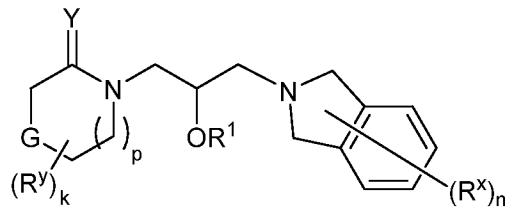
153. The compound of claim 150, wherein the compound is of Formula (I^C-c):



I^C-c

or a pharmaceutically acceptable salt thereof.

154. The compound of claim 150, wherein the compound is of Formula (II^C):



II^C

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, and n are as described herein,

G is NR^{2C}, $CR^{3C}R^{4C}$, O or S;

R^{2C} is selected from the group consisting of optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-C(O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(=NR^B)R^A$, $-C(=NR^B)N(R^B)_2$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-S(=O)R^A$, $-SO_2R^A$, and $-SO_2N(R^B)_2$;

R^{3C} is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

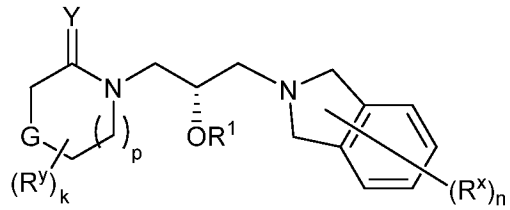
R^{4C} is selected from the group consisting of hydrogen, halo, or optionally substituted aliphatic;

each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$, or two adjacent R^y groups may be taken together with their intervening atoms to form a saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

p is 0, 1, or 2; and

k is 0, 1, 2, 3, or 4.

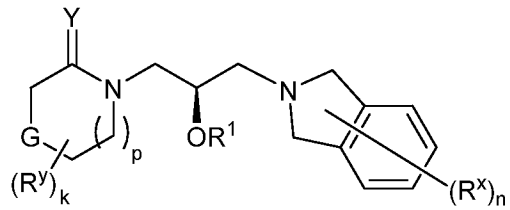
155. The compound of claim 154, wherein the compound is of Formula (**II^C-a**):



II^C-a

or a pharmaceutically acceptable salt thereof.

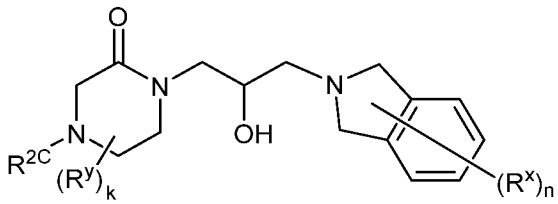
156. The compound of claim 154, wherein the compound is of Formula (**II^C-b**):



II^C-b

or a pharmaceutically acceptable salt thereof.

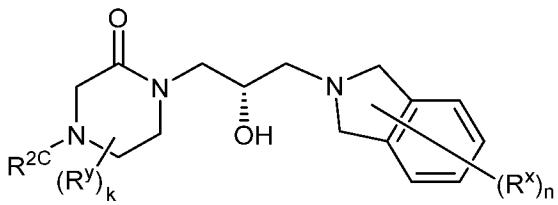
157. The compound of claim 154, wherein the compound is of Formula (**III^C**):



III^C

or a pharmaceutically acceptable salt thereof.

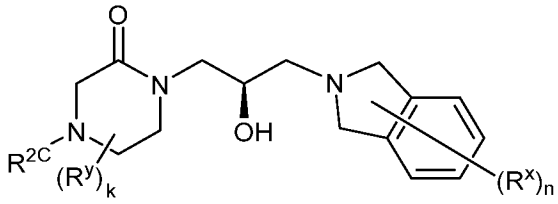
158. The compound of claim 157, wherein the compound is of Formula (**III^C-a**):



III^C-a

or a pharmaceutically acceptable salt thereof.

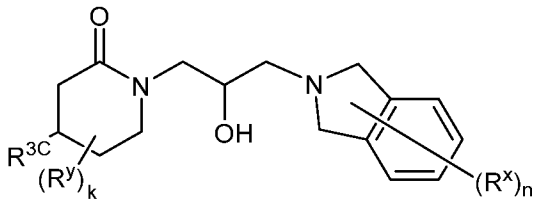
159. The compound of claim 157, wherein the compound is of Formula (**III^C-b**):



III^C-b

or a pharmaceutically acceptable salt thereof.

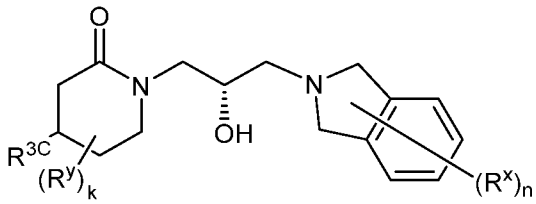
160. The compound of claim 154, wherein the compound is of Formula (**IV^C**):



IV^C

or a pharmaceutically acceptable salt thereof.

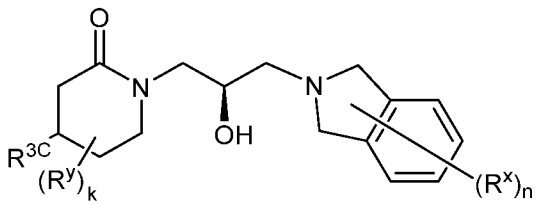
161. The compound of claim 160, wherein the compound is of Formula (**IV^C-a**):



IV^C-a

or a pharmaceutically acceptable salt thereof.

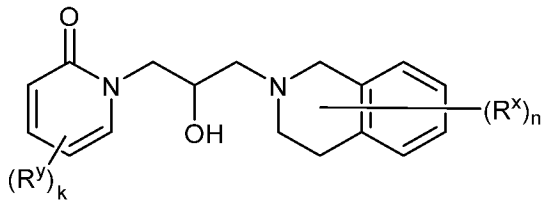
162. The compound of claim 160, wherein the compound is of Formula (**IV^C-b**):



IV^C-b

or a pharmaceutically acceptable salt thereof.

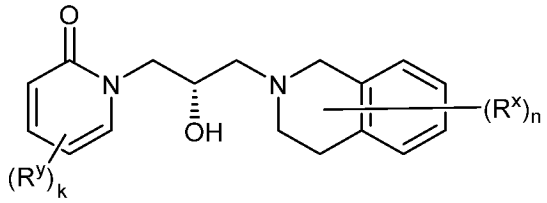
163. The compound of claim 150, wherein the compound is of Formula ($\mathbf{V^C}$):



$\mathbf{V^C}$

or a pharmaceutically acceptable salt thereof.

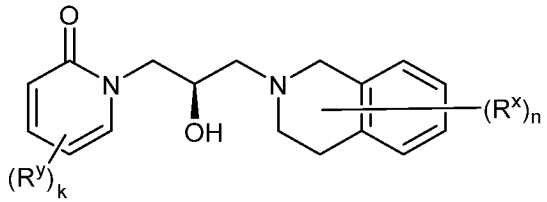
164. The compound of claim 163, wherein the compound is of Formula ($\mathbf{V^C}$-**a**):



$\mathbf{V^C}$-**a**

or a pharmaceutically acceptable salt thereof.

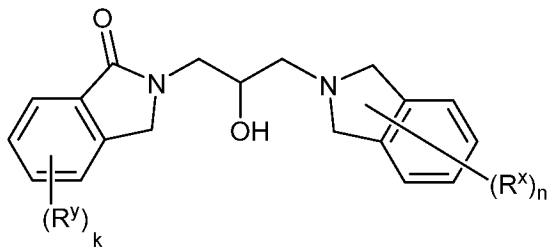
165. The compound of claim 163, wherein the compound is of Formula ($\mathbf{V^C}$-**b**):



$\mathbf{V^C}$-**b**

or a pharmaceutically acceptable salt thereof.

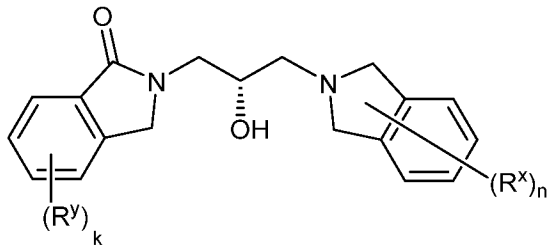
166. The compound of claim 150, wherein the compound is of Formula ($\mathbf{VI^C}$):



$\mathbf{VI^C}$

or a pharmaceutically acceptable salt thereof.

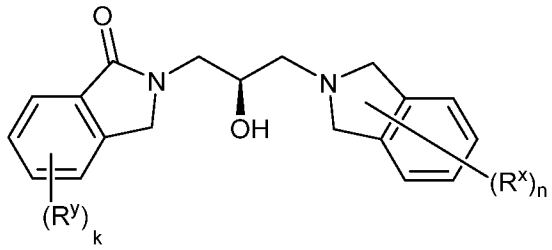
167. The compound of claim 150, wherein the compound is of Formula (**VI^C-a**):



VI^C-a

or a pharmaceutically acceptable salt thereof.

168. The compound of claim 166, wherein the compound is of Formula (**VI^C-b**):



VI^C-b

or a pharmaceutically acceptable salt thereof.

169. The compound of any one of claims 150-156, wherein R^1 is hydrogen.

170. The compound of any one of claims 150-169, wherein n is 0.

171. The compound of any one of claims 150-169, wherein n is 1.

172. The compound of any one of claims 150-169, wherein n is 2.

173. The compound of any one of claims 150-156 and 169-172, wherein Y is O.

174. The compound of any one of claims 150-156 and 169-172, wherein p is 1.

175. The compound of any one of claims 154-174, wherein k is 0.

176. The compound of any one of claims 154-174, wherein k is 1.

177. The compound of any one of claims 154-174, wherein k is 2.

178. The compound of any one of claims 154-156 and 169-177, wherein G is NR^2.

179. The compound of claim 178, wherein R^{2C} is optionally substituted aryl.

180. The compound of claim 179, wherein R^{2C} is optionally substituted phenyl.

181. The compound of claim 180, wherein R^{2C} is unsubstituted phenyl.

182. The compound of claim 180, wherein R^{2C} is halophenyl.

183. The compound of claim 180, wherein R^{2C} is fluorophenyl.

184. The compound of claim 180, wherein R^{2C} is chlorophenyl.

185. The compound of claim 180, wherein R^{2C} is phenyl substituted with optionally substituted C_{1-6} alkyl.

186. The compound of claim 185, wherein R^{2C} is phenyl substituted with optionally substituted C_{1-3} alkyl.

187. The compound of claim 186, wherein R^{2C} is phenyl substituted with methyl.

188. The compound of claim 186, wherein R^{2C} is phenyl substituted with $–CH_2OH$.

189. The compound of claim 180, wherein R^{2C} is phenyl substituted with a heterocyclic ring.

190. The compound of claim 189, wherein R^{2C} is phenyl substituted with morpholinyl.

191. The compound of claim 190, wherein R^{2C} is phenyl substituted with tetrahydropyranyl.

192. The compound of claim 178, wherein R^{2C} is optionally substituted heteroaryl.

193. The compound of claim 192, wherein R^{2C} is optionally substituted quinoline.

194. The compound of claim 192, wherein R^{2C} is optionally substituted pyridine.

195. The compound of claim 194, wherein R^{2C} is pyridine substituted with a heterocyclic ring.

196. The compound of claim 178, wherein R^{2C} is optionally substituted aliphatic.

197. The compound of claim 196, wherein R^{2C} is unsubstituted aliphatic.

198. The compound of claim 196, wherein R^{2C} is $-CH_2$-aryl.

199. The compound of claim 198, wherein R^{2C} is benzyl.

200. The compound of claim 196, wherein R^{2C} is $-CH_2$-heteroaryl.

201. The compound of claim 200, wherein R^{2C} is $-CH_2$-pyridyl.

202. The compound of claim 178, wherein R^{2C} is $-C(=O)R^A$.

203. The compound of claim 202, wherein R^A is optionally substituted aliphatic.

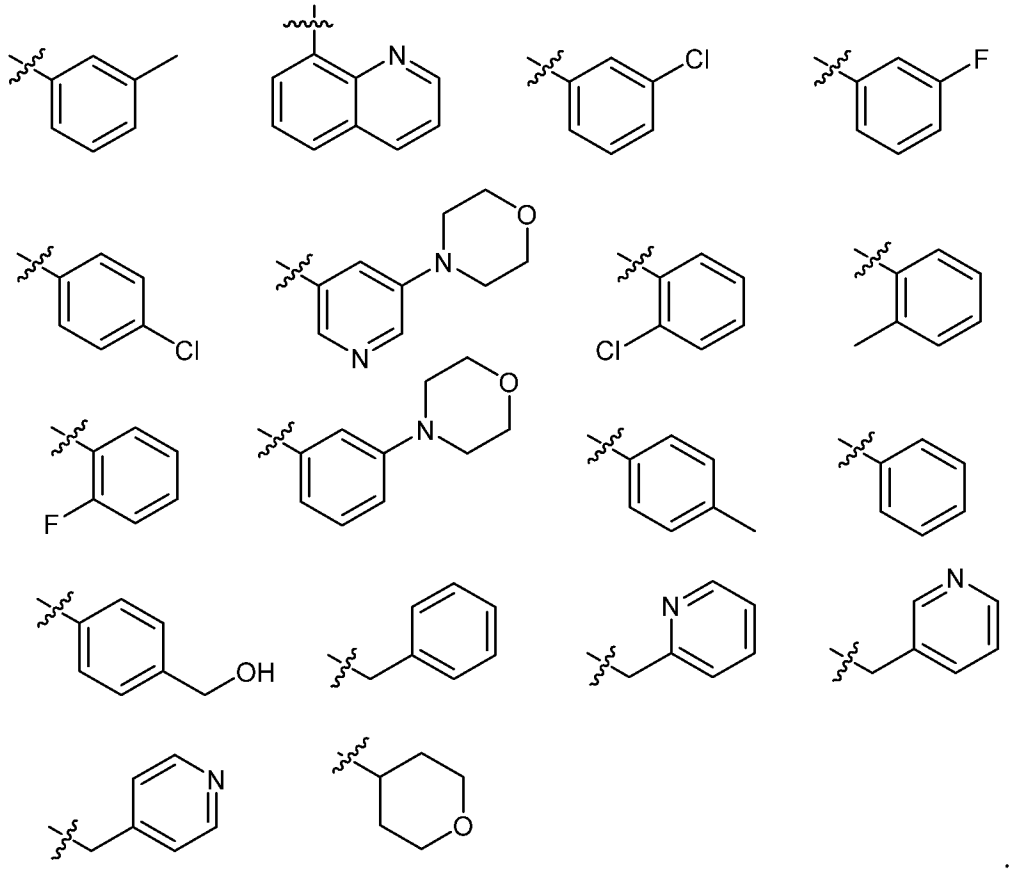
204. The compound of claim 203, wherein R^{2C} is acetyl.

205. The compound of claim 178, wherein R^{2C} is $-SO_2R^A$.

206. The compound of claim 205, wherein R^A is optionally substituted aliphatic.

207. The compound of claim 206, wherein R^{2C} is $-SO_2CH_3$.

208. The compound of claim 178, wherein R^{2C} is selected from the group consisting of:



209. The compound of any one of claims 154-156 and 169-177, wherein G is $CR^{3C}R^{4C}$.

210. The compound of claim 209, wherein R^{4C} is hydrogen.

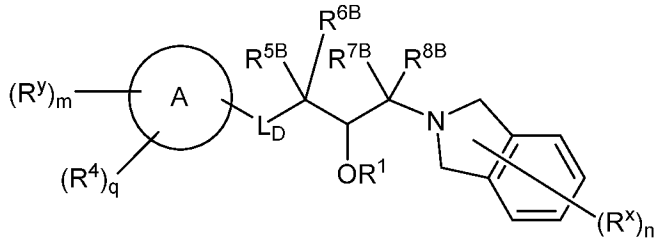
211. The compound of claim 209 or 210, wherein R^{3C} is optionally substituted aryl.

212. The compound of any one of claims 154-156 and 169-177, wherein G is O.

213. The compound of claim 211 or 212, wherein k is 0.

214. The compound of any one of claims 211-213, wherein n is 0.

215. The compound of claim 1 of formula ($\mathbf{I^D}$):



$\mathbf{I^D}$

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L_D is –O–, –N(R)–,–C(R^{2A})(R^{3A})–, -O-C$R^{2A}R^{3A}$-, -N(R)-C$R^{2A}R^{3A}$-, -O-C$R^{2A}R^{3A}$-O-, -N(R)-C$R^{2A}R^{3A}$-O, -N(R)-C$R^{2A}R^{3A}$-N(R)-, -O-C$R^{2A}R^{3A}$-N(R)-, -C$R^{2A}R^{3A}$-O-, -C$R^{2A}R^{3A}$-N(R)-, -O-C$R^{2A}R^{3A}$-CR^9R^{10}-, -N(R)-C$R^{2A}R^{3A}$-CR^9R^{10}-, -C$R^{2A}R^{3A}$-CR^9R^{10}-O-, -C$R^{2A}R^{3A}$-CR^9R^{10}-N(R)-, or –C$R^{2A}R^{3A}$-CR^9R^{10}-;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

R^{2A} and R^{3A} are independently selected from the group consisting of hydrogen, halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl; optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -N(R^B)$_2$, -SR^A, -C(=O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)$_2$, -C(O)N(R^B)N(R^B)$_2$, -OC(O)R^A, -OC(O)N(R^B)$_2$, -NR^BC(O)R^A, -NR^BC(O)N(R^B)$_2$, -NR^BC(O)N(R^B)N(R^B)$_2$, -NR^BC(O)OR^A, -SC(O)R^A, -C(=NR^B)R^A, -C(=NNR^B)R^A, -C(=NOR^A)R^A, -C(=NR^B)N(R^B)$_2$, -NR^BC(=NR^B)R^B, -C(=S)R^A, -C(=S)N(R^B)$_2$, -NR^BC(=S)R^A, -S(O)R^A, -OS(O)$_2R^A$, -SO_2R^A, -N$R^B$$SO_2R^A$, and -$SO_2$N($R^B$)$_2$; or R^{2A} and R^{3A} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

Ring A is a monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^4 is $-L_1$-Cy^D;

L_1 is a bond, –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, $–SO_2–$, $–SO_2N(R)–$, $–N(R)SO_2–$, –OC(O)–, –C(O)O–, or an optionally substituted, straight or branched, C_{1-6} aliphatic chain wherein one, two, or three methylene units of L_1 are optionally and independently replaced by –O–, –S–, –N(R)–, –C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)–, –N(R)C(O)O–, –OC(O)N(R)–, $–SO_2–$, $–SO_2N(R)–$, $–N(R)SO_2–$, –OC(O)–, or –C(O)O–;

Cy^D is an optionally substituted, monocyclic, bicyclic or tricyclic, saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{5B}, R^{6B}, R^{7B}, and R^{8B} are independently hydrogen, halo, or optionally substituted aliphatic;

R^9 and R^{10} are independently selected from the group consisting of hydrogen, halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl; optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$; or R^9 and R^{10} are taken together with their intervening atoms to form an optionally substituted carbocyclic or heterocyclic ring;

each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl; optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, and -OR';

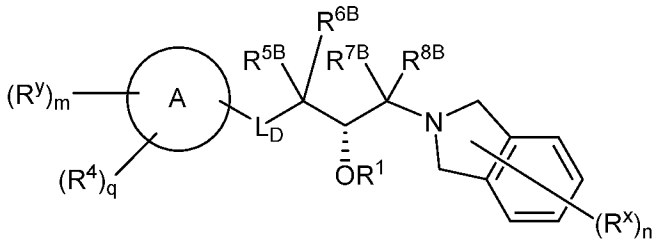
R' is hydrogen or optionally substituted aliphatic;

n is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

m is 0, 1, 2, 3, 4, 5, 6, 7, or 8, as valency permits; and

q is 0 or 1.

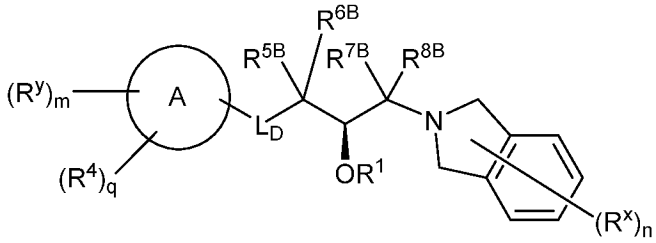
216. The compound of claim 215, wherein the compound is of formula (**I^D-a**):



I^D-a

or a pharmaceutically acceptable salt thereof.

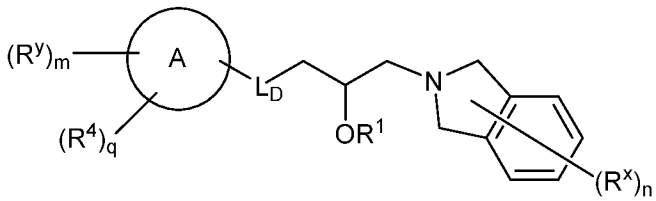
217. The compound of claim 215, wherein the compound is of formula (**I^D-b**):



I^D-b

or a pharmaceutically acceptable salt thereof.

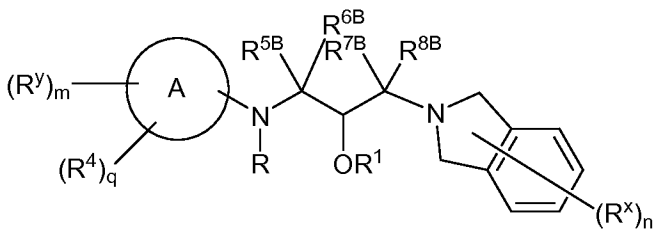
218. The compound of claim 215, wherein the compound is of formula (**I^D-c**):



I^D-c

or a pharmaceutically acceptable salt thereof.

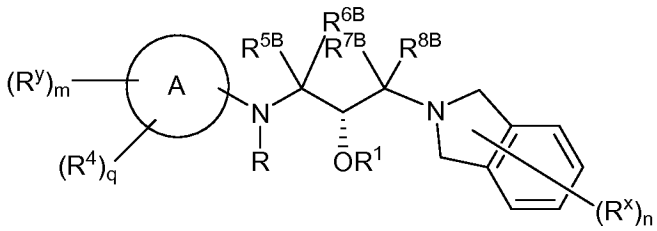
219. The compound of claim 215, wherein the compound is of formula (**II^D**):



II^D

or a pharmaceutically acceptable salt thereof.

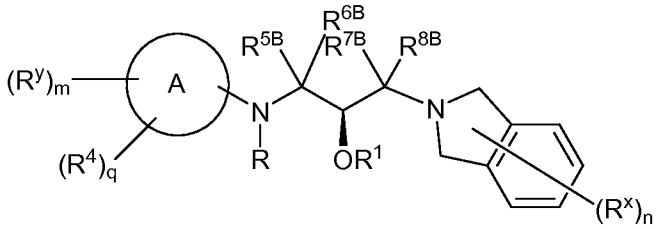
220. The compound of claim 219, wherein the compound is of formula (**II^D-a**):



II^D-a

or a pharmaceutically acceptable salt thereof.

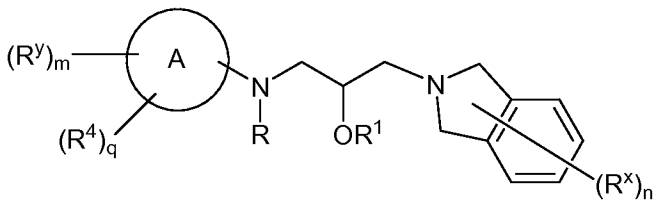
221. The compound of claim 219, wherein the compound is of formula (**II^D-b**):



II^D-b

or a pharmaceutically acceptable salt thereof.

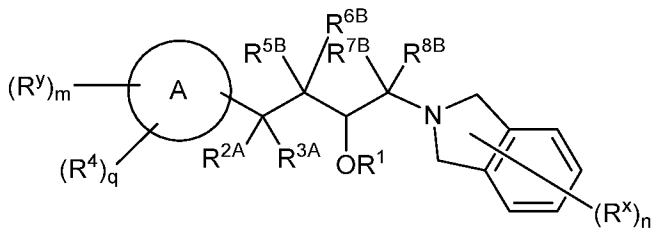
222. The compound of claim 219, wherein the compound is of formula (**II^D-c**):



II^D-c

or a pharmaceutically acceptable salt thereof.

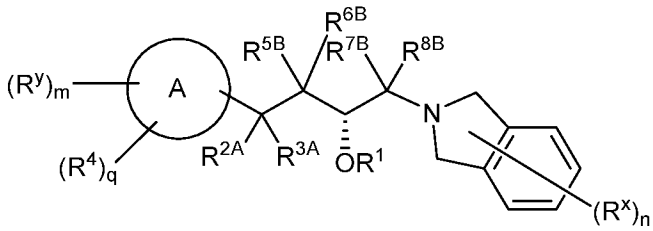
223. The compound of claim 215, wherein the compound is of formula (**III^D**):



III^D

or a pharmaceutically acceptable salt thereof.

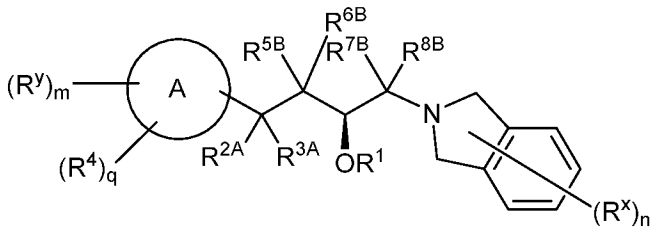
224. The compound of claim 223, wherein the compound is of formula (**III^D-a**):



III^D-a

or a pharmaceutically acceptable salt thereof.

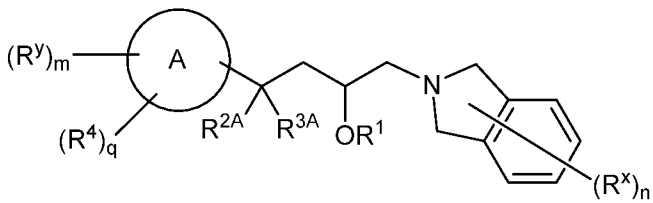
225. The compound of claim 223, wherein the compound is of formula (**III^D-b**):



III^D-b

or a pharmaceutically acceptable salt thereof.

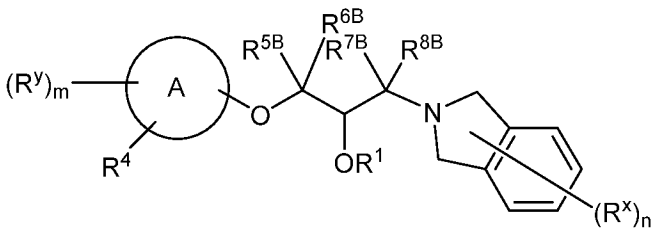
226. The compound of claim 223, wherein the compound is of formula (**III^D-c**):



III^D-c

or a pharmaceutically acceptable salt thereof.

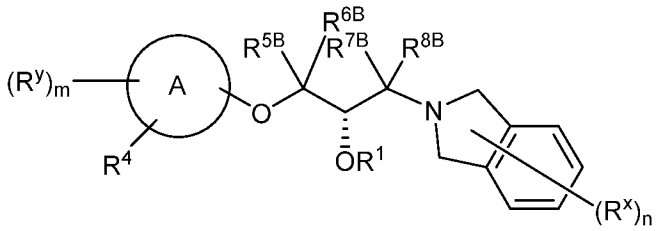
227. The compound of claim 215, wherein the compound is of formula (**IV^D**):



IV^D

or a pharmaceutically acceptable salt thereof.

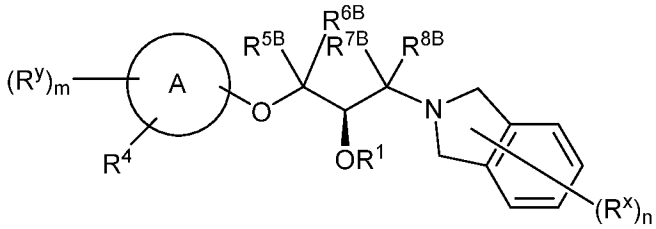
228. The compound of claim 227, wherein the compound is of formula (**IV^D-a**):



IV^D-a

or a pharmaceutically acceptable salt thereof.

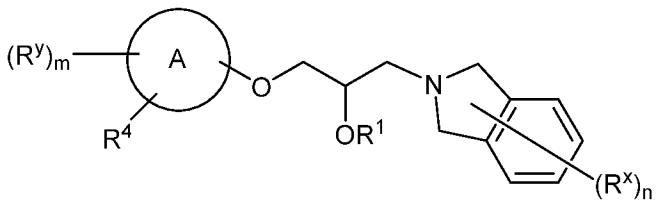
229. The compound of claim 227, wherein the compound is of formula (**IV^D-b**):



IV^D-b

or a pharmaceutically acceptable salt thereof.

230. The compound of claim 227, wherein the compound is of formula (**IV^D-c**):



IV^D-c

or a pharmaceutically acceptable salt thereof.

231. The compound of any one of claims 215-218, wherein L_D is $–CR^{2A}R^{3A}$-O-.

232. The compound of claim 231, wherein L_D is $–CH_2$-O-.

233. The compound of any one of claims 215-218, wherein L_D is $–CR^{2A}R^{3A}$-N(R)-.

234. The compound of claim 233, wherein L_D is $–CH_2$-NH-.

235. The compound of any one of claims 215-234, wherein R^1 is hydrogen.

236. The compound of any one of claims 215-235, wherein n is 0.

237. The compound of any one of claims 215-235, wherein n is 1.

238. The compound of any one of claims 215-235, wherein n is 2.

239. The compound of any one of claims 215-218 and 223-227, wherein R^{2A} and R^{3A} are each hydrogen.

240. The compound of any one of claims 215-218 and 223-227, wherein R^{2A} is hydrogen and R^{3A} is not hydrogen.

241. The compound of claim 240, wherein R^{3A} is optionally substituted aliphatic.

242. The compound of claim 241, wherein R^{3A} is C_{1-6} alkyl.

243. The compound of claim 242, wherein R^{3A} is methyl.

244. The compound of any one of claims 215-218 and 223-227, wherein R^{2A} and R^{3A} are not hydrogen.

245. The compound of claim 244, wherein R^{2A} and R^{3A} are optionally substituted aliphatic.

246. The compound of claim 245, wherein R^{2A} and R^{3A} are methyl.

247. The compound of any one of claims 215-218, wherein R is hydrogen.

248. The compound of any one of claims 215-247, wherein Ring A is aromatic.

249. The compound of claim 248, wherein Ring A is phenyl.

250. The compound of claim 248, wherein Ring A is a monocyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

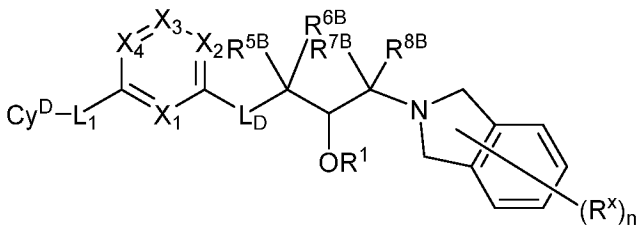
251. The compound of claim 250, wherein Ring A is pyridyl.

252. The compound of claim 250, wherein Ring A is pyrimidyl.

253. The compound of claim 250, wherein Ring A is pyridazinyl.

254. The compound of any one of claims 215-253, wherein q is 1.

255. The compound of claim 215, wherein the compound is of formula ($\mathbf{V^D}$):



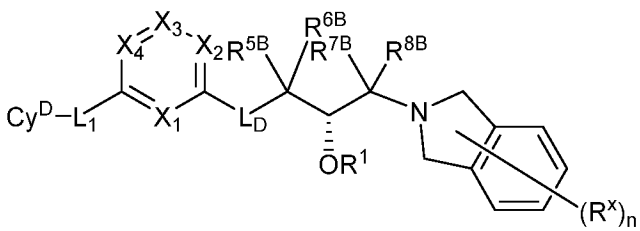
$\mathbf{V^D}$

or a pharmaceutically acceptable salt thereof,

wherein

X_1, X_2, X_3, and X_4 are independently selected from the group consisting of N, CH, and CR^y, provided that at least one of X_2, X_3, and X_4 is not N.

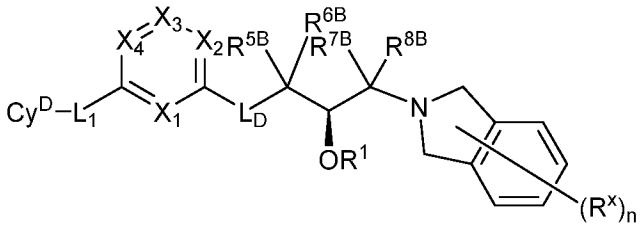
256. The compound of claim 255, wherein the compound is of formula ($\mathbf{V^D}$-**a**):



$\mathbf{V^D}$-**a**

or a pharmaceutically acceptable salt thereof.

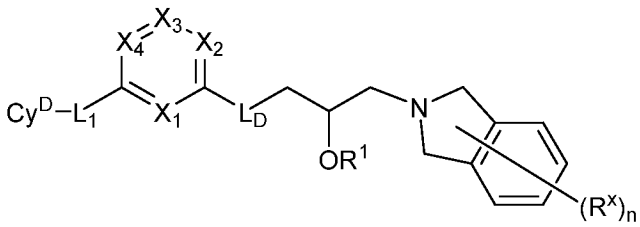
257. The compound of claim 255, wherein the compound is of formula ($\mathbf{V^D}$-**b**):



V^D-b

or a pharmaceutically acceptable salt thereof.

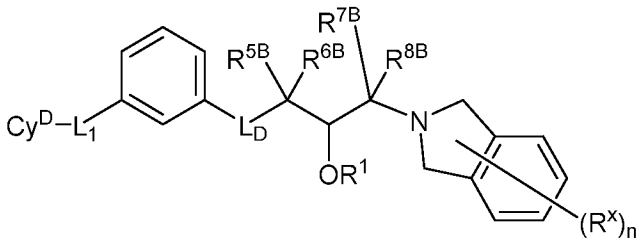
258. The compound of claim 255, wherein the compound is of formula (**V^D-c**):



V^D-c

or a pharmaceutically acceptable salt thereof.

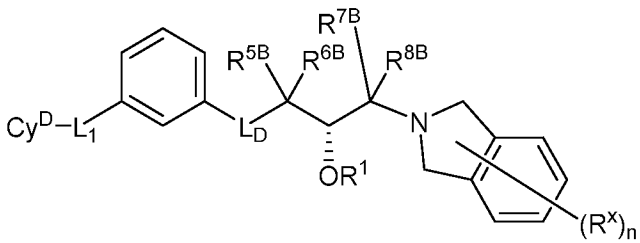
259. The compound of claim 255, wherein the compound is of formula (**VI^D**):



VI^D

or a pharmaceutically acceptable salt thereof.

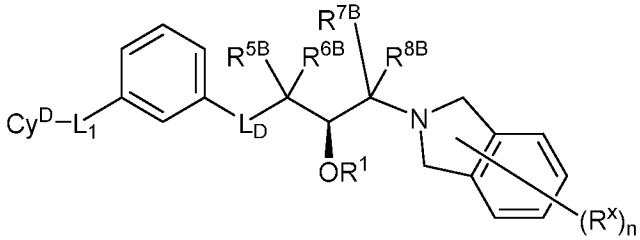
260. The compound of claim 259, wherein the compound is of formula (**VI^D-a**):



VI^D-a

or a pharmaceutically acceptable salt thereof.

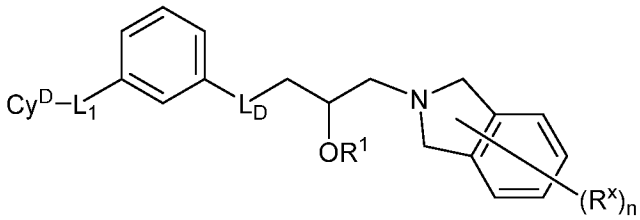
261. The compound of claim 259, wherein the compound is of formula (**VI^D-b**):



VI^D-b

or a pharmaceutically acceptable salt thereof.

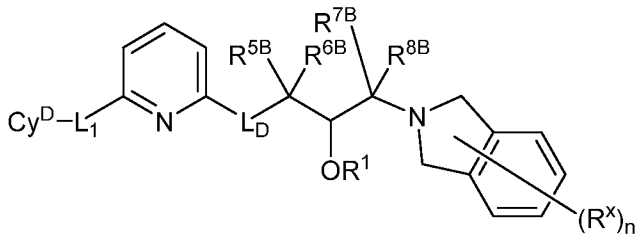
262. The compound of claim 259, wherein the compound is of formula (**VI^D-c**):



VI^D-c

or a pharmaceutically acceptable salt thereof.

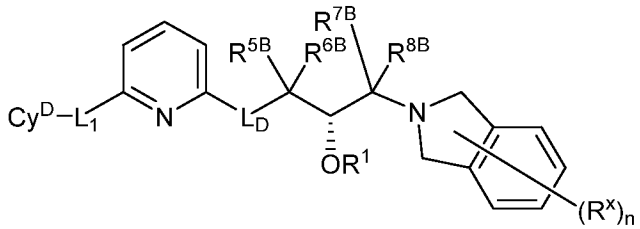
263. The compound of claim 255, wherein the compound is of formula (**VII^D**):



VII^D

or a pharmaceutically acceptable salt thereof.

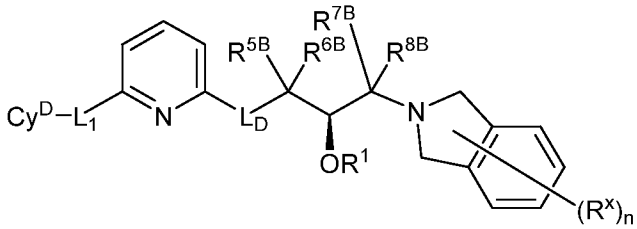
264. The compound of claim 263, wherein the compound is of formula (**VII^D-a**):



VII^D-a

or a pharmaceutically acceptable salt thereof.

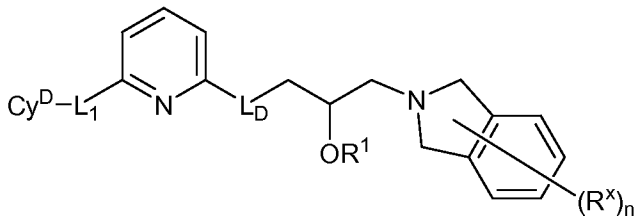
265. The compound of claim 263, wherein the compound is of formula (**VII^D-b**):



VII^D-b

or a pharmaceutically acceptable salt thereof.

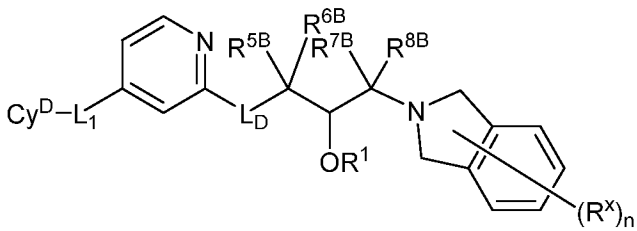
266. The compound of claim 263, wherein the compound is of formula (**VII^D-c**):



VII^D-c

or a pharmaceutically acceptable salt thereof.

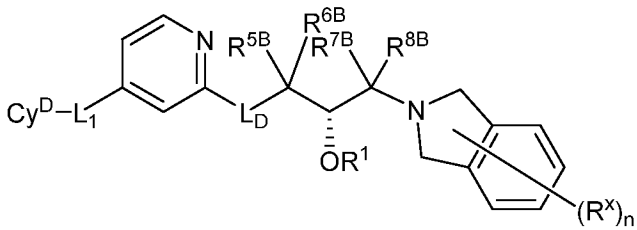
267. The compound of claim 255, wherein the compound is of formula (**VIII^D**):



VIII^D

or a pharmaceutically acceptable salt thereof.

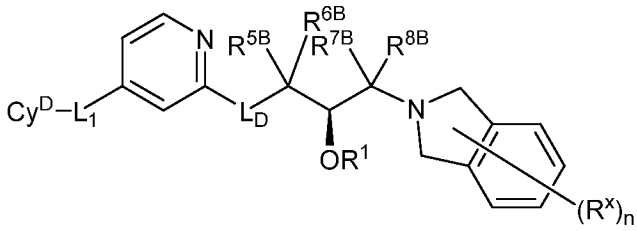
268. The compound of claim 267, wherein the compound is of formula (**VIII^D-a**):



VIII^D-a

or a pharmaceutically acceptable salt thereof.

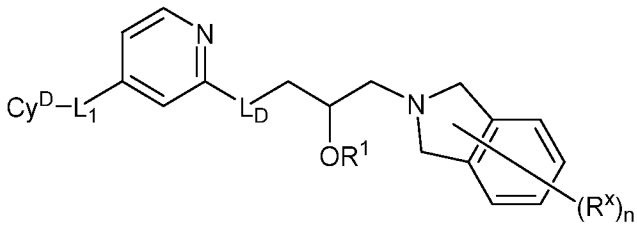
269. The compound of claim 267, wherein the compound is of formula (**VIII^D-b**):



VIII^D-b

or a pharmaceutically acceptable salt thereof.

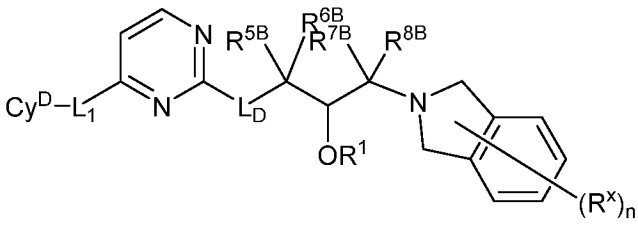
270. The compound of claim 267, wherein the compound is of formula (**VIII^D-c**):



VIII^D-c

or a pharmaceutically acceptable salt thereof.

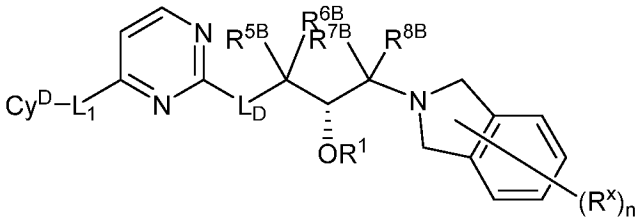
271. The compound of claim 255, wherein the compound is of formula (**IX^D**):



IX^D

or a pharmaceutically acceptable salt thereof.

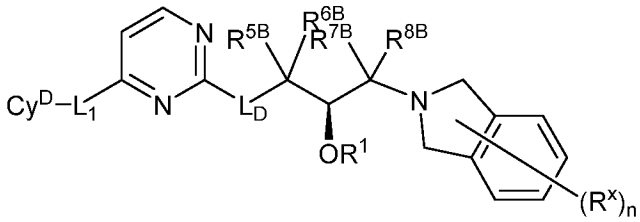
272. The compound of claim 271, wherein the compound is of formula (**IX^D-a**):



IX^D-a

or a pharmaceutically acceptable salt thereof.

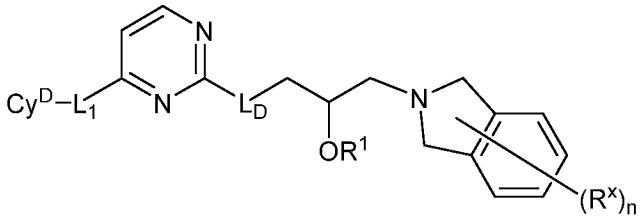
273. The compound of claim 271, wherein the compound is of formula (**IX^D-b**):



IX^D-b

or a pharmaceutically acceptable salt thereof.

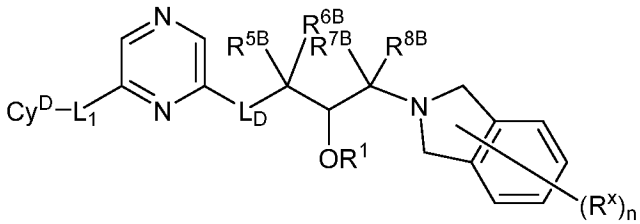
274. The compound of claim 271, wherein the compound is of formula (**IX^D-c**):



IX^D-c

or a pharmaceutically acceptable salt thereof.

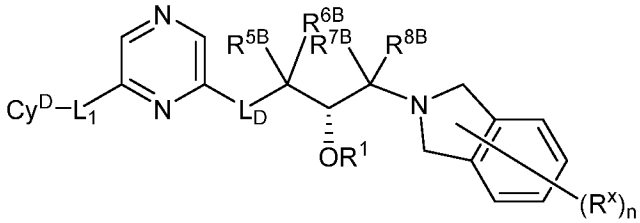
275. The compound of claim 255, wherein the compound is of formula (**X^D**):



X^D

or a pharmaceutically acceptable salt thereof.

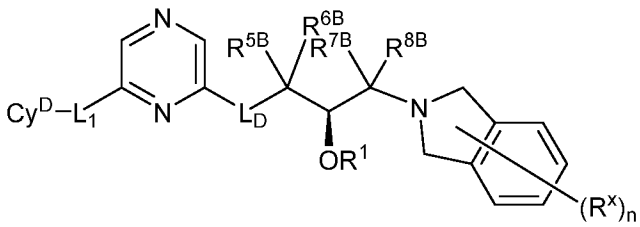
276. The compound of claim 275, wherein the compound is of formula (**X^D-a**):



X^D-a

or a pharmaceutically acceptable salt thereof.

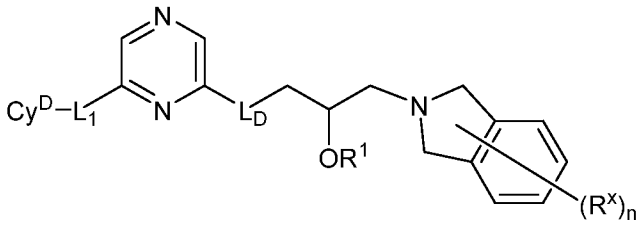
277. The compound of claim 275, wherein the compound is of formula ($\mathbf{X^D}$-**b**):



$\mathbf{X^D}$-**b**

or a pharmaceutically acceptable salt thereof.

278. The compound of claim 275, wherein the compound is of formula ($\mathbf{X^D}$-**c**):



$\mathbf{X^D}$-**c**

or a pharmaceutically acceptable salt thereof.

279. The compound of any one of claims 215-278, wherein L_1 is a bond.

280. The compound of any one of claims 215-278, wherein L_1 is –C(O)NH-.

281. The compound of any one of claims 215-280, wherein Cy^D is optionally substituted phenyl.

282. The compound of any one of claims 215-280, wherein Cy^D is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

283. The compound of claim 282, wherein Cy^D is optionally substituted pyrazole, optionally substituted pyridyl, or optionally substituted pyrimidyl.

284. The compound of any one of claims 215-280, wherein Cy^D is an optionally substituted 9- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

285. The compound of claim 284, wherein Cy^D is optionally substituted indazole, optionally substituted quinoline, optionally substituted benzimidazole, optionally substituted benzothiazole, optionally substituted deazapurine, optionally substituted indole, optionally substituted purine, optionally substituted pyrazolopyridine, optionally substituted pyrrolopyridine, optionally substituted pyrroloprimidine, optionally substituted imidazopyridine, or optionally substituted imidazopyridine.

286. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds in Table 1A.

287. A pharmaceutical composition comprising a compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

288. A kit or packaged pharmaceutical comprising a compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof, and instructions for use thereof.

289. A method of inhibiting PRMT5 comprising contacting a cell with an effective amount of a compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof.

290. A method of altering gene expression comprising contacting a cell with an effective amount of a compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof.

291. A method of altering transcription comprising contacting a cell with an effective amount of a compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof.

292. The method of any one of claims 289-291, wherein the cell is *in vitro*.

293. The method of any one of claims 289-291, wherein the cell is in a subject.

294. A method of treating a PRMT5-mediated disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 287.

295. The method of claim 294, wherein the disorder is a proliferative disorder.

296. The method of claim 295, wherein the disorder is cancer.

297. The method of claim 296, wherein the cancer is hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer.

298. The method of claim 294, wherein the disorder is a metabolic disorder.

299. The method of claim 298, wherein the metabolic disorder is diabetes.

300. The method of claim 298, wherein the metabolic disorder is obesity.

301. The method of claim 294, wherein the disorder is a blood disorder.

302. The method of claim 301, wherein the disorder is a hemoglobinopathy.

303. The method of claim 302, wherein the disorder is sickle cell anemia.

304. The method of claim 302, wherein the disorder is β-thalessemia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/077256

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 A61K31/4035 A61K31/4155 A61K31/4184 A61K31/4402
A61K31/4709 A61K31/538 C07D401/12 C07D407/12 C07D413/12
C07D209/44 A61P35/00 A61P3/04 A61P3/10 A61P7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DD 63 776 A (HEIDENBLUTH, K.; TÖNJES, H.; FALTUS, H.; SCHMIDT, J.) 20 September 1968 (1968-09-20) column 1; examples 22-24, 28, 32, 34, 36 -----	1,215, 218,235, 236,239, 247-249, 287
X	DD 68 906 A (HEIDENBLUTH, K.; FALTUS, H.; TÖNJES, H.; SCHMIDT, J.) 20 September 1969 (1969-09-20) Examples 1-3: Starting and end products; column 1 ----- -/--	1,215, 218,235, 239,240, 244-246, 248,249, 287

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2014	14/04/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sotoca Usina, E

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/015805 A1 (LILLY CO ELI [US]; BLASZCZAK LARRY CHRIS [US]; PULLEY SHON ROLAND [US]) 8 February 2007 (2007-02-08) Example 30: Step A and step B	1,215, 218,235, 236,240, 242,247, 249,287
X	WO 2008/100621 A2 (SUNESIS PHARMACEUTICALS INC [US]; AMERIKS MICHAEL K [US]; ARIENTI KRIS) 21 August 2008 (2008-08-21) compounds 305, 339	1,287
X	WO 95/11680 A1 (HOECHST ROUSSEL PHARMA [US]) 4 May 1995 (1995-05-04) page 232 - page 233; example 239	1,287
X	SUNKO D E ET AL: "On the Reaction of alpha-Phthalimidoacid Chlorides with Substituted Sodiomalonates. A Method for the Preparation of alpha-Amino Ketones and Related Compounds", ARHIV ZA KEMIJU,, vol. 26, 1 January 1954 (1954-01-01), pages 7-14, XP009176093, ISSN: 0365-3730 compound VIII	1,215, 218,223, 226,235, 236,239, 248,249
X	WO 2004/060882 A1 (ASTRAZENECA AB [SE]; LEUNG CARMEN [CA]; TOMASZEWSKI MIROSLAW [CA]; WOO) 22 July 2004 (2004-07-22) page 41; example 10	1,215, 218,227, 229,235, 237,239, 248,249
X	CN 101 012 223 A (XI AN XIN AN MEDICINE SCIENCE [CN]) 8 August 2007 (2007-08-08) pages 7-8; example 1; compound B	1,215, 218,248, 250
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 December 2012 (2012-12-04), "2H-Isoindole-2-ethanol,.alpha.-[(4-amino-3,5-dimethyl-1H-pyrazol-1-yl)methyl]-1,3-dihydro-", XP002722566, Database accession no. 1410908-63-2 the whole document	1,215, 218,227, 230,235, 236,239, 250

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 24 April 2011 (2011-04-24), "2H-Isoindole-2-ethanol,.-alpha.-[(cyclopr opylamino)methyl]-1,3-dihydro-", XP002722567, Database accession no. 1284717-34-5 the whole document -----	1,215, 218,219, 222,235, 236,239
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 May 2008 (2008-05-28), "Acetamine, N-[2-[3-(1,3-dihydro-2H-isoindol-2-yl)-2-h ydroxypropoxy]phenyl]-", XP002722568, Database accession no. 1023185-95-6 the whole document -----	1,215, 218,227, 230,235, 236,239, 249
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 18 March 2008 (2008-03-18), "1H-Indole-3-acetic acid, 5-[3-(1,3-dihydro-2H-isoindol-2-yl)-2-hydr oxypropoxy]-, methyl ester", XP002722569, Database accession no. 1008707-00-3 the whole document -----	1,215, 218,227, 230,235, 236,239, 249
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 27 December 2004 (2004-12-27), "Benzeneacetic acid, 2-(4-chlorophenoxy)-1-[(1,3-dihydro-2H-iso indol-2-yl)methyl]ethyl ester", XP002722570, Database accession no. 803623-34-9 the whole document -----	1,215, 218,227, 230,235, 236,239, 248,249
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 26 December 2004 (2004-12-26), "2H-Isoindole-2-ethanol, 1,3-dihydro-.alpha.-[(4-methylphenoxy)meth yl]-,2-propionate", XP002722571, Database accession no. 802601-62-3 the whole document ----- -/--	1,215, 218,227, 230,235, 236,239, 248,249

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 25 December 2004 (2004-12-25), "Acetic acid, 2-phenoxy-, 2-(1,3-dihydro-2H-isoindole-2-yl)-1-[(phen ylmethoxy)methyl]ethyl ester", XP002722572, Database accession no. 802313-31-1 the whole document ----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 December 2004 (2004-12-22), "Acetic acid, 2-phenoxy-, 2-(1,3-dihydro-2H-isoindol-2-yl)-1-[(4-met hylphenoxy)methyl] ethyl ester", XP002722573, Database accession no. 801197-71-7 the whole document ----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 27 October 2004 (2004-10-27), "Benzeneacetic acid, 1-[(1,3-dihydro-2H-isoindol-2-yl)methyl]-3 -phenylpropyl ester", XP002722574, Database accession no. 770646-48-5 the whole document ----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 September 2004 (2004-09-02), "Benzeneacetic acid,.alpha.-phenyl-,1-[(1,3-dihydro-2H-is oindol-2-yl)methyl]-2-(2-methylphenoxy)eth yl ester", XP002722575, Database accession no. 737696-45-6 the whole document ----- WO 02/14277 A1 (TANABE SEIYAKU CO [JP]; YAMADA HARUTAMI [JP]; ANDO AKIRA [JP]; KAWANIS) 21 February 2002 (2002-02-21) the whole document -/--	1,215, 231,232, 235,236, 239,248, 249 1,215, 218,227, 230,235, 236,239, 248,249 1,215, 218,223, 226,235, 236,239, 248,249 1,215, 218,227, 230,235, 236,248, 249 1,215, 218,231, 232,237, 239,248, 249,259, 262,279, 281

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 21 February 2002 (2002-02-21), Yamada, Harutami; Ando, Akira; Kawanishi, Hiroyuki; Nagata, koichi; Yasuhara, Mikiko: "Preparation of biphenylcarboxamidoisoindoline derivatives as apolipoprotein B secretion inhibitors", XP002722582, Database accession no. 2002:142672 Compound 400726-94-5 [1,1'-Biphenyl]-2-carboxamide, N-[2-(2,3-dihydroxypropyl)-2,3-dihydro-1H- isoindol-5-yl]-4'-(trifluoromethyl)-, hydrochloride (1:1) -----	1,215, 218,231, 232,237, 239,248, 249,259, 262,279, 281
A	WO 2011/079236 A1 (UNIV OHIO STATE RES FOUND [US]; BAIOCCHI ROBERT [US]; LI CHENGLONG [US) 30 June 2011 (2011-06-30) pages 1-5; claims 1-10 -----	1-304
X,P	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 24 November 2013 (2013-11-24), "2H-Isoindole-2-ethanol1,3-dihydro-.alpha. -(1-piperazinylmethyl)-", XP002722576, Database accession no. 1479608-80-4 the whole document -----	1
X,P	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 6 October 2013 (2013-10-06), "2H-Isoindole-2-ethanol,.alpha-[(3-aminoph enoxy)methyl]-1,3-dihydrp-", XP002722577, Database accession no. 1456315-86-8 the whole document -----	1,215, 218,227, 235,236, 239,249
X,P	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 October 2013 (2013-10-04), "2H-Isoindole-2-ethanol,.alpha.-[(4-amino- 1H-pyrazol-1-yl)methyl]-1,3-dihydro-", XP002722578, Database accession no. 1455191-29-3 the whole document ----- -/--	1,215, 218,227, 230,235, 236,239, 250

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 October 2013 (2013-10-04), "2H-Isoindole-2-ethanol,.alpha.-[(2minophe noxy)methyl]-1,3-dihydro-", XP002722579, Database accession no. 1455081-19-2 the whole document -----	1,215, 218,227, 230,235, 236,248, 249

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/077256

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-304(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.2

Claims Nos.: 1-304(partially)

The the application is seen as not complying with the criterion of clarity according to Article 6 PCT. Claim 1 states that Lz is a linker, this expression is not clear. All the claims are stated to be dependent (directly or via other dependent claims) on claim 1, nevertheless claims 163-165 are outside of the scope of claim 1. Claim 279 is stated to be dependent on claims 215-278 where L1 is a bond, yet none of these claims allow L1 to be a bond.

Several discrepancies are seen between the claims and the description, where the description contains Markush formulae much broader than that of the application.

D1 discloses examples 22-24, 28, 32, 34, 36 and column 1 discloses its use as medicaments. It is seen as novelty hindering for claims 1, 215, 218, 235, 236, 239, 247-249, 287 under Article 33(2) PCT.

D2 discloses the starting- and end-products of examples 1-3, and column 1 discloses its use as medicaments. It is seen as novelty hindering for claims 1, 215, 218, 235, 236, 239, 247-249, 287 under Article 33(2) PCT.

D3 discloses steps A and B of example 30. It is seen as novelty hindering for claims 1, 215, 218, 235, 236, 240, 242, 247, 249, 287 under Article 33(2) PCT.

D4 discloses compounds 305 and 339, which are seen as novelty hindering for claims 1 and 287 under Article 33(2) PCT.

D5 discloses example 239 which is seen as novelty hindering for claims 1 and 287 under Article 33(2) PCT.

D6 discloses on page 12 compound VIII which is seen as novelty hindering for claims 1, 215, 218, 223, 226, 227, 236, 239, 248 and 249 under Article 33(2) PCT.

Furthermore, the present application contains 304 claims. There are so many dependent claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as they create a smoke screen in front of the skilled reader when assessing what should be the subject-matter to search.

As no answer was sent by the applicant relating to be subject matter to be searched,, the extent of the search would consequently be limited to claims 2, 94, 150, 215 and 286 where Lz has a definitive definition, which appears to comprise a reasonable definition of what is understood to be the invention for which protection is sought.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/077256

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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