

ARGININE METHYLTRANSFERASE 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. 61/781,051, filed March 14, 2013, and U.S.S.N. 61/876,034 filed September 10, 2013, the entire contents of which is incorporated herein by reference.

Background of the Invention

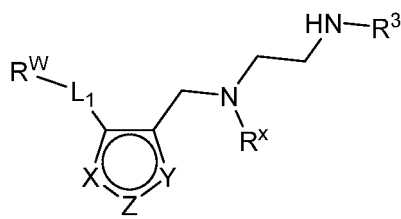
[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases.

[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.*, arginine methyltransferases), many of which are associated with specific genetic alterations that can cause human disease.

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

Detailed Description of Certain Embodiments

[0005] Arginine methyltransferases are attractive targets for modulation given their 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 arginine methyltransferases. Such compounds have the general Formula (I):



or a pharmaceutically acceptable salt thereof, wherein X, Y, Z, L₁, R^W, R³, and R^x are as defined herein.

[0006] In some embodiments, pharmaceutical compositions are provided which comprise a compound described herein (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0007] In certain embodiments, compounds described herein inhibit activity of an arginine methyltransferase (RMT) (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8). In certain embodiments, methods of inhibiting an arginine methyltransferase are provided which comprise contacting the arginine methyltransferase with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The RMT may be purified or crude, and may be present in a cell, tissue, or a subject. Thus, such methods encompass inhibition of RMT activity both *in vitro* and *in vivo*. In certain embodiments, the RMT is wild-type. In certain embodiments, the RMT is overexpressed. In certain embodiments, the RMT is a mutant. In certain embodiments, the RMT is in a cell. In some embodiments, the RMT is expressed at normal levels in a subject, but the subject would benefit from RMT inhibition (*e.g.*, because the subject has one or more mutations in an RMT substrate that causes an increase in methylation of the substrate with normal levels of RMT). In some embodiments, the RMT is in a subject known or identified as having abnormal RMT activity (*e.g.*, overexpression).

[0008] In certain embodiments, methods of modulating gene expression in a cell are provided which comprise contacting a cell with an effective amount of a compound of 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.

[0009] In certain embodiments, methods of modulating transcription in a cell are provided which comprise contacting a cell with an effective amount of a compound of 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.

[0010] In some embodiments, methods of treating an RMT-mediated disorder (*e.g.*, a PRMT1-, PRMT3-, CARM1-, PRMT6-, or PRMT8-mediated disorder) are provided which comprise administering to a subject suffering from an RMT-mediated disorder an effective amount of a compound described herein (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the RMT-mediated disorder is a proliferative disorder. In certain embodiments, compounds described herein are useful for treating cancer. In certain embodiments, compounds described herein are useful for treating breast cancer, prostate cancer, lung cancer, colon cancer, bladder cancer, or leukemia. In certain embodiments, the RMT-mediated disorder is a muscular disorder. In certain embodiments, the RMT-mediated disorder is an autoimmune disorder. In certain embodiments, the RMT-mediated disorder is a neurological disorder. In certain embodiments, the RMT-mediated disorder is a vascular disorder. In certain embodiments, the RMT-mediated disorder is a metabolic disorder.

[0011] Compounds described herein are also useful for the study of arginine methyltransferases in biological and pathological phenomena, the study of intracellular signal transduction pathways mediated by arginine methyltransferases, and the comparative evaluation of new RMT inhibitors.

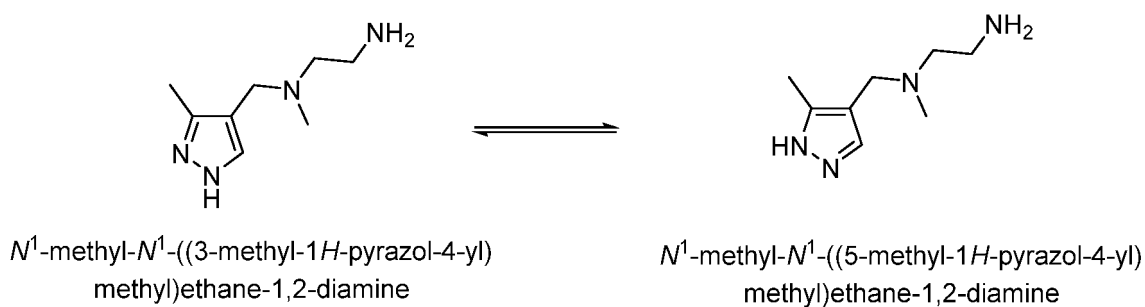
[0012] This application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

[0013] 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.

[0014] 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.

[0015] 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.



[0016] 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.

[0017] 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.

[0018] “Radical” refers to a point of attachment on a particular group. Radical includes divalent radicals of a particular group.

[0019] “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 (“C₁₋₉ alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁₋₈ alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“C₁₋₇ alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂₋₆ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), iso-butyl (C₄), n-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and n-hexyl (C₆). Additional examples of alkyl groups include n-heptyl (C₇), n-octyl (C₈) 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 C₁₋₁₀ alkyl (*e.g.*, –CH₃). In certain embodiments, the alkyl group is substituted C₁₋₁₀ alkyl.

[0020] 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 (“C₁₋₈ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 6 carbon atoms (“C₁₋₆ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 4 carbon atoms (“C₁₋₄ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 3 carbon atoms (“C₁₋₃ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 2 carbon atoms (“C₁₋₂ 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 –CF₃, –CF₂CF₃, –CF₂CF₂CF₃, –CCl₃, –CFCl₂, –CF₂Cl, and the like.

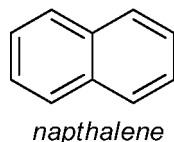
[0021] “Alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds), and optionally one or more triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) (“C₂₋₂₀ alkenyl”). In certain embodiments, alkenyl does not comprise triple bonds. In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some

embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ 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 C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), 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 C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₁₀ alkenyl.

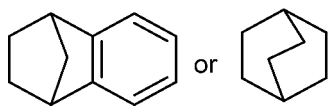
[0022] “Alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds), and optionally one or more double bonds (*e.g.*, 1, 2, 3, or 4 double bonds) (“C₂₋₂₀ alkynyl”). In certain embodiments, alkynyl does not comprise double bonds. In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptyne (C₇), octyne (C₈), 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 C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is substituted C₂₋₁₀ alkynyl.

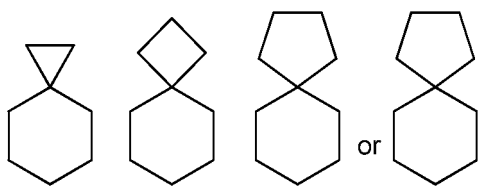
[0023] “Fused” or “ortho-fused” are used interchangeably herein, and refer to two rings that have two atoms and one bond in common, *e.g.*,



[0024] “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.*,



[0025] “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.*,



Spiro-fusion at a bridgehead atom is also contemplated.

[0026] “Carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In certain embodiments, a carbocyclyl group refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀

carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or is a fused, bridged or spiro-fused 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 C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₀ carbocyclyl.

[0027] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ cycloalkyl”). In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). 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 C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₃₋₁₀ cycloalkyl.

[0028] “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-fused 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.

[0029] 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.

[0030] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, 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 three 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 C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, 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.

[0031] “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 (“C₆ aryl”;

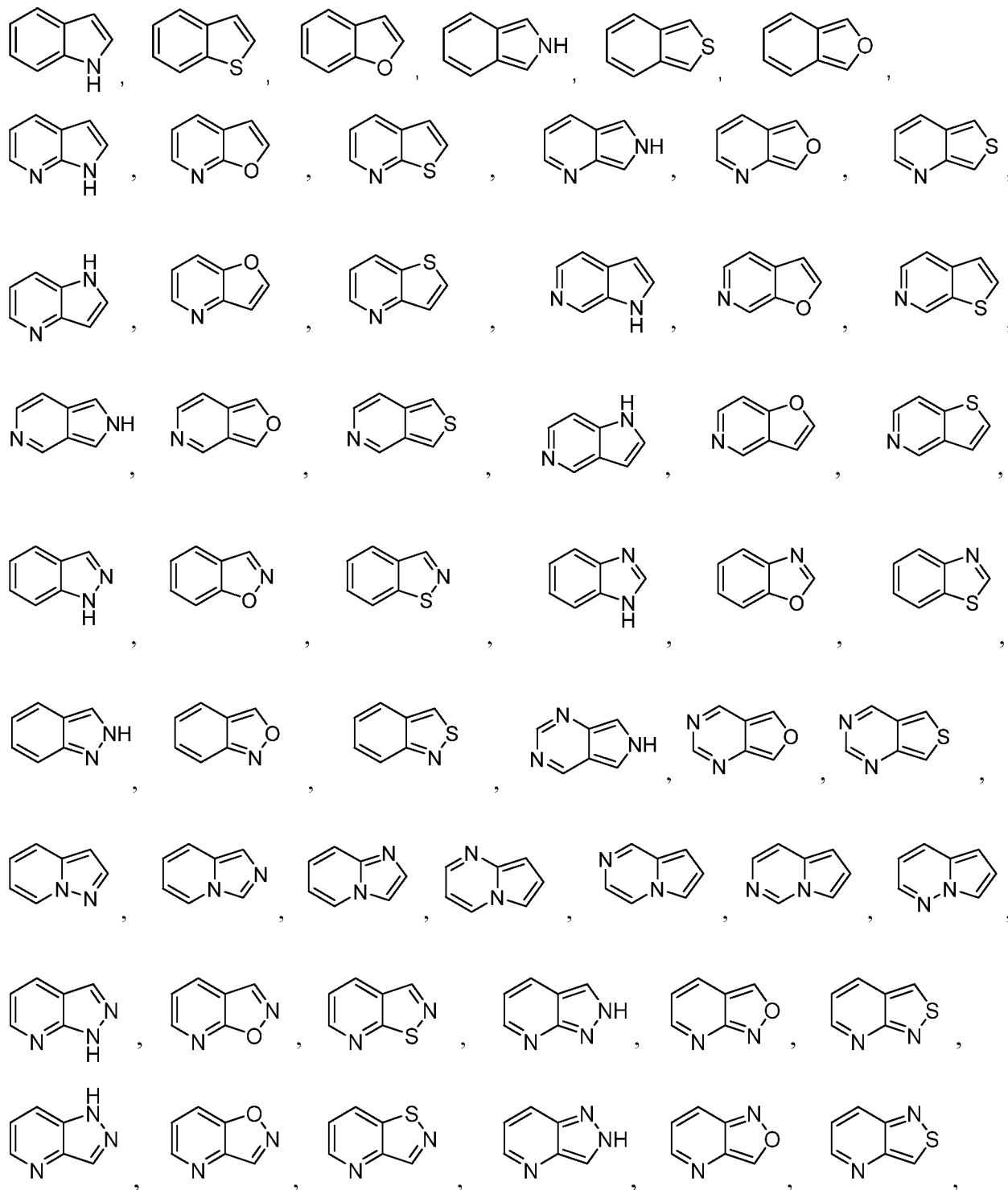
e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as 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 C₆₋₁₄ aryl. In certain embodiments, the aryl group is substituted C₆₋₁₄ aryl.

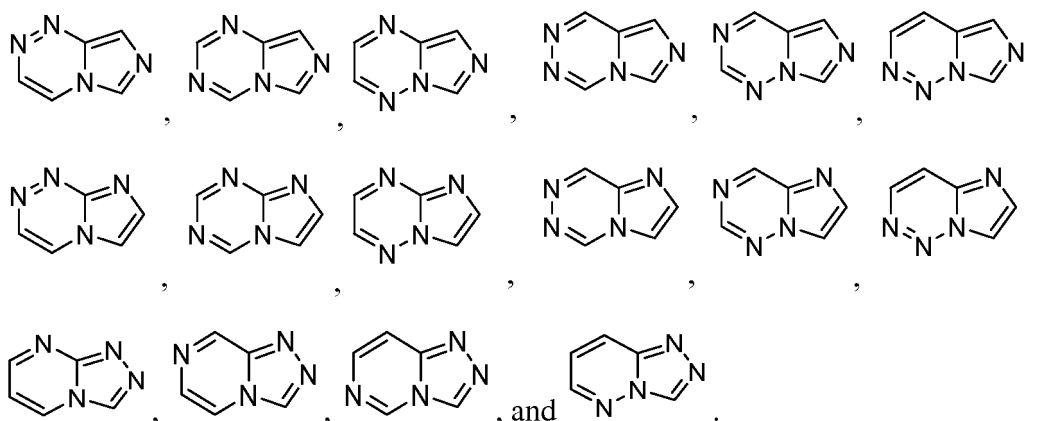
[0032] “Heteroaryl” refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each 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).

[0033] 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.

[0034] 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 thiophenyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, any one of the following formulae:





In any of the monocyclic or bicyclic heteroaryl groups, the point of attachment can be any carbon or nitrogen atom, as valency permits.

[0035] “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.

[0036] In some embodiments, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, “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.

[0037] Exemplary carbon atom substituents include, but are not limited to, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{OP}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, 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 $=\text{O}$, $=\text{S}$, $=\text{NN}(\text{R}^{\text{bb}})_2$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$, or $=\text{NOR}^{\text{cc}}$;

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, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{cc}})_2$, 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;

NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHSO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃ - C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ 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.

[0038] 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⁻), NO₃⁻, ClO₄⁻, OH⁻, H₂PO₄⁻, HSO₄⁻, sulfonate ions (*e.g.*, methanesulfonate, 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).

[0039] “Halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0040] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents 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, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{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, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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.

[0041] 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, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, 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.

[0042] Amide nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *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.

[0043] Carbamate nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{OR}^{\text{aa}}$) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl 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-biphenyl)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*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonyl ethyl 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-dimethoxyacrylvinyl 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.

[0044] 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 phenacysulfonamide.

[0045] 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-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-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).

[0046] 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.

[0047] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (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-trimethylsilyl ethyl, 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), dimethylhexylsilyl, *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-naphthyl 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-butenate, *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).

[0048] 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.

[0049] 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.

[0050] “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.

[0051] 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.

[0052] “Condition,” “disease,” and “disorder” are used interchangeably herein.

[0053] “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”).

[0054] 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.

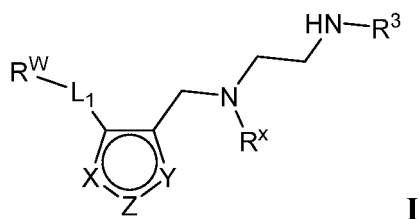
[0055] A “therapeutically effective amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic 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.

[0056] 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.

[0057] 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. Methyltransferases 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.

[0058] As generally described above, provided herein are compounds useful as arginine methyltransferase (RMT) inhibitors. In some embodiments, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

X is N, Z is NR^4 , and Y is CR^5 ; or

X is NR^4 , Z is N, and Y is CR^5 ; or

X is CR^5 , Z is NR^4 , and Y is N; or

X is CR^5 , Z is N, and Y is NR^4 ;

R^x is optionally substituted C_{1-4} alkyl or optionally substituted C_{3-4} cycloalkyl;

L_1 is a bond, -O-, - $\text{N}(\text{R}^B)$ -, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O) $\text{N}(\text{R}^B)$ -, -C(O) $\text{N}(\text{R}^B)\text{N}(\text{R}^B)$ -, -OC(O)-, -OC(O) $\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{O})$ -, - $\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{O})\text{O}$ -, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B) $\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{=NR}^B)$ -, -C(S)-, -C(S) $\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{S})$ -, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, - $\text{N}(\text{R}^B)\text{SO}_2$ -, -SO₂ $\text{N}(\text{R}^B)$ -, or an optionally substituted C_{1-6} saturated or unsaturated hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain is optionally and independently replaced with -O-, - $\text{N}(\text{R}^B)$ -, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O) $\text{N}(\text{R}^B)$ -, -C(O) $\text{N}(\text{R}^B)\text{N}(\text{R}^B)$ -, -OC(O)-, -OC(O) $\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{O})$ -, - $\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{O})\text{O}$ -, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B) $\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{=NR}^B)$ -, -C(S)-, -C(S) $\text{N}(\text{R}^B)$ -, - $\text{NR}^B\text{C}(\text{S})$ -, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, - $\text{N}(\text{R}^B)\text{SO}_2$ -, or -SO₂ $\text{N}(\text{R}^B)$ -;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or an R^B and R^W on the same nitrogen atom may be taken together with the intervening nitrogen to form an optionally substituted heterocyclic ring;

R^W is hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, provided that when L_1 is a bond, R^W is not optionally substituted aryl or optionally substituted heteroaryl;

R^3 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl; or optionally substituted C_{1-4} alkyl-Cy;

Cy is optionally substituted C_{3-7} cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

R^5 is hydrogen, halo, -CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{3-4} cycloalkyl.

[0059] In certain embodiments, R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl; or optionally substituted C_{1-4} alkyl-Cy.

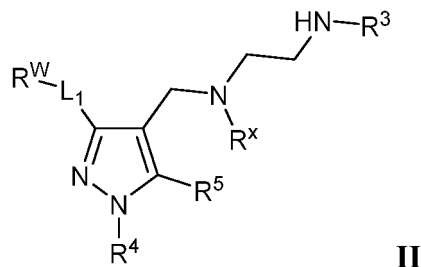
[0060] In certain embodiments, when L_1 is a bond, then R^W is not hydrogen. In certain embodiments, when L_1 is a bond, R^W is not hydrogen, optionally substituted aryl, or optionally substituted heteroaryl.

[0061] However, in certain embodiments, L_1 is a bond and R^W is hydrogen, halogen, or optionally substituted C_{1-6} alkyl. In certain embodiments, L_1 is a bond, R^W is hydrogen, halogen, or optionally substituted C_{1-6} alkyl, X is CR^5 , Z is N, and Y is NR^4 , wherein R^4 is optionally substituted carbocyclyl or optionally substituted heterocyclyl, and in such instances R^4 is also referred to as Ring A.

[0062] As generally described herein, R^W may also be referred to as Ring A, wherein Ring A is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, provided that when L_1 is a bond, R^W is not optionally substituted aryl or optionally substituted heteroaryl. R^W and Ring A are thus

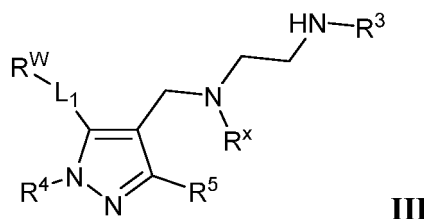
used interchangeably herein when R^W describes a cyclic moiety. Furthermore, as described above, in certain embodiments, Ring A and R^4 are used interchangeably herein when R^4 encompass an optionally substituted carbocyclyl or optionally substituted heterocyclyl group.

[0063] In certain embodiments, a provided compound is of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein R^W , L_1 , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, L_1 is a bond and R^W is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl). In certain embodiments, L_1 is an optionally substituted C_{2-6} alkylene, optionally substituted C_{2-6} alkenylene, or optionally substituted C_{2-6} alkynylene chain, and R^W is optionally substituted aryl or optionally substituted heteroaryl.

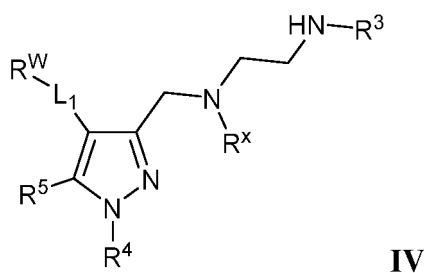
[0064] In certain embodiments, a provided compound is of Formula (III):



or a pharmaceutically acceptable salt thereof, wherein R^W , L_1 , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, L_1 is a bond and R^W is an optionally substituted bicyclic carbocyclyl (*e.g.*, an

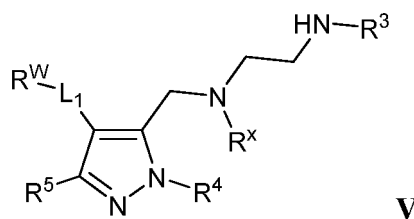
optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl). In certain embodiments, L_1 is an optionally substituted C_{2-6} alkylene, optionally substituted C_{2-6} alkenylene, or optionally substituted C_{2-6} alkynylene chain, and R^W is optionally substituted aryl or optionally substituted heteroaryl.

[0065] In certain embodiments, a provided compound is of Formula (IV):



or a pharmaceutically acceptable salt thereof, wherein R^W , L_1 , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, L_1 is a bond and R^W is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl). In certain embodiments, L_1 is an optionally substituted C_{2-6} alkylene, optionally substituted C_{2-6} alkenylene, or optionally substituted C_{2-6} alkynylene chain, and R^W is optionally substituted aryl or optionally substituted heteroaryl.

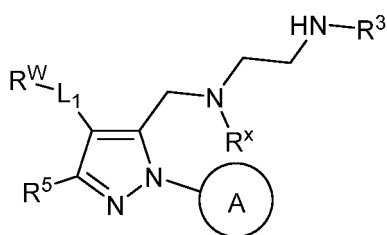
[0066] In certain embodiments, a provided compound is of Formula (V):



or a pharmaceutically acceptable salt thereof, wherein R^W , L_1 , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is optionally

substituted C₃₋₆ carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, L₁ is a bond and R^W is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl). In certain embodiments, L₁ is an optionally substituted C₂₋₆alkylene, optionally substituted C₂₋₆alkenylene, or optionally substituted C₂₋₆alkynylene chain, and R^W is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R⁴ is an optionally substituted carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

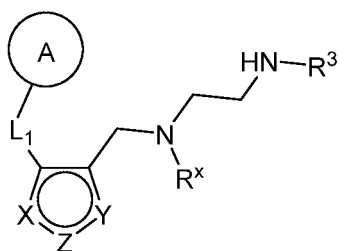
[0067] In certain embodiments, when R⁴ is Ring A, wherein Ring A is an optionally substituted carbocyclyl or optionally substituted heterocyclyl, a provided compound is of Formula (XII-a5):



XII-a5

or a pharmaceutically acceptable salt thereof, wherein R^W, L₁, R³, R⁵, R^x, and Ring A are as described herein. In certain embodiments, R^x is optionally substituted C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, R³ is hydrogen or C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, R⁵ is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, halogen, or optionally substituted C₁₋₄alkyl. In certain embodiments, L₁ is a bond and R^W is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R⁵ is hydrogen. In certain embodiments, L₁ is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L₁ is a bond and R^W is optionally substituted C₁₋₆alkyl, *e.g.*, unsubstituted C₁₋₄alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl. In certain embodiments, Ring A is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

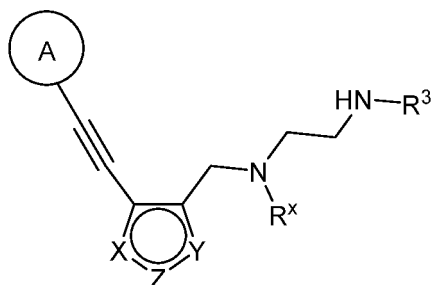
[0068] In certain embodiments, a provided compound is of Formula (VI):



VI

or a pharmaceutically acceptable salt thereof, wherein L_1 , Ring A, R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, L_1 is a bond and R^W is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl). In certain embodiments, L_1 is an optionally substituted C_{2-6} alkylene, optionally substituted C_{2-6} alkenylene, or optionally substituted C_{2-6} alkynylene chain, and Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl.

[0069] In certain embodiments, a provided compound is of Formula (VI-a):

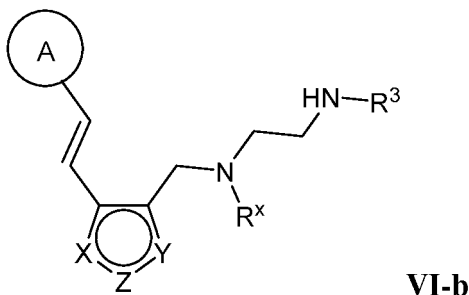


VI-a

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain

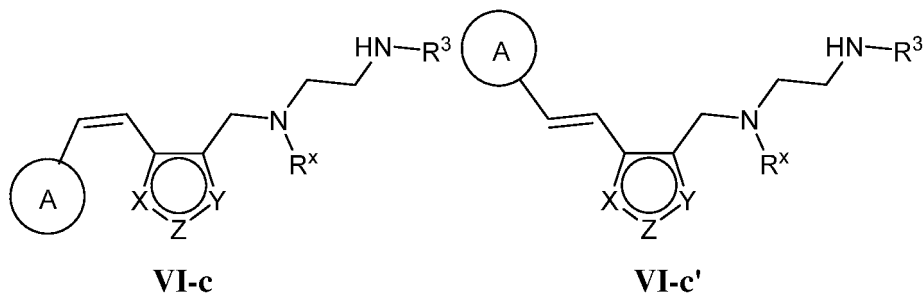
embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0070] In certain embodiments, a provided compound is of Formula (VI-b):



or a pharmaceutically acceptable salt thereof, wherein Ring A, R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

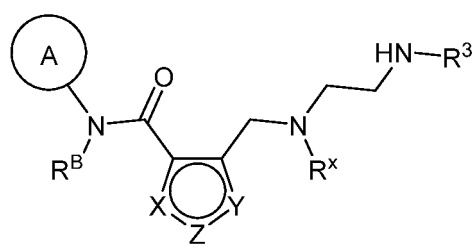
[0071] In certain embodiments, a provided compound is of Formula (VI-c) or (VI-c'):



or a pharmaceutically acceptable salt thereof, wherein Ring A, R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N,

and Y is CR⁵. In certain embodiments, X is CR⁵, Z is NR⁴, and Y is N. In certain embodiments, X is CR⁵, Z is N, and Y is NR⁴. In certain embodiments, R⁴ is hydrogen or optionally substituted C₁₋₆ alkyl (*e.g.*, methyl). In certain embodiments, R⁵ is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C₃₋₆ carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

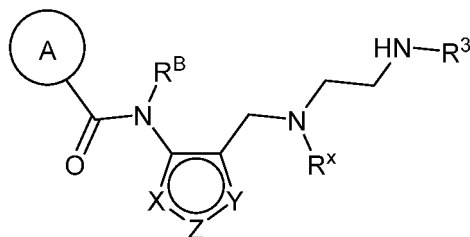
[0072] In certain embodiments, a provided compound is of Formula (VI-d):



VI-d

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^B, R³, R⁴, R⁵, and R^x are as described herein. In certain embodiments, R^x is optionally substituted C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, R³ is hydrogen or C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR⁴, and Y is CR⁵. In certain embodiments, X is NR⁴, Z is N, and Y is CR⁵. In certain embodiments, X is CR⁵, Z is NR⁴, and Y is N. In certain embodiments, X is CR⁵, Z is N, and Y is NR⁴. In certain embodiments, R⁴ is hydrogen or optionally substituted C₁₋₆ alkyl (*e.g.*, methyl). In certain embodiments, R⁵ is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C₃₋₆ carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

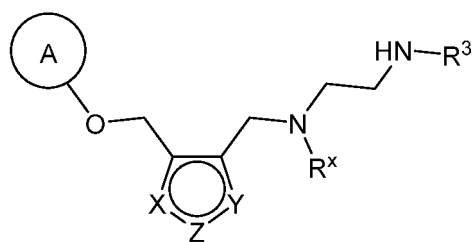
[0073] In certain embodiments, a provided compound is of Formula (VI-e):



VI-e

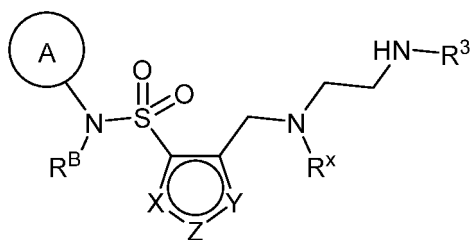
or a pharmaceutically acceptable salt thereof, wherein Ring A, R^B , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0074] In certain embodiments, a provided compound is of Formula (VI-f):



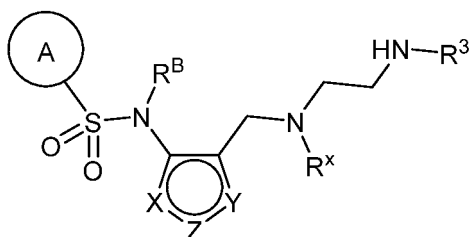
or a pharmaceutically acceptable salt thereof, wherein Ring A, R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0075] In certain embodiments, a provided compound is of Formula (VI-g):

**VI-g**

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^B , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

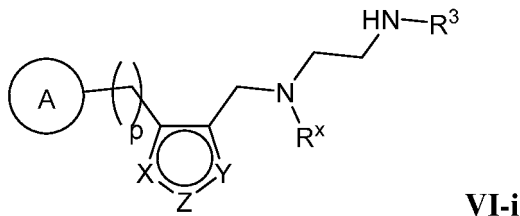
[0076] In certain embodiments, a provided compound is of Formula **(VI-h)**:

**VI-h**

or a pharmaceutically acceptable salt thereof, wherein Ring A, R^B , R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain

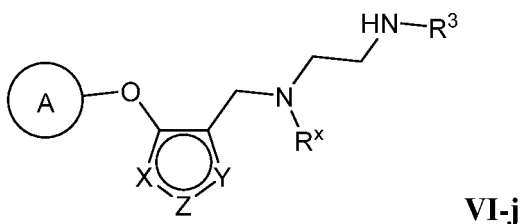
embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0077] In certain embodiments, a provided compound is of Formula (VI-i):



or a pharmaceutically acceptable salt thereof, wherein Ring A, R^3 , R^4 , R^5 , and R^x are as described herein, and p is 1, 2, 3, 4, 5, or 6. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl). In certain embodiments, p is 1, 2, or 3.

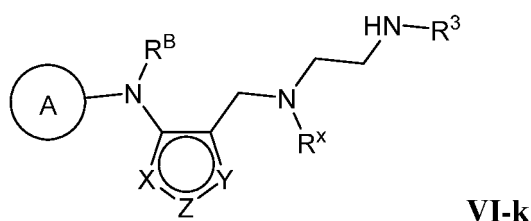
[0078] In certain embodiments, a provided compound is of Formula (VI-j):



or a pharmaceutically acceptable salt thereof, wherein Ring A, R^3 , R^4 , R^5 , and R^x are as described herein. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, R^3 is hydrogen or C_{1-4} alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or

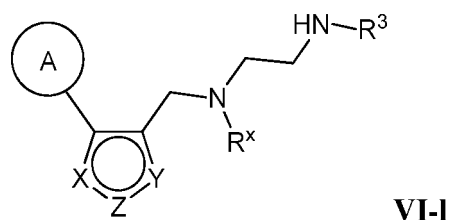
optionally substituted C₁₋₆ alkyl (*e.g.*, methyl). In certain embodiments, R⁵ is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C₃₋₆ carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0079] In certain embodiments, a provided compound is of Formula (VI-k):



or a pharmaceutically acceptable salt thereof, wherein Ring A, R^B, R³, R⁴, R⁵, and R^x are as described herein. In certain embodiments, R^x is optionally substituted C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, R³ is hydrogen or C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, X is N, Z is NR⁴, and Y is CR⁵. In certain embodiments, X is NR⁴, Z is N, and Y is CR⁵. In certain embodiments, X is CR⁵, Z is NR⁴, and Y is N. In certain embodiments, X is CR⁵, Z is N, and Y is NR⁴. In certain embodiments, R⁴ is hydrogen or optionally substituted C₁₋₆ alkyl (*e.g.*, methyl). In certain embodiments, R⁵ is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C₃₋₆ carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0080] In certain embodiments, a provided compound is of Formula (VI-l):



or a pharmaceutically acceptable salt thereof, wherein Ring A, R^B, R³, R⁴, R⁵, and R^x are as described herein. In certain embodiments, R^x is optionally substituted C₁₋₄ alkyl (*e.g.*, methyl). In certain embodiments, R³ is hydrogen or C₁₋₄ alkyl (*e.g.*, methyl). In certain

embodiments, X is N, Z is NR^4 , and Y is CR^5 . In certain embodiments, X is NR^4 , Z is N, and Y is CR^5 . In certain embodiments, X is CR^5 , Z is NR^4 , and Y is N. In certain embodiments, X is CR^5 , Z is N, and Y is NR^4 . In certain embodiments, R^4 is hydrogen or optionally substituted C_{1-6} alkyl (*e.g.*, methyl). In certain embodiments, R^5 is hydrogen. In certain embodiments, Ring A (a subset of R^W) is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, Ring A (a subset of R^W) is optionally substituted C_{3-6} carbocyclyl or optionally substituted 5-6 membered heterocyclyl. In certain embodiments, Ring A (a subset of R^W) is an optionally substituted bicyclic carbocyclyl (*e.g.*, an optionally substituted spiro-fused bicyclic carbocyclyl) or optionally substituted bicyclic heterocyclyl (*e.g.*, optionally substituted spiro-fused bicyclic heterocyclyl).

[0081] As defined generally above, L_1 is a bond, $-\text{O}-$, $-\text{N}(\text{R}^B)-$, $-\text{S}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{N}(\text{R}^B)-$, $-\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})-$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})\text{O}-$, $-\text{SC}(\text{O})-$, $-\text{C}(=\text{NR}^B)-$, $-\text{C}(=\text{NNR}^B)-$, $-\text{C}(=\text{NOR}^A)-$, $-\text{C}(=\text{NR}^B)\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(=\text{NR}^B)-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{S})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{SO}_2-$, $-\text{N}(\text{R}^B)\text{SO}_2-$, $-\text{SO}_2\text{N}(\text{R}^B)-$, or an optionally substituted C_{1-6} saturated or unsaturated hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain is optionally and independently replaced with $-\text{O}-$, $-\text{N}(\text{R}^B)-$, $-\text{S}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{N}(\text{R}^B)-$, $-\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})-$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})\text{O}-$, $-\text{SC}(\text{O})-$, $-\text{C}(=\text{NR}^B)-$, $-\text{C}(=\text{NNR}^B)-$, $-\text{C}(=\text{NOR}^A)-$, $-\text{C}(=\text{NR}^B)\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(=\text{NR}^B)-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{S})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{SO}_2-$, $-\text{N}(\text{R}^B)\text{SO}_2-$, or $-\text{SO}_2\text{N}(\text{R}^B)-$. In some embodiments, L_1 is a bond. In some embodiments, L_1 is $-\text{O}-$, $-\text{N}(\text{R}^B)-$, $-\text{S}-$. In some embodiments, L_1 is $-\text{O}-$. In some embodiments, L_1 is $-\text{N}(\text{R}^B)-$. In some embodiments, L_1 is $-\text{NH}-$. In some embodiments, L_1 is $-\text{C}(\text{O})-$. In some embodiments, L_1 is $-\text{C}(\text{O})\text{N}(\text{R}^B)-$ or $-\text{NR}^B\text{C}(\text{O})-$. In some embodiments, L_1 is $-\text{C}(\text{O})\text{NH}-$. In some embodiments, L_1 is $-\text{NHC}(\text{O})-$. In some embodiments, L_1 is $-\text{N}(\text{R}^B)\text{SO}_2-$ or $-\text{SO}_2\text{N}(\text{R}^B)-$. In some embodiments, L_1 is $-\text{NHSO}_2-$. In some embodiments, L_1 is $-\text{SO}_2\text{NH}-$.

[0082] In some embodiments, L_1 is an optionally substituted C_{1-6} saturated or unsaturated hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain is optionally and independently replaced with $-\text{O}-$, $-\text{N}(\text{R}^B)-$, $-\text{S}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{N}(\text{R}^B)-$, $-\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})-$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{O})\text{O}-$, $-\text{SC}(\text{O})-$, $-\text{C}(=\text{NR}^B)-$, $-\text{C}(=\text{NNR}^B)-$, $-\text{C}(=\text{NOR}^A)-$, $-\text{C}(=\text{NR}^B)\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(=\text{NR}^B)-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{S})\text{N}(\text{R}^B)-$, $-\text{NR}^B\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{SO}_2-$, $-\text{N}(\text{R}^B)\text{SO}_2-$, or $-\text{SO}_2\text{N}(\text{R}^B)-$. In some embodiments, L_1 is an optionally

substituted C₁₋₆ saturated or unsaturated hydrocarbon chain. In some embodiments, L₁ is an optionally substituted C₁₋₆ alkylene chain. In some embodiments, L₁ is an unsubstituted C₁₋₆ alkylene chain. In some embodiments, L₁ is an optionally substituted C₂₋₆ alkenylene chain. In some embodiments, L₁ is an unsubstituted C₂₋₆ alkenylene chain. In some embodiments, L₁ is -CH=CH-. In some embodiments, L₁ is an optionally substituted C₂₋₆ alkynylene chain. In some embodiments, L₁ is an unsubstituted C₂₋₆ alkynylene chain. In some embodiments, L₁ is -C≡C-. In some embodiments, L₁ is an optionally substituted C₁₋₆ saturated or unsaturated hydrocarbon chain, wherein one methylene unit of the hydrocarbon chain is optionally and independently replaced with -O-, -N(R^B)-, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O)N(R^B)-, -C(O)N(R^B)N(R^B)-, -OC(O)-, -OC(O)N(R^B)-, -NR^BC(O)-, -NR^BC(O)N(R^B)-, -NR^BC(O)N(R^B)N(R^B)-, -NR^BC(O)O-, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B)N(R^B)-, -NR^BC(=NR^B)-, -C(S)-, -C(S)N(R^B)-, -NR^BC(S)-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, -N(R^B)SO₂-, or -SO₂N(R^B)-. In some embodiments, L₁ is an optionally substituted C₁₋₆ saturated or unsaturated hydrocarbon chain, wherein two methylene units of the hydrocarbon chain is optionally and independently replaced with -O-, -N(R^B)-, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O)N(R^B)-, -C(O)N(R^B)N(R^B)-, -OC(O)-, -OC(O)N(R^B)-, -NR^BC(O)-, -NR^BC(O)N(R^B)-, -NR^BC(O)N(R^B)N(R^B)-, -NR^BC(O)O-, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B)N(R^B)-, -NR^BC(=NR^B)-, -C(S)-, -C(S)N(R^B)-, -NR^BC(S)-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, -N(R^B)SO₂-, or -SO₂N(R^B)-. In some embodiments, L₁ is an optionally substituted C₁₋₆ saturated or unsaturated hydrocarbon chain, wherein three methylene units of the hydrocarbon chain is optionally and independently replaced with -O-, -N(R^B)-, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O)N(R^B)-, -C(O)N(R^B)N(R^B)-, -OC(O)-, -OC(O)N(R^B)-, -NR^BC(O)-, -NR^BC(O)N(R^B)-, -NR^BC(O)N(R^B)N(R^B)-, -NR^BC(O)O-, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B)N(R^B)-, -NR^BC(=NR^B)-, -C(S)-, -C(S)N(R^B)-, -NR^BC(S)-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, -N(R^B)SO₂-, or -SO₂N(R^B)-. In some embodiments, L₁ is an optionally substituted C₁₋₆ saturated or unsaturated hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain is optionally and independently replaced with -O-, -N(R^B)-, -S-, -C(O)-, -C(O)N(R^B)-, -NR^BC(O)-, -SO₂-, -N(R^B)SO₂-, or -SO₂N(R^B)-. In some embodiments, L₁ is -CH₂O- or -OCH₂-.

[0083] As defined generally above, R^W is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; provided that when L₁ is a bond, R^W is not optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, when L₁ is a bond, then R^W is

not hydrogen. In some embodiments, when L_1 is a bond, R^W is not hydrogen, optionally substituted aryl, or optionally substituted heteroaryl.

[0084] In certain embodiments, L_1 is a bond, and R^W is hydrogen, halogen, or optionally substituted C_{1-6} alkyl. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-6} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl. In certain embodiments, L_1 is a bond, R^W is hydrogen, halogen, or optionally substituted C_{1-6} alkyl, X is CR^5 , Z is N, and Y is NR^4 , and R^4 is optionally substituted carbocyclyl or optionally substituted heterocyclyl (in such instances, R^4 may also be referred to as Ring A).

[0085] In some embodiments, R^W is hydrogen.

[0086] In some embodiments, R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo.

[0087] In some embodiments, R^W is optionally substituted C_{1-6} alkyl. In some embodiments, R^W is unsubstituted C_{1-6} alkyl. In some embodiments, R^W is methyl, ethyl, propyl, or butyl. In some embodiments, R^W is isopropyl, isobutyl, or isoamyl. In some embodiments, R^W is optionally substituted C_{2-6} alkenyl. In some embodiments, R^W is C_{2-6} alkynyl.

[0088] In some embodiments, R^W is optionally substituted carbocyclyl. In some embodiments, R^W is optionally substituted C_{3-6} carbocyclyl. In some embodiments, R^W is unsubstituted cyclopropyl. In some embodiments, R^W is substituted cyclopropyl. In some embodiments, R^W is unsubstituted cyclobutyl. In some embodiments, R^W is substituted cyclobutyl. In some embodiments, R^W is unsubstituted cyclopentyl. In some embodiments, R^W is substituted cyclopentyl. In some embodiments, R^W is unsubstituted cyclohexyl. In some embodiments, R^W is substituted cyclohexyl. In some embodiments, R^W is optionally substituted cyclopentenyl or optionally substituted cyclohexenyl.

[0089] In some embodiments, R^W is optionally substituted heterocyclyl. In some embodiments, R^W is an optionally substituted 4- to 7-membered heterocyclyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is azetidiny or oxetanyl. In some embodiments, R^W is optionally substituted tetrahydrofuranyl, optionally substituted pyrrolidinyl, optionally substituted dihydropyrrolyl, or optionally substituted pyrrolyl-2,5-dione. In some embodiments, R^W is optionally substituted piperidinyl, optionally substituted tetrahydropyranyl, optionally substituted dihydropyranyl, optionally substituted dihydropyridinyl, and optionally substituted thianyl. In certain embodiments, R^W is optionally substituted piperidinyl. In

some embodiments, R^W is optionally substituted piperazinyl, optionally substituted morpholinyl, optionally substituted dithianyl, and optionally substituted dioxanyl. In some embodiments, R^W is a 5- or 6-membered heterocyclyl group fused to a C₆ aryl ring. In some embodiments, R^W is optionally substituted indolinyl, optionally substituted isoindolinyl, optionally substituted dihydrobenzofuranyl, optionally substituted dihydrobenzothienyl, or optionally substituted benzoxazolinonyl. In some embodiments, R^W is optionally substituted tetrahydroquinolinyl or optionally substituted tetrahydroisoquinolinyl.

[0090] In some embodiments, R^W is optionally substituted aryl. In some embodiments, R^W is optionally substituted phenyl. In some embodiments, R^W is unsubstituted phenyl. In some embodiments, R^W is substituted phenyl. In some embodiments, R^W is monosubstituted phenyl. In some embodiments, R^W is disubstituted phenyl. In some embodiments, R^W is trisubstituted phenyl. In some embodiments, R^W is optionally substituted naphthyl. In some embodiments, R^W is unsubstituted naphthyl.

[0091] In some embodiments, R^W is optionally substituted heteroaryl. In some embodiments, R^W is an optionally substituted 5- to 10-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 5- to 8-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 5- to 6-membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 5- to 6-membered heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 9- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 9-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 9-

membered bicyclic heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 9-membered bicyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 10-membered bicyclic heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^W is an optionally substituted 10-membered bicyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur.

[0092] In some embodiments, R^W is substituted or unsubstituted pyrrolyl, substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyrimidyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted indolyl, substituted or unsubstituted isoindolyl, substituted or unsubstituted indazolyl, substituted or unsubstituted benzotriazolyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted isobenzothiophenyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzoisofuranyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted benzoxazolyl, substituted or unsubstituted benzoxadiazolyl, substituted or unsubstituted benzisoxazolyl, substituted or unsubstituted benzthiazolyl, substituted or unsubstituted benzisothiazolyl, substituted or unsubstituted benzthiadiazolyl, substituted or unsubstituted indolizynyl, substituted or unsubstituted purinyl, substituted or unsubstituted pyrrolopyridinyl, substituted or unsubstituted triazolopyridinyl, substituted or unsubstituted naphthyridinyl, substituted or unsubstituted pteridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted quinazolinyl, or substituted or unsubstituted phthalazinyl.

[0093] As generally described herein, R^W may also be referred to as Ring A, wherein Ring A is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally

substituted aryl, or optionally substituted heteroaryl, provided that when L_1 is a bond, R^W is not optionally substituted aryl or optionally substituted heteroaryl. R^W and Ring A are thus used interchangeably herein when R^W describes a cyclic moiety. Furthermore, as described above, in certain embodiments, Ring A and R^4 are used interchangeably herein when R^4 encompass an optionally substituted carbocyclyl or optionally substituted heterocyclyl group.

[0094] In some embodiments, Ring A (corresponding to R^W or R^4) is optionally substituted carbocyclyl. In some embodiments, Ring A is optionally substituted C_{3-6} carbocyclyl. In some embodiments, Ring A is optionally substituted C_{3-8} carbocyclyl. In some embodiments, Ring A is optionally substituted C_3 carbocyclyl, C_4 carbocyclyl, C_5 carbocyclyl, C_6 carbocyclyl, C_7 carbocyclyl, or C_8 carbocyclyl. In some embodiments, Ring A is unsubstituted cyclopropyl. In some embodiments, Ring A is substituted cyclopropyl. In some embodiments, Ring A is unsubstituted cyclobutyl. In some embodiments, Ring A is substituted cyclobutyl. In some embodiments, Ring A is unsubstituted cyclopentyl. In some embodiments, Ring A is substituted cyclopentyl. In some embodiments, Ring A is unsubstituted cyclohexyl. In some embodiments, Ring A is substituted cyclohexyl. In some embodiments, Ring A is optionally substituted cyclopentenyl or optionally substituted cyclohexenyl.

[0095] In some embodiments, Ring A (corresponding to R^W or R^4) is optionally substituted bicyclic carbocyclyl. In certain embodiments, Ring A is a fused bicyclic carbocyclyl, *e.g.*, Ring A is an optionally substituted C_{3-10} carbocyclyl radical comprising an optionally substituted C_{3-10} carbocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring fused thereto. In certain embodiments, Ring A is a bridged bicyclic carbocyclyl, *e.g.*, an optionally substituted C_{3-10} carbocyclyl radical bridged by a group comprising 1, 2, 3, 4, or 5 linear atoms. In certain embodiments, Ring A is a spiro-fused bicyclic carbocyclyl, *e.g.*, an optionally substituted C_{3-10} carbocyclyl radical comprising an optionally substituted C_{3-10} carbocyclyl ring spiro-fused thereto.

[0096] In some embodiments, Ring A (corresponding to R^W or R^4) is optionally substituted heterocyclyl. In some embodiments, Ring A is an optionally substituted 4- to 7-membered heterocyclyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is azetidiny or oxetany. In some embodiments, Ring A is optionally substituted tetrahydrofurany, optionally substituted pyrrolidinyl, optionally substituted dihydropyrrolyl, or optionally substituted pyrrolyl-2,5-dione. In some embodiments, Ring A is optionally substituted piperidinyl, optionally substituted tetrahydropyrany, optionally substituted dihydropyrany, optionally substituted

dihydropyridinyl, and optionally substituted thianyl. In certain embodiments, Ring A is optionally substituted piperidinyl. In some embodiments, Ring A is optionally substituted piperazinyl, optionally substituted morpholinyl, optionally substituted dithianyl, and optionally substituted dioxanyl. In some embodiments, Ring A is a 5- or 6-membered heterocyclyl group fused to a C₆ aryl ring. In some embodiments, Ring A is optionally substituted indolinyl, optionally substituted isoindolinyl, optionally substituted dihydrobenzofuranyl, optionally substituted dihydrobenzothienyl, or optionally substituted benzoxazolinonyl. In some embodiments, Ring A is optionally substituted tetrahydroquinolinyl or optionally substituted tetrahydroisoquinolinyl.

[0097] In some embodiments, Ring A (corresponding to R^W or R⁴) is optionally substituted bicyclic heterocyclyl. In certain embodiments, Ring A is a fused bicyclic heterocyclyl, *e.g.*, Ring A is an optionally substituted 3- to 10- membered heterocyclyl radical comprising an optionally substituted C₃₋₁₀ carbocyclyl, optionally substituted 3- to 10- membered heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring fused thereto. In certain embodiments, Ring A is a bridged bicyclic heterocyclyl, *e.g.*, an optionally substituted 3- to 10- membered heterocyclyl radical bridged by a group comprising 1, 2, 3, 4, or 5 linear atoms. In certain embodiments, Ring A is a spiro-fused bicyclic heterocyclyl, *e.g.*, an optionally substituted 3- to 10- membered heterocyclyl radical comprising an optionally substituted C₃₋₁₀ carbocyclyl ring or optionally substituted 3- to 10- membered heterocyclyl ring spiro-fused thereto.

[0098] In some embodiments, Ring A (corresponding to R^W) is optionally substituted aryl. In some embodiments, Ring A is optionally substituted phenyl. In some embodiments, Ring A is unsubstituted phenyl. In some embodiments, Ring A is substituted phenyl. In some embodiments, Ring A is monosubstituted phenyl. In some embodiments, Ring A is disubstituted phenyl. In some embodiments, Ring A is trisubstituted phenyl. In some embodiments, Ring A is optionally substituted naphthyl. In some embodiments, Ring A is unsubstituted naphthyl.

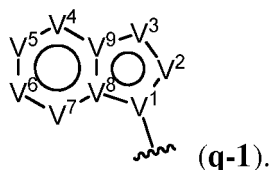
[0099] In some embodiments, Ring A (corresponding to R^W) is optionally substituted heteroaryl. In some embodiments, Ring A is an optionally substituted 5- to 10-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 5- to 8-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some

embodiments, Ring A is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 5- to 6-membered heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 5- to 6-membered heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 9- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 9-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 9-membered bicyclic heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 9-membered bicyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 10-membered bicyclic heteroaryl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is an optionally substituted 10-membered bicyclic heteroaryl having 1 heteroatom selected from nitrogen, oxygen, and sulfur.

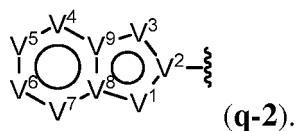
[00100] In some embodiments, Ring A (corresponding to R^W) is substituted or unsubstituted pyrrolyl, substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyrimidyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted indolyl, substituted or unsubstituted isoindolyl, substituted or

unsubstituted indazolyl, substituted or unsubstituted benzotriazolyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted isobenzothiophenyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzoisofuranyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted benzoxazolyl, substituted or unsubstituted benzoxadiazolyl, substituted or unsubstituted benzisoxazolyl, substituted or unsubstituted benzthiazolyl, substituted or unsubstituted benzisothiazolyl, substituted or unsubstituted benzthiadiazolyl, substituted or unsubstituted indoliziny, substituted or unsubstituted purinyl, substituted or unsubstituted pyrrolopyridinyl, substituted or unsubstituted triazolopyridinyl, substituted or unsubstituted naphthyridinyl, substituted or unsubstituted pteridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted quinazolinyl, or substituted or unsubstituted phthalazinyl.

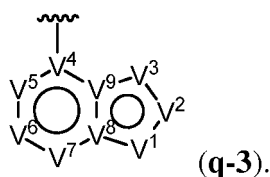
[00101] In certain embodiments, R^W (or Ring A) is of Formula (q-1):



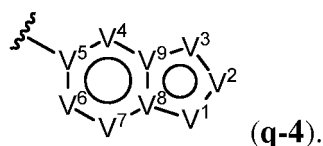
[00102] In certain embodiments, R^W (or Ring A) is of Formula (q-2):



[00103] In certain embodiments, R^W (or Ring A) is of Formula (q-3):



[00104] In certain embodiments, R^W (or Ring A) is of Formula (q-4):



[00105] As used herein, each instance of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 may independently be O, S, N, NR^N , C, or CR^C , as valency permits, wherein at least one of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 is O, S, N, NR^N , and wherein:

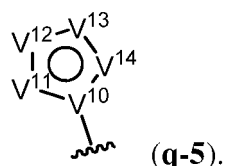
each instance of R^C is independently selected from the group consisting of hydrogen, halo, -CN, -NO₂, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -N(R^B)₂, -SR^A, -C(=O)R^A, -C(O)OR^A, -C(OSR^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, -SO₂R^A, -NR^BSO₂R^A, or -SO₂N(R^B)₂; and

each instance of R^N is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, 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(=NNR^B)R^A, -C(=NOR^A)R^A, -C(=NR^B)N(R^B)₂, -C(=S)R^A, -C(=S)N(R^B)₂, -S(=O)R^A, -SO₂R^A, -SO₂N(R^B)₂, and a nitrogen protecting group.

[00106] In certain embodiments, V^1 is O, S, N or NR^N. In certain embodiments, V^1 is N or NR^N. In certain embodiments, V^1 is O. In certain embodiments, V^1 is S. In certain embodiments, only one of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 is selected from the group consisting of O, S, N, and NR^N. In certain embodiments, only one of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 is selected from the group consisting of N and NR^N. In certain embodiments, only one of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 is O. In certain embodiments, only one of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 is S. In certain embodiments, only two of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, S, N, and NR^N. In certain embodiments, only two of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of N and NR^N. In certain embodiments, only two of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, N and NR^N. In certain embodiments, only two of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of S, N and NR^N. In certain embodiments, only three of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, S, N, and NR^N. In certain embodiments, only three of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of N and NR^N. In certain embodiments, only three of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, N and NR^N. In certain embodiments, only three of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and

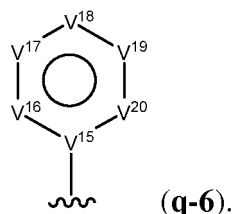
V^9 are each independently selected from the group consisting of S, N and NR^N . In certain embodiments, only four of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, S, N, and NR^N . In certain embodiments, only four of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of N and NR^N . In certain embodiments, only four of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, N and NR^N . In certain embodiments, only four of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of S, N and NR^N . In certain embodiments, only five of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of O, S, N, and NR^N . In certain embodiments, only five of V^1 , V^2 , V^3 , V^4 , V^5 , V^6 , V^7 , V^8 , and V^9 are each independently selected from the group consisting of N and NR^N .

[00107] In certain embodiments, R^W (or Ring A) is an optionally substituted 5-membered heteroaryl ring. In certain embodiments, R^W (or Ring A) is of Formula (q-5):



[00108] As used herein, each instance of V^{10} , V^{11} , V^{12} , V^{13} , and V^{14} may independently be O, S, N, NR^N , C, or CR^C , as valency permits, wherein R^N and R^C are as defined herein, and wherein at least one of V^{10} , V^{11} , V^{12} , V^{13} , and V^{14} is O, S, N, or NR^N . In certain embodiments, only one of V^{10} , V^{11} , V^{12} , V^{13} , and V^{14} is selected from the group consisting of O, S, N, and NR^N . In certain embodiments, only two of V^{10} , V^{11} , V^{12} , V^{13} , and V^{14} are selected from the group consisting of O, S, N, and NR^N . In certain embodiments, only three of V^{10} , V^{11} , V^{12} , V^{13} , and V^{14} are selected from the group consisting of O, S, N, and NR^N . In certain embodiments, only four of V^{10} , V^{11} , V^{12} , V^{13} , and V^{14} are selected from the group consisting of O, S, N, and NR^N .

[00109] In certain embodiments, R^W (or Ring A) is an optionally substituted 6-membered heteroaryl ring. In certain embodiments, R^W (or Ring A) is of Formula (q-6):

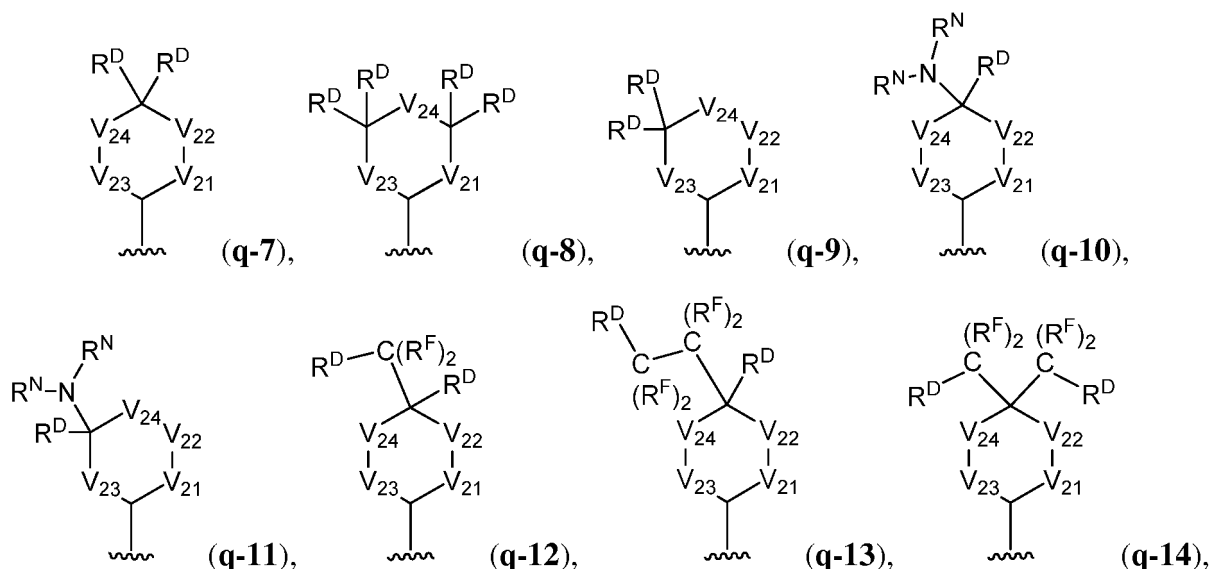


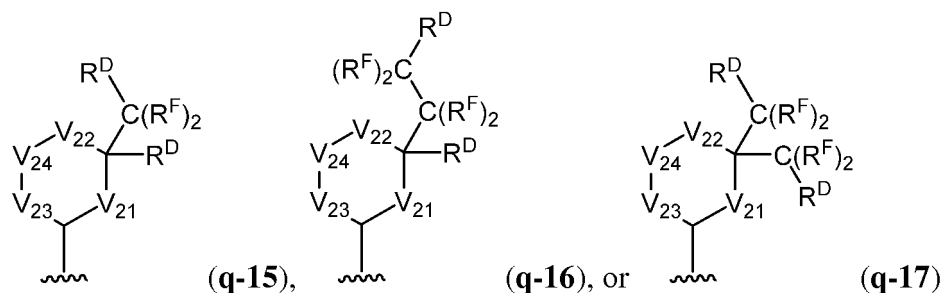
[00110] In compounds of Formula (q-6), V^{15} , V^{16} , V^{17} , V^{18} , V^{19} , and V^{20} are each independently selected from the group consisting of N or CR^C , wherein at least one of V^{15} ,

V^{16} , V^{17} , V^{18} , V^{19} , and V^{20} is N. In certain embodiments, only one of V^{15} , V^{16} , V^{17} , V^{18} , V^{19} , and V^{20} is N. In certain embodiments, only two of V^{15} , V^{16} , V^{17} , V^{18} , V^{19} , and V^{20} are N. In certain embodiments, only three of V^{15} , V^{16} , V^{17} , V^{18} , V^{19} , and V^{20} are N.

[00111] In certain embodiments, Ring A (corresponding to R^W or R^4) is an optionally substituted carbocyclyl or optionally substituted heterocyclyl, *e.g.*, an optionally substituted C_6 carbocyclyl, optionally substituted 6-membered heterocyclyl, optionally substituted C_6 carbocyclyl radical comprising an optionally substituted C_{3-10} carbocyclyl ring or optionally substituted 3- to 10- membered heterocyclyl ring spiro-fused thereto, or an optionally substituted 6-membered heterocyclyl radical comprising an optionally substituted C_{3-10} carbocyclyl ring or optionally substituted 3- to 10- membered heterocyclyl ring spiro-fused thereto. Furthermore, in certain embodiments, L_1 is a bond, R^W is hydrogen, halogen, or optionally substituted C_{1-6} alkyl, X is CR^5 , Z is N, and Y is NR^4 , and R^4 is optionally substituted carbocyclyl or optionally substituted heterocyclyl, *e.g.*, an optionally substituted C_6 carbocyclyl, optionally substituted 6-membered heterocyclyl, optionally substituted C_6 carbocyclyl radical comprising an optionally substituted C_{3-10} carbocyclyl ring or optionally substituted 3- to 10- membered heterocyclyl ring spiro-fused thereto, or an optionally substituted 6-membered heterocyclyl radical comprising an optionally substituted C_{3-10} carbocyclyl ring or optionally substituted 3- to 10- membered heterocyclyl ring spiro-fused thereto.

[00112] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-7) – (q-17):





wherein:

V^{21} , V^{22} , V^{23} , and V^{24} are each independently O, S, NR^N , C=O, or $C(R^C)_2$ as valency permits, provided no more than two of V^{21} , V^{22} , V^{23} , and V^{24} is a heteroatom O, S, and NR^N , alternatively wherein one of V^{21} , V^{22} , V^{23} , and V^{24} and another of V^{21} , V^{22} , V^{23} , and V^{24} adjacent to each other are joined to form an $N=C(R^C)$ or $C(R^C)=C(R^C)$ group provided the ring thus formed is not an aromatic ring;

each instance of R^C is independently hydrogen, halo, -CN, -NO₂, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, 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, -SO₂R^A, -NR^BSO₂R^A, or -SO₂N(R^B)₂;

each instance of R^N is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, 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(=NNR^B)R^A, -C(=NOR^A)R^A, -C(=NR^B)N(R^B)₂, -C(=S)R^A, -C(=S)N(R^B)₂, -S(=O)R^A, -SO₂R^A, -SO₂N(R^B)₂, or a nitrogen protecting group, or two R^N groups are joined to form an optionally substituted heterocyclic ring, or one R^N group and one R^D group are joined to form an optionally substituted heterocyclic ring;

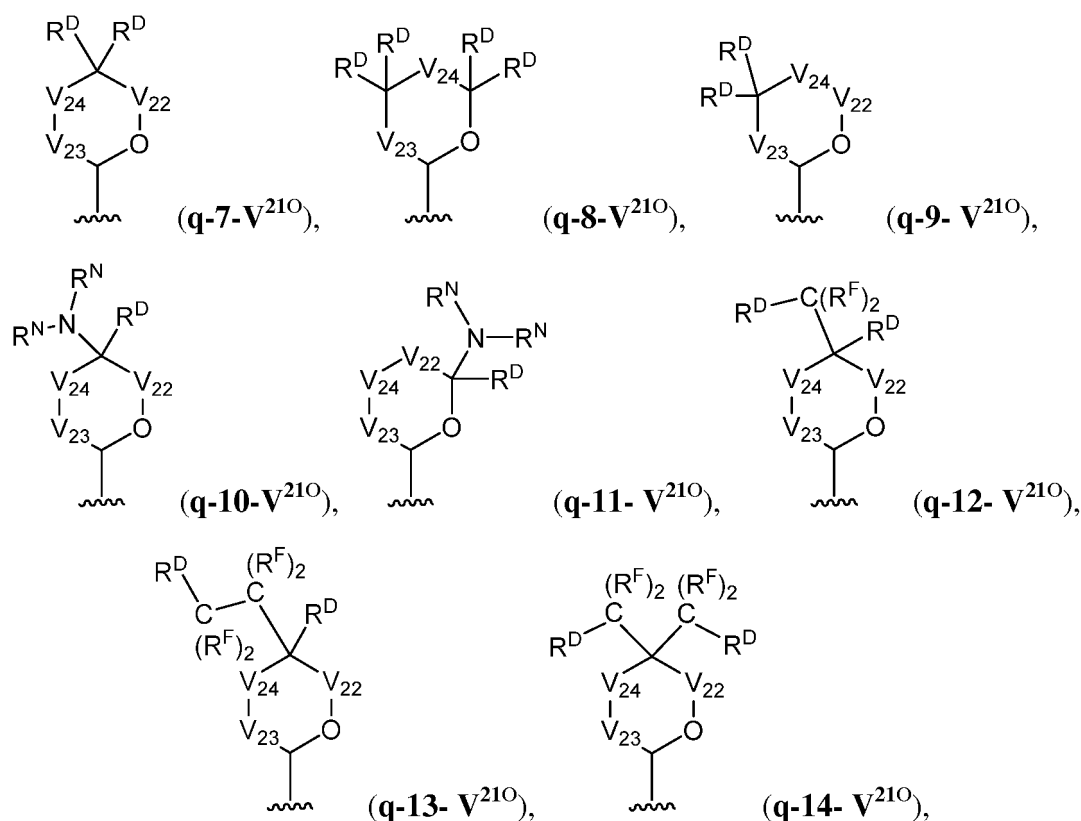
each instance of R^F is independently hydrogen or halo; and

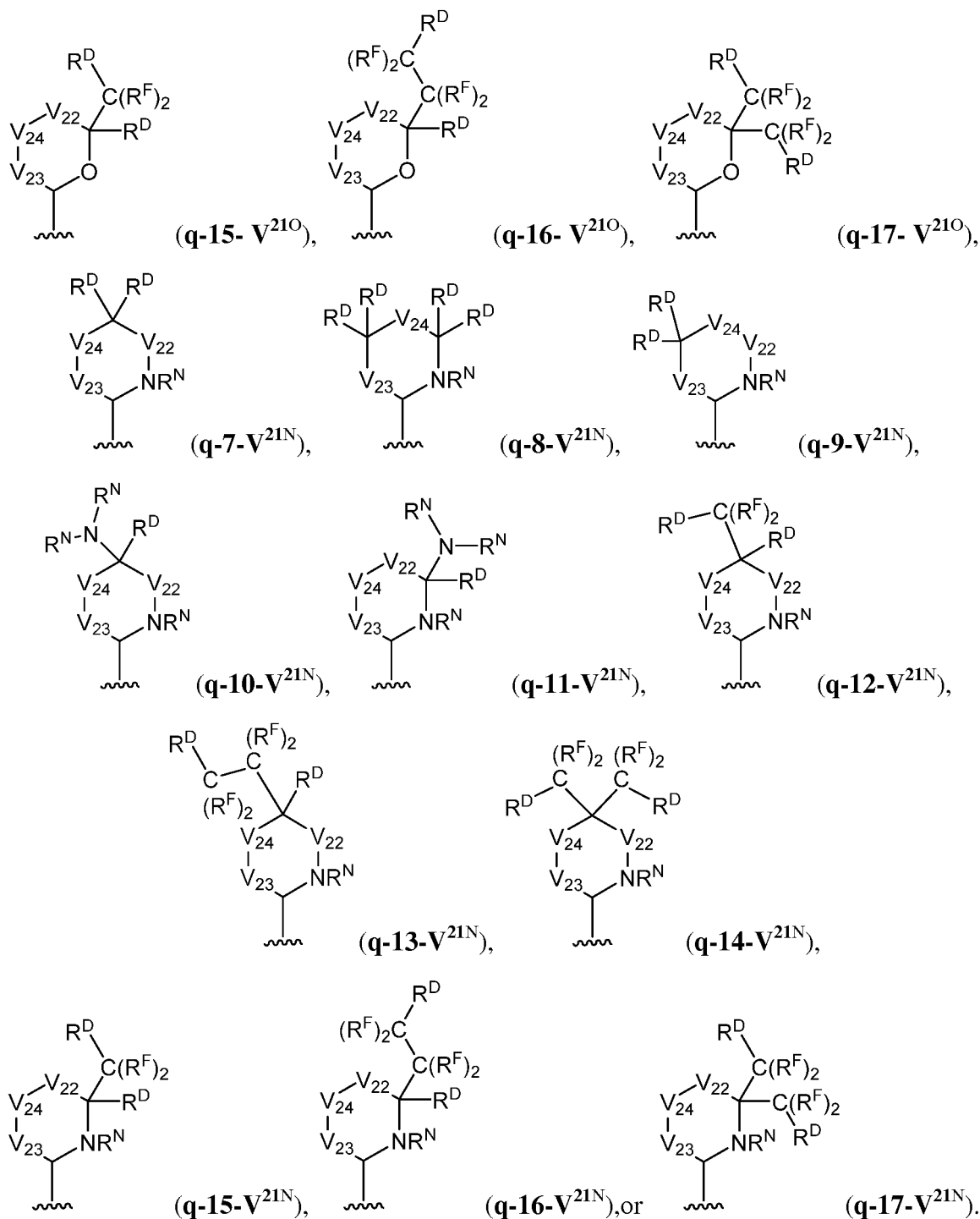
each instance of R^D is independently hydrogen, halo, -CN, -NO₂, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -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, -

$\text{NR}^{\text{B}}\text{C}(\text{O})\text{N}(\text{R}^{\text{B}})_2$, $-\text{NR}^{\text{B}}\text{C}(\text{O})\text{N}(\text{R}^{\text{B}})\text{N}(\text{R}^{\text{B}})_2$, $-\text{NR}^{\text{B}}\text{C}(\text{O})\text{OR}^{\text{A}}$, $-\text{SC}(\text{O})\text{R}^{\text{A}}$, $-\text{C}(=\text{NR}^{\text{B}})\text{R}^{\text{A}}$, $-\text{C}(=\text{NNR}^{\text{B}})\text{R}^{\text{A}}$, $-\text{C}(=\text{NOR}^{\text{A}})\text{R}^{\text{A}}$, $-\text{C}(=\text{NR}^{\text{B}})\text{N}(\text{R}^{\text{B}})_2$, $-\text{NR}^{\text{B}}\text{C}(=\text{NR}^{\text{B}})\text{R}^{\text{B}}$, $-\text{C}(=\text{S})\text{R}^{\text{A}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{B}})_2$, $-\text{NR}^{\text{B}}\text{C}(=\text{S})\text{R}^{\text{A}}$, $-\text{S}(\text{O})\text{R}^{\text{A}}$, $-\text{OS}(\text{O})_2\text{R}^{\text{A}}$, $-\text{SO}_2\text{R}^{\text{A}}$, $-\text{NR}^{\text{B}}\text{SO}_2\text{R}^{\text{A}}$, or $-\text{SO}_2\text{N}(\text{R}^{\text{B}})_2$; or two R^{D} groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring.

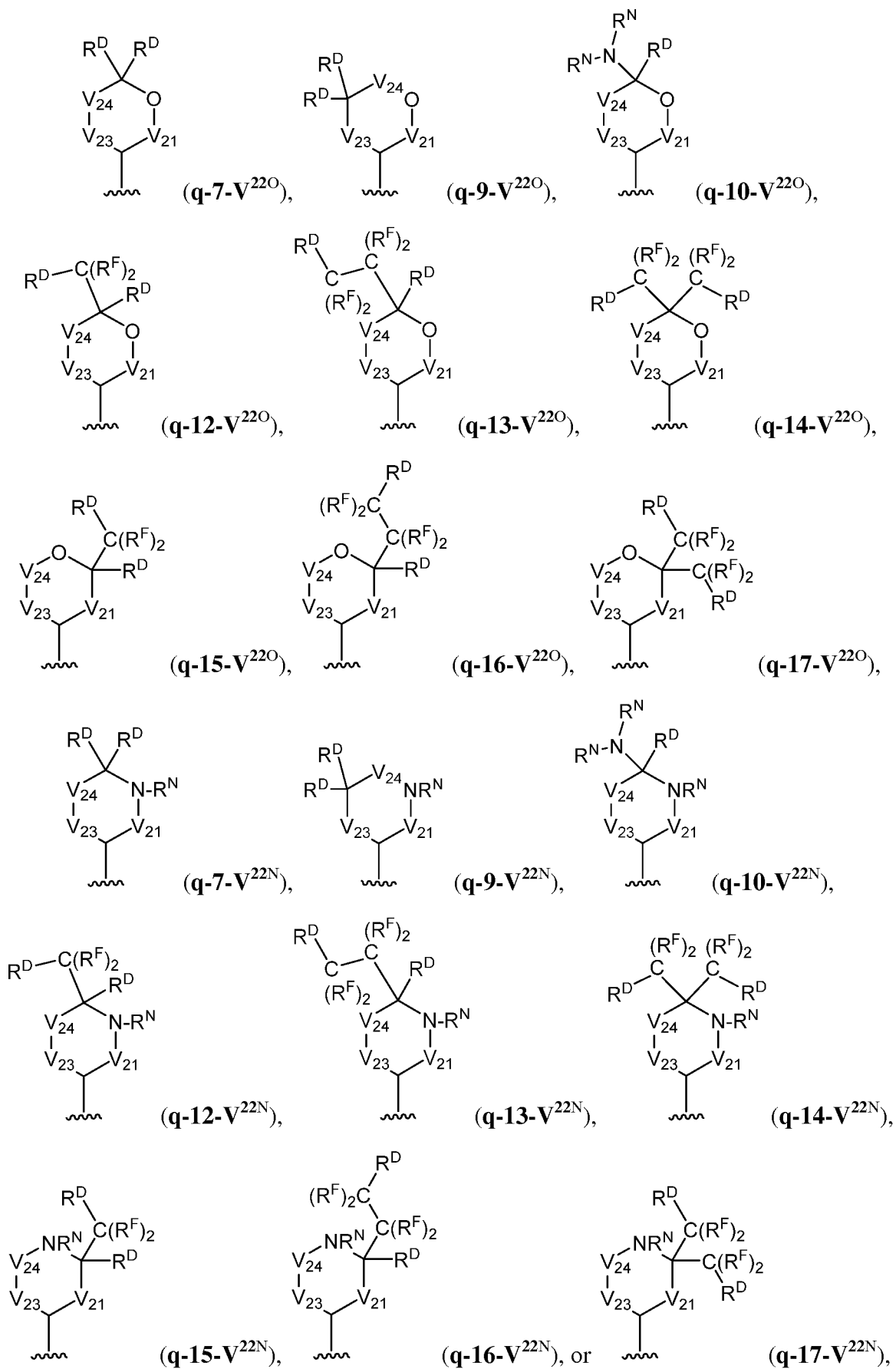
[00113] In certain embodiments, each instance of V^{21} , V^{22} , V^{23} , and V^{24} is $\text{C}(\text{R}^{\text{C}})_2$. In certain embodiments, one instance of V^{21} , V^{22} , V^{23} , and V^{24} is O. In certain embodiments, one instance of V^{21} , V^{22} , V^{23} , and V^{24} is S. In certain embodiments, one instance of V^{21} , V^{22} , V^{23} , and V^{24} is NR^{N} . In certain embodiments, only one of V^{21} , V^{22} , V^{23} , and V^{24} is a heteroatom selected from O, S, and NR^{N} . In certain embodiments, two of V^{21} , V^{22} , V^{23} , and V^{24} is a heteroatom selected from O, S, and NR^{N} .

[00114] In certain embodiments, V^{21} is a heteroatom selected from O, S, and NR^{N} . In certain embodiments, V^{21} is O. In certain embodiments, V^{21} is NR^{N} . For example, in certain embodiments, wherein V^{21} is O or NR^{N} , provided is an Ring A (R^{W} or R^{4}) group of Formula:

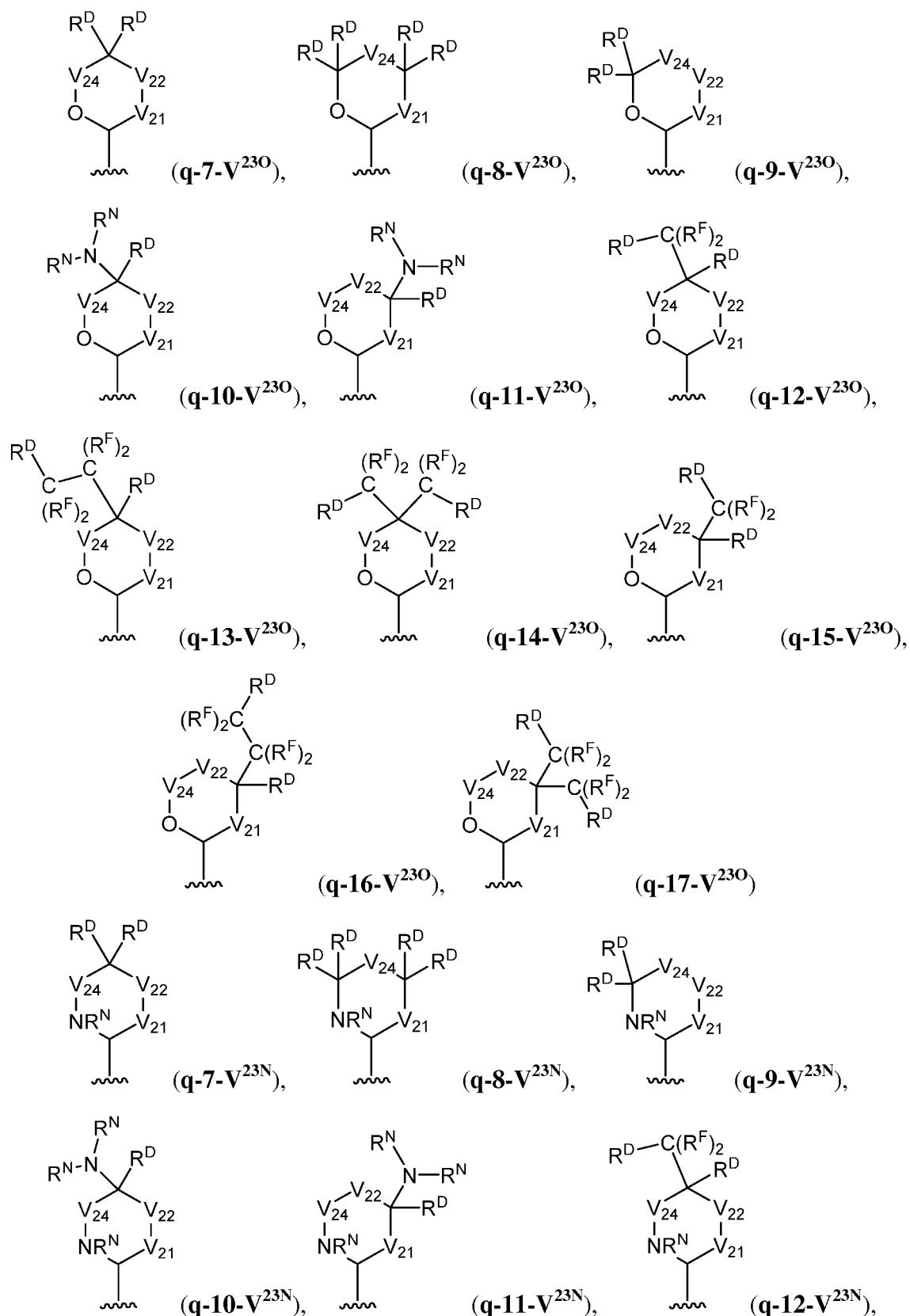


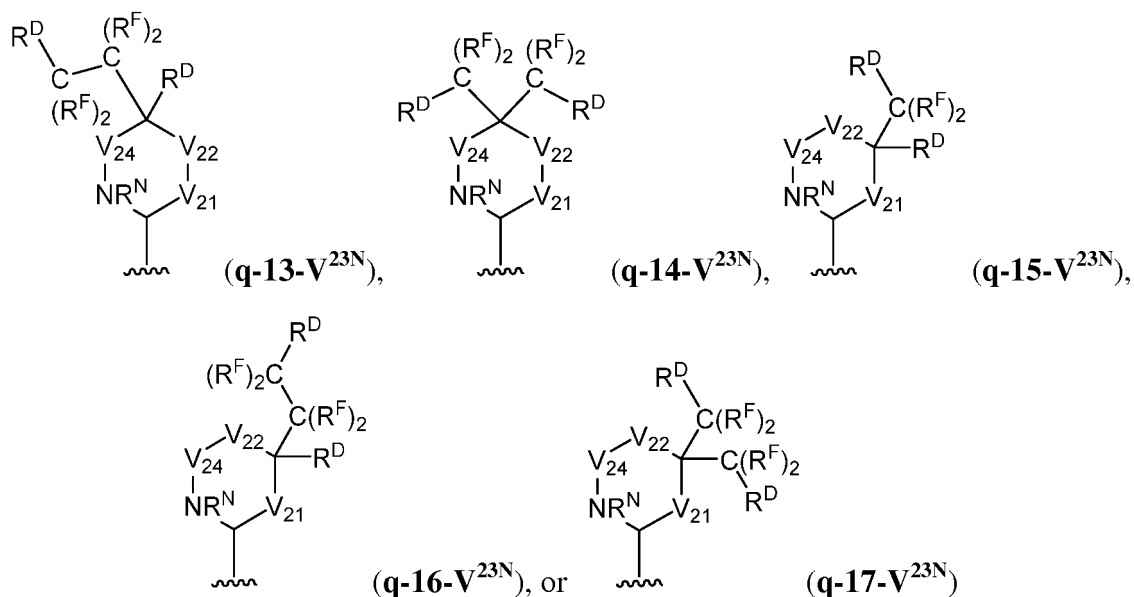


[00115] In certain embodiments, V^{22} is a heteroatom selected from O, S, and NR^N . In certain embodiments, V^{22} is O. In certain embodiments, V^{22} is NR^N . For example, in certain embodiments, wherein V^{22} is O or NR^N , provided is an Ring A (R^W or R^4) group of Formula:

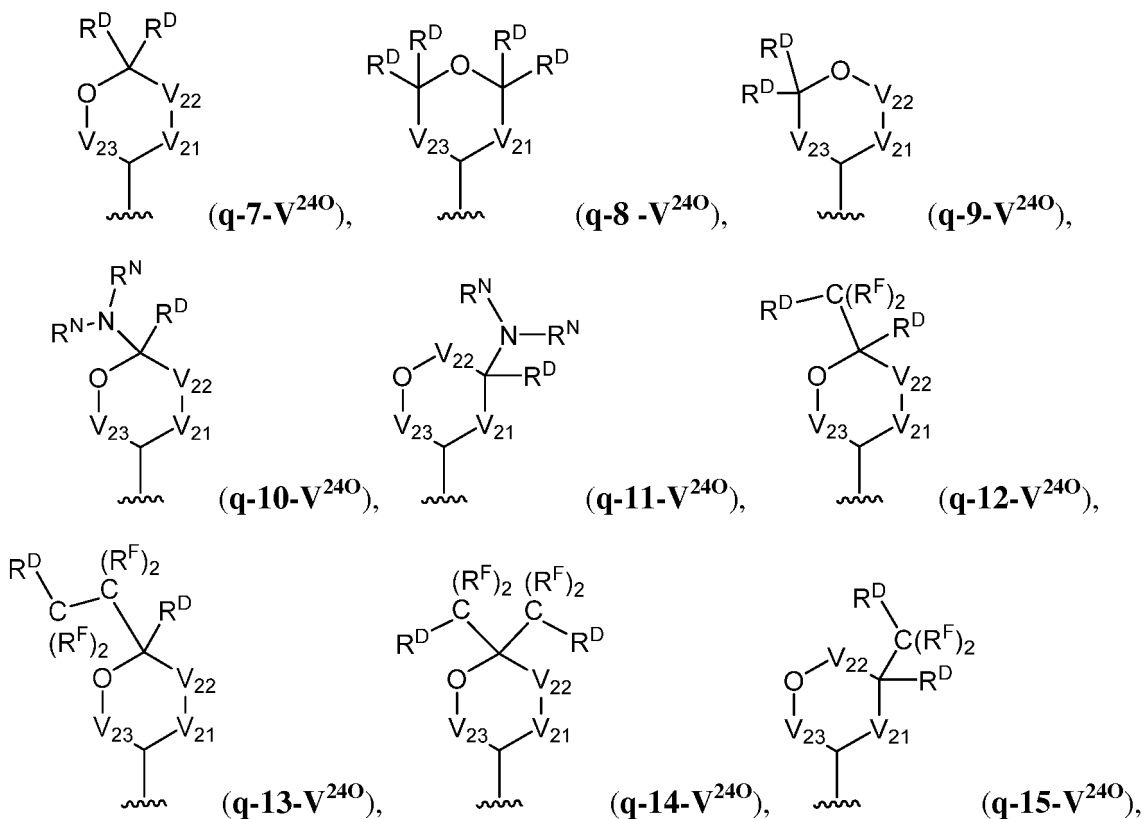


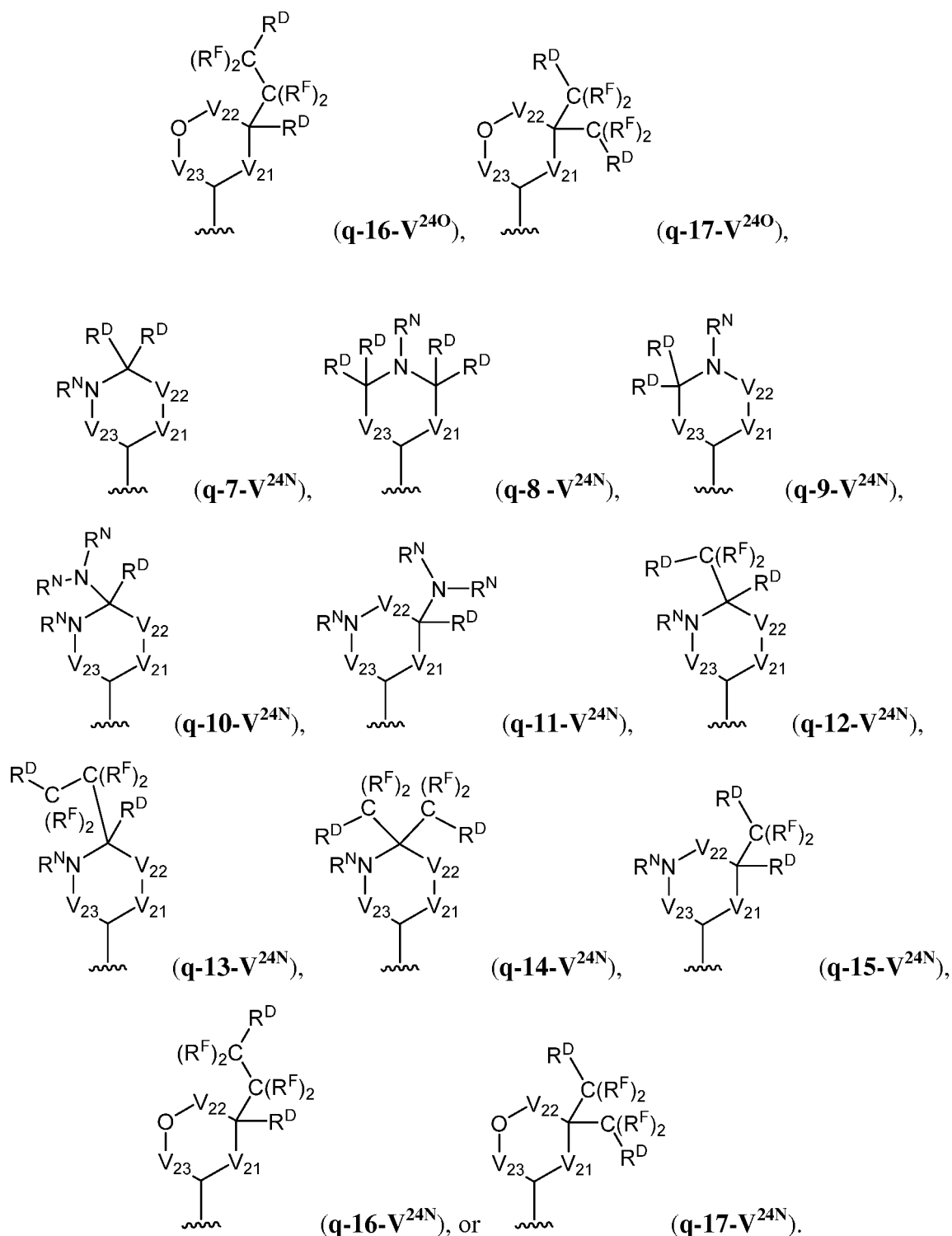
[00116] In certain embodiments, V^{23} is a heteroatom selected from O, S, and NR^N . In certain embodiments, V^{23} is O. In certain embodiments, V^{23} is NR^N . For example, in certain embodiments, wherein V^{23} is O or NR^N , provided is an Ring A (R^W or R^4) group of Formula:





[00117] In certain embodiments, V^{24} is a heteroatom selected from O, S, and NR^N . In certain embodiments, V^{24} is O. In certain embodiments, V^{24} is NR^N . For example, in certain embodiments, wherein V^{24} is O or NR^N , provided is Ring A (R^W or R^4) group of Formula:





[00118] In certain embodiments, at least one instance of R^D is hydrogen, *e.g.*, each instance for (q-10); 1 or 2 instances for (q-7), (q-9), (q-12), (q-13), (q-14), (q-15), (q-16), and (q-17); and 1, 2, 3, or 4 instances for (q-8). However, in certain embodiments, at least one instance of R^D is a non-hydrogen group, *e.g.*, each instance for (q-10); 1 or 2 instances for (q-7), (q-9), (q-12), (q-13), (q-14), (q-15), (q-16), and (q-17); and 1, 2, 3, or 4 instances for (q-8). For example, in certain embodiments, each instance of R^D is a non-hydrogen group.

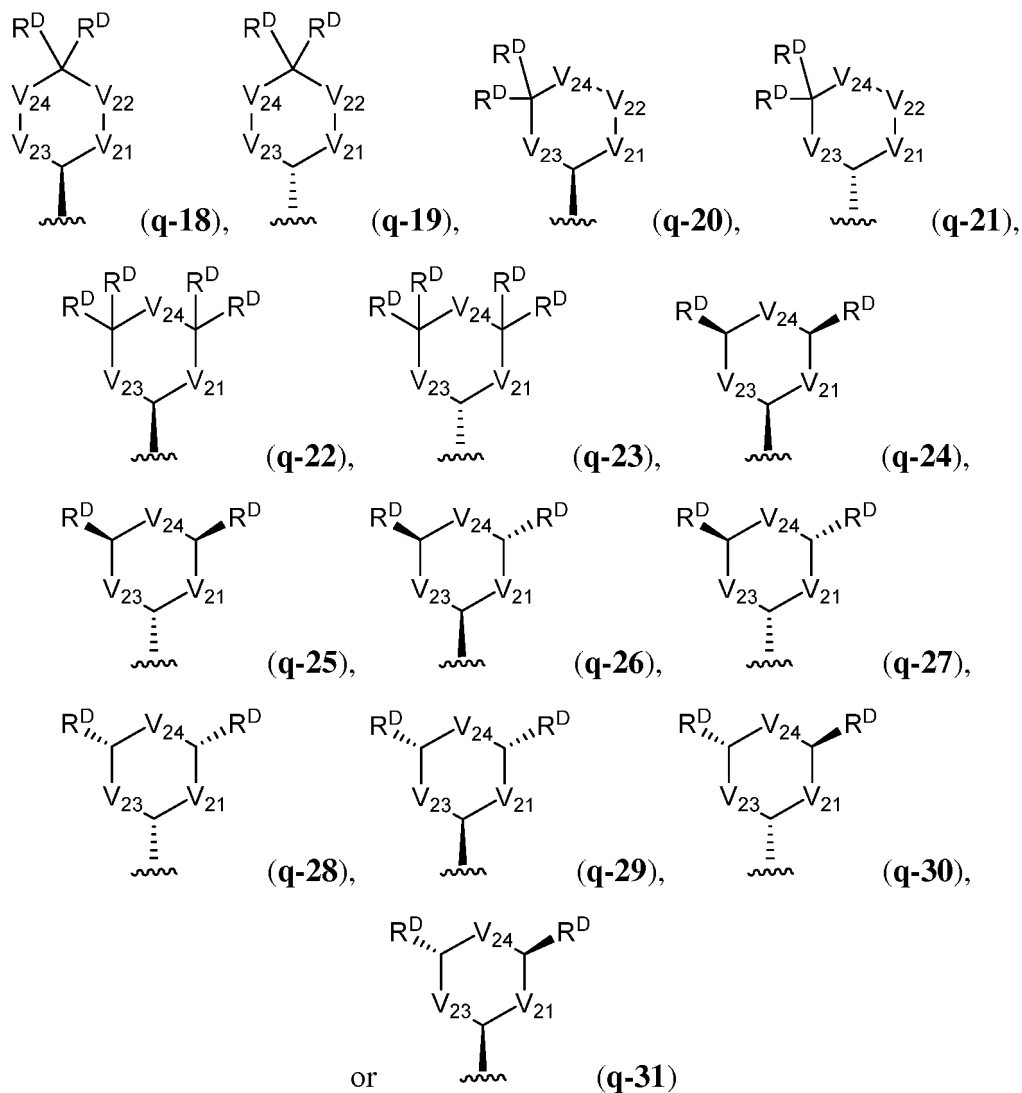
[00119] In certain embodiments, two R^D groups are joined to form an optionally substituted carbocyclic ring, *e.g.*, an optionally substituted C_{3-6} carbocyclic ring. In certain embodiments, two R^D groups are joined to form an optionally substituted C_3 carbocyclic ring, optionally substituted C_4 carbocyclic ring, optionally substituted C_5 carbocyclic ring, or optionally substituted C_6 carbocyclic ring. In certain embodiments, the R^D groups are joined to form an unsubstituted carbocyclic ring. However, in certain embodiments, the R^D groups are joined to form a substituted carbocyclic ring, *e.g.*, substituted with one or more alkyl groups.

[00120] In certain embodiments, two R^D groups are joined to form an optionally substituted heterocyclic ring, *e.g.*, an optionally substituted 3- to 6- membered heterocyclic ring comprising 1 or 2 heteroatoms selected from oxygen, nitrogen, or sulfur. In certain embodiments, two R^D groups are joined to form an optionally substituted 3- membered heterocyclic ring, optionally substituted 4- membered heterocyclic ring, optionally substituted 5- membered heterocyclic ring, or optionally substituted 6- membered heterocyclic ring. In certain embodiments, the R^D groups are joined to form an unsubstituted heterocyclic ring. However, in certain embodiments, the R^D groups are joined to form a substituted heterocyclic ring, *e.g.*, substituted with one or more alkyl groups.

[00121] In certain embodiments, two R^N groups are joined to form an optionally substituted heterocyclic ring, *e.g.*, an optionally substituted 3- to 6- membered heterocyclic ring. In certain embodiments, two R^N groups are joined to form an optionally substituted 5- membered heterocyclic ring, or optionally substituted 6- membered heterocyclic ring. In certain embodiments, the R^N groups are joined to form an unsubstituted heterocyclic ring. However, in certain embodiments, the R^N groups are joined to form a substituted heterocyclic ring, *e.g.*, substituted with one or more alkyl groups.

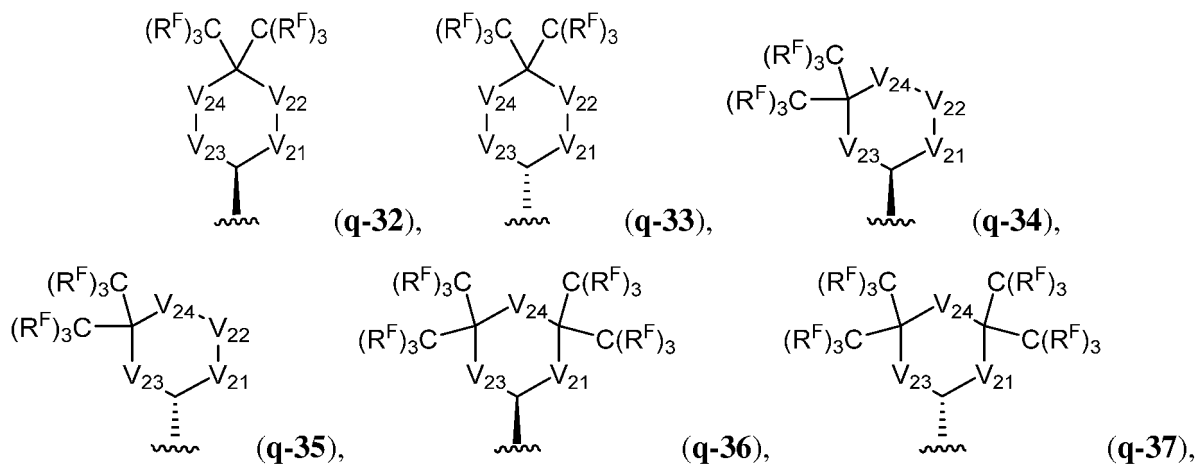
[00122] In certain embodiments, one R^N group and one R^D group (*e.g.*, wherein the N atom to which the R^N group is attached and the R^D group are joined to the same carbon atom) are joined to form an optionally substituted heterocyclic ring, *e.g.*, an optionally substituted 3- to 6- membered heterocyclic ring. In certain embodiments, one R^N group and one R^D group are joined to form an optionally substituted 5- membered heterocyclic ring, or optionally substituted 6- membered heterocyclic ring. In certain embodiments, one R^N group and one R^D group are joined to form an unsubstituted heterocyclic ring. However, in certain embodiments, one R^N group and one R^D group are joined to form a substituted heterocyclic ring, *e.g.*, substituted with one or more alkyl groups.

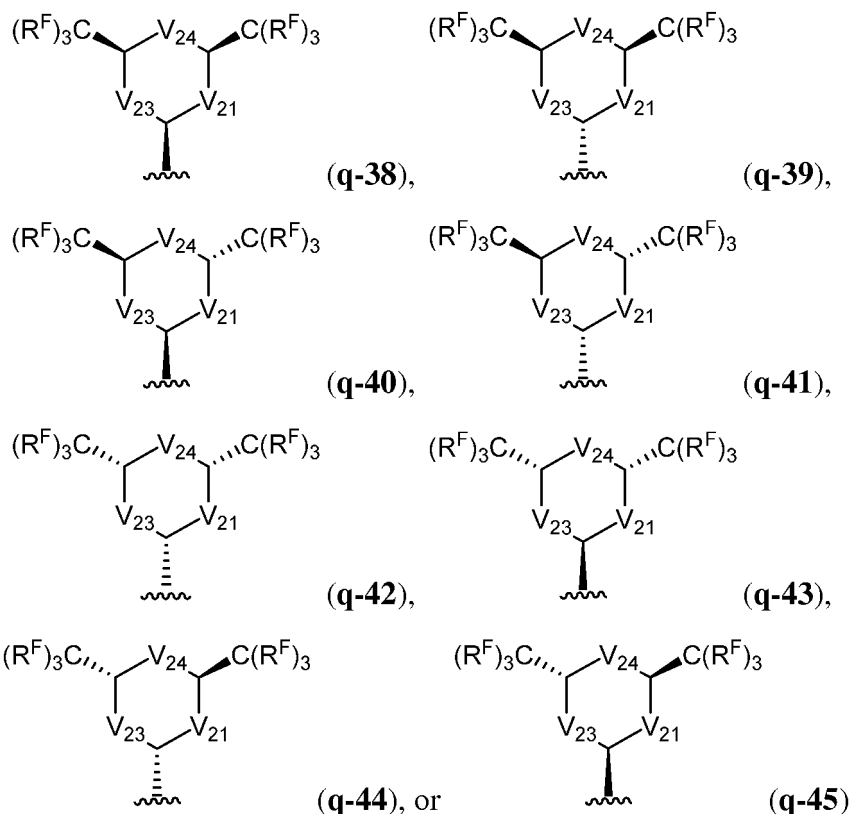
[00123] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-18) – (q-31):



wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^D are defined herein.

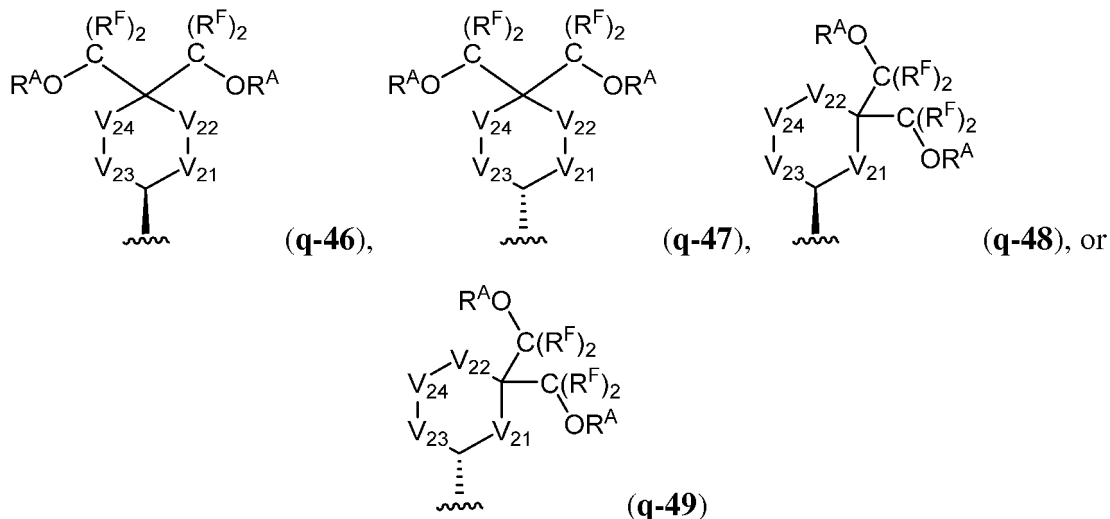
[00124] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-32) – (q-45):





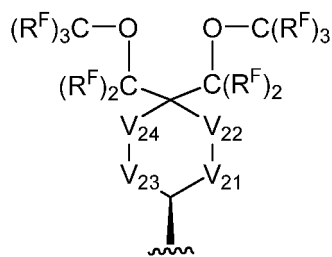
wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^F are defined herein.

[00125] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-46) – (q-49):

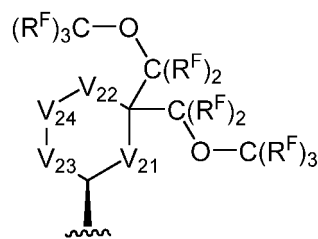


wherein V^{21} , V^{22} , V^{23} , V^{24} , R^A , and R^F are defined herein.

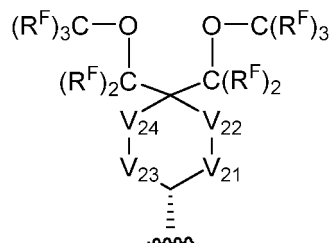
[00126] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-50) – (q-57):



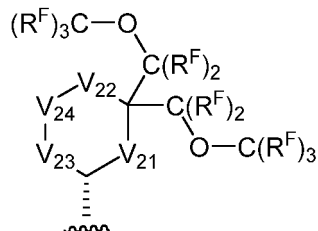
(q-50),



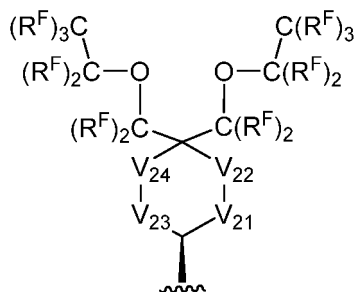
(q-51),



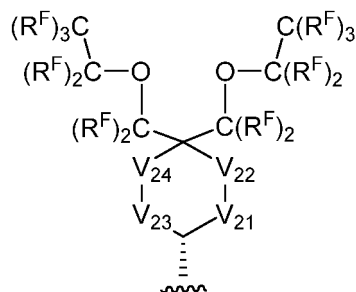
(q-52),



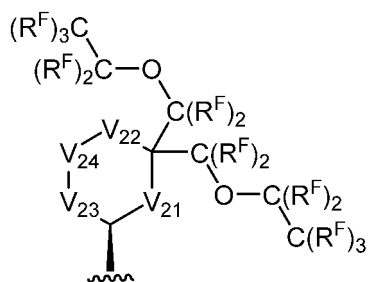
(q-53),



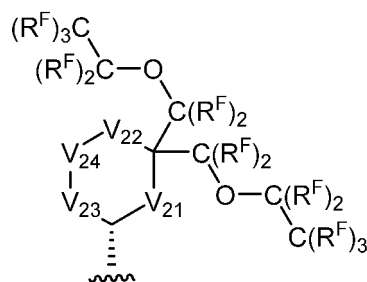
(q-54),



(q-55),



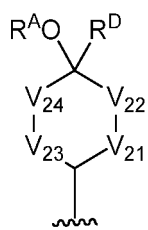
(q-56), or



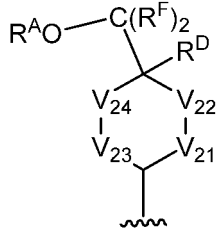
(q-57)

wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^F are defined herein.

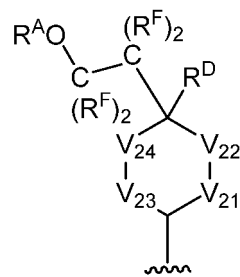
[00127] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-58) – (q-72):



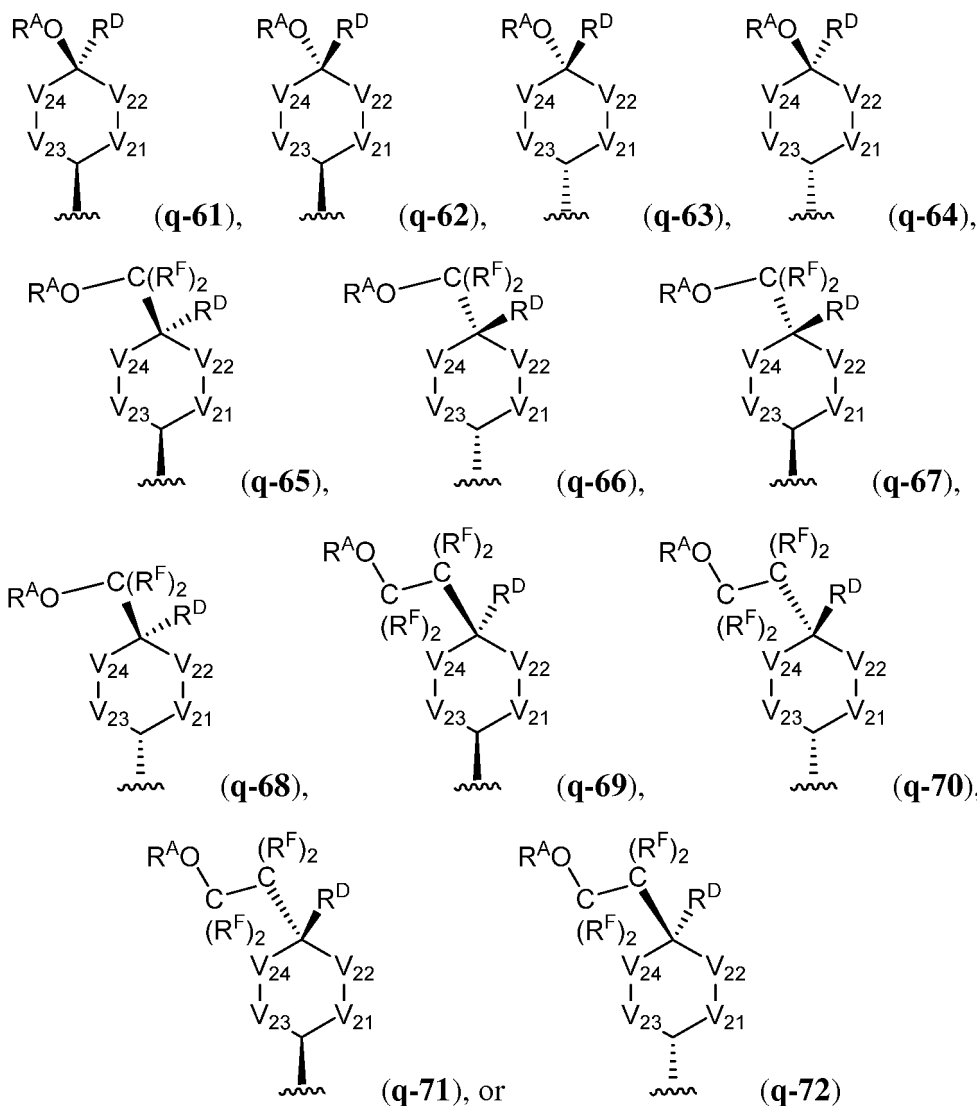
(q-58),



(q-59),

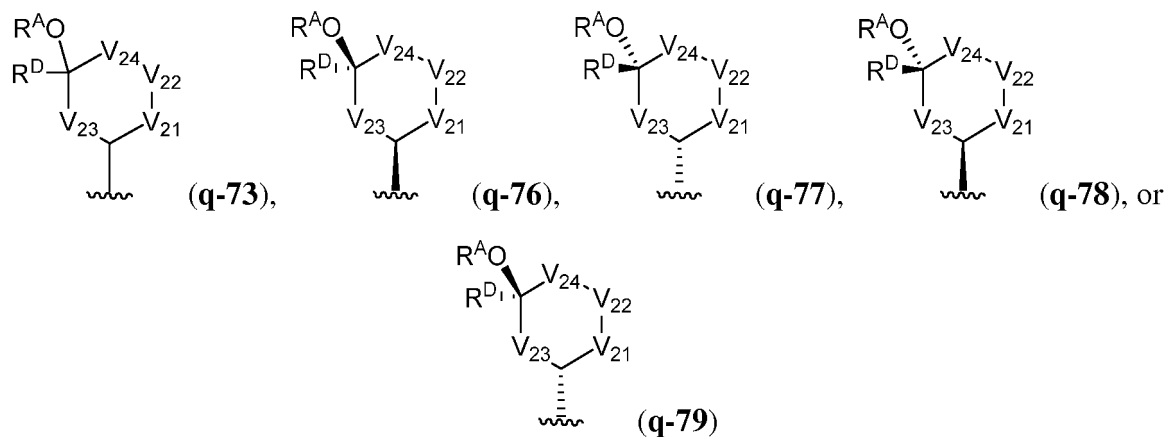


(q-60),



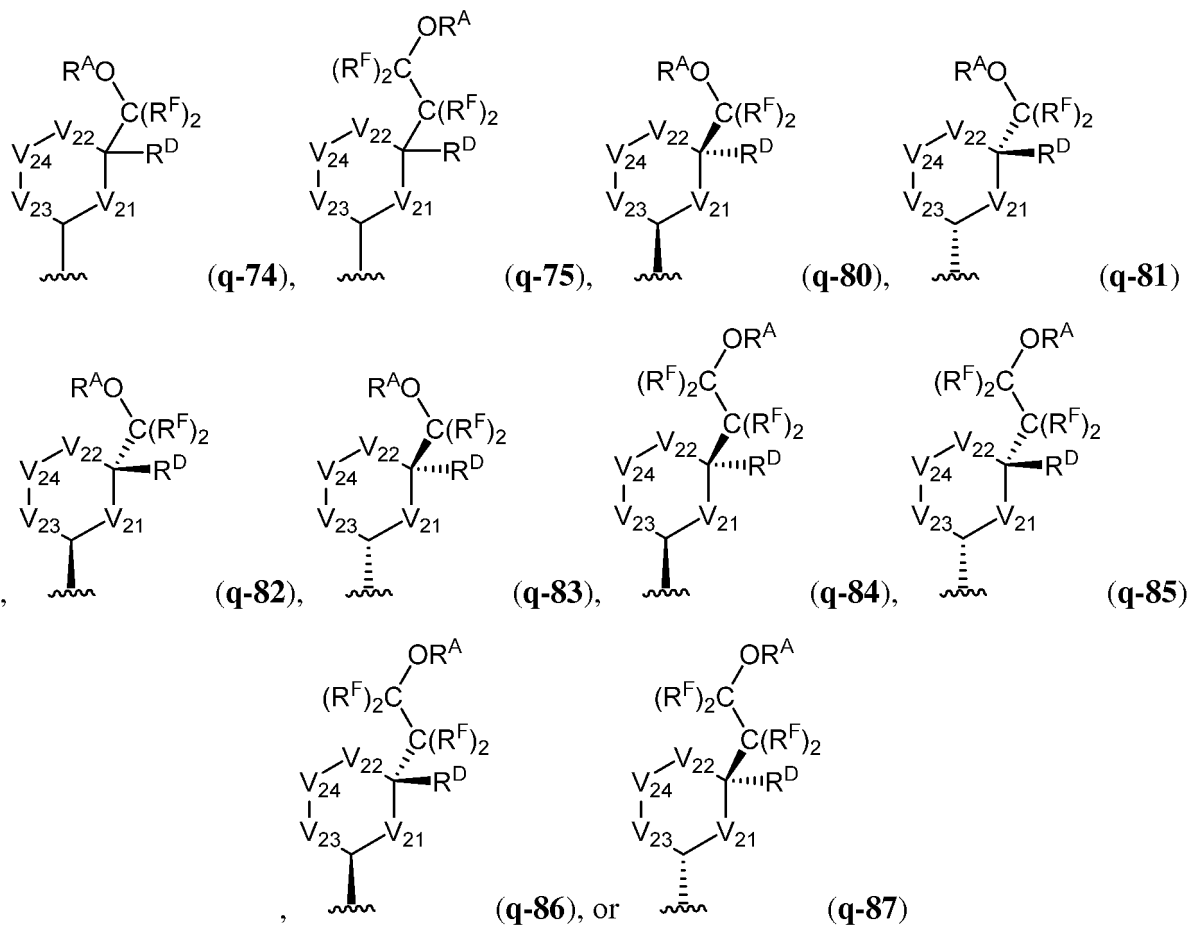
wherein V^{21} , V^{22} , V^{23} , V^{24} , R^A , R^D , and R^F are defined herein.

[00128] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-73) and (q-76) – (q-79):



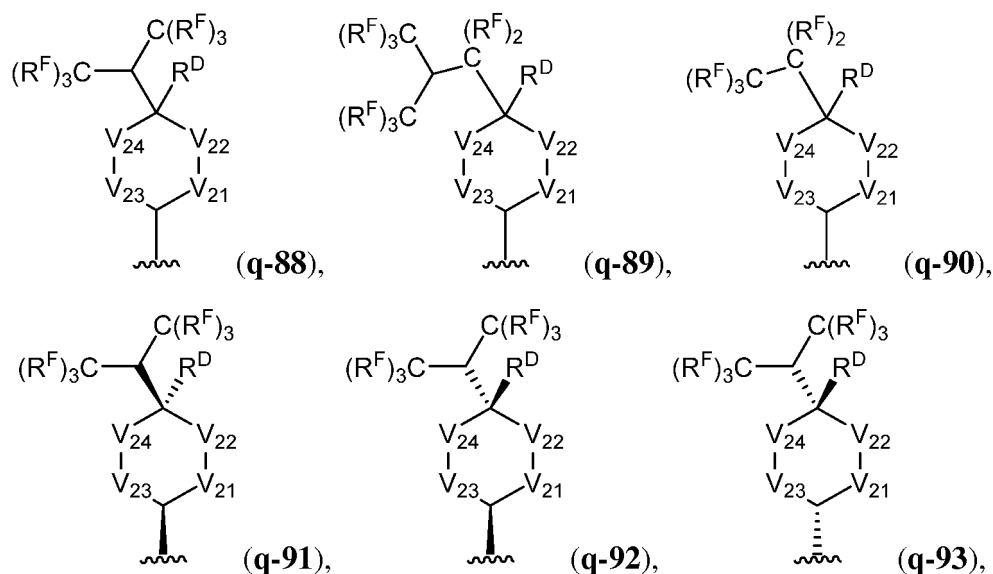
wherein V^{21} , V^{22} , V^{23} , V^{24} , R^A , R^D , and R^F are defined herein.

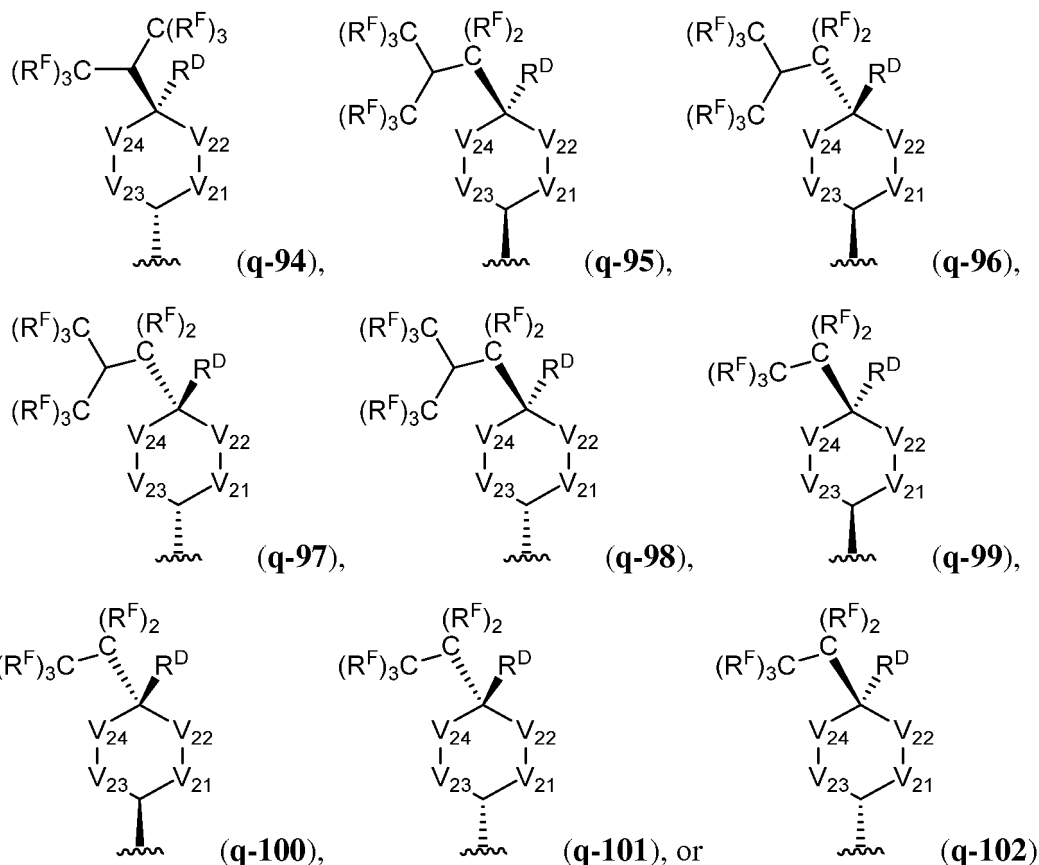
[00129] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-74), (q-75) and (q-80) – (q-87):



wherein V^{21} , V^{22} , V^{23} , V^{24} , R^A , R^D , and R^F are defined herein.

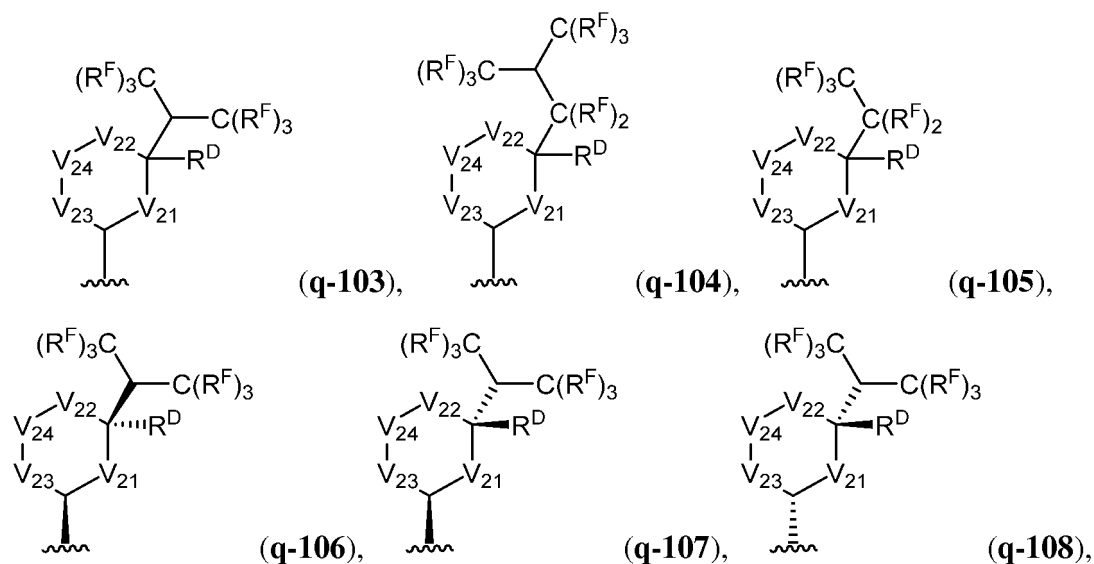
[00130] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-88) – (q-102):

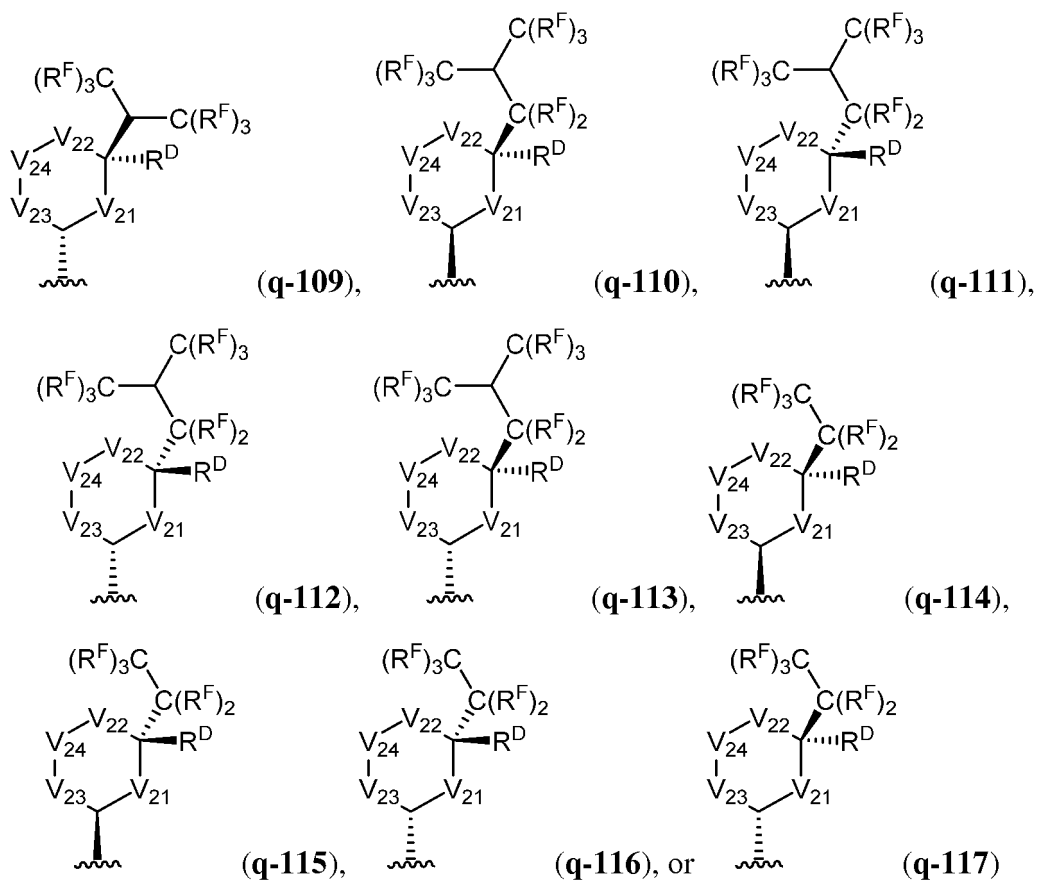




wherein V^{21} , V^{22} , V^{23} , V^{24} , R^D , and R^F are defined herein.

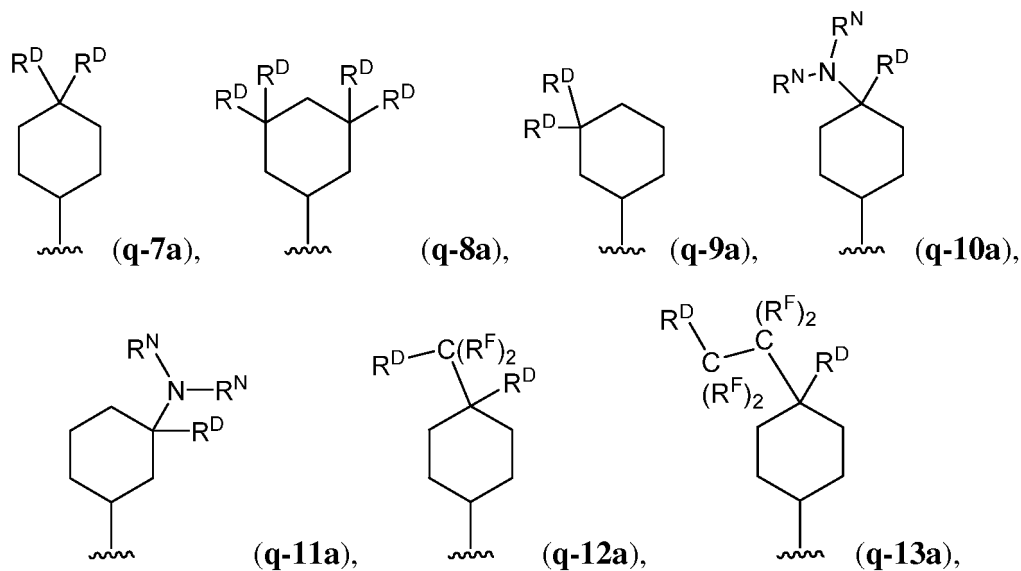
[00131] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-103) – (q-117):

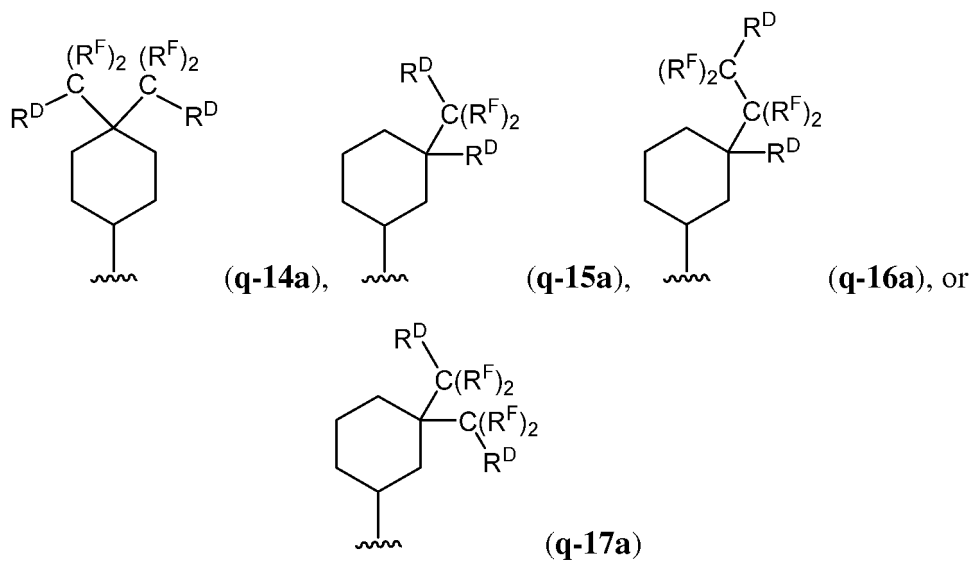




wherein V^{21} , V^{22} , V^{23} , V^{24} , R^D , and R^F are defined herein.

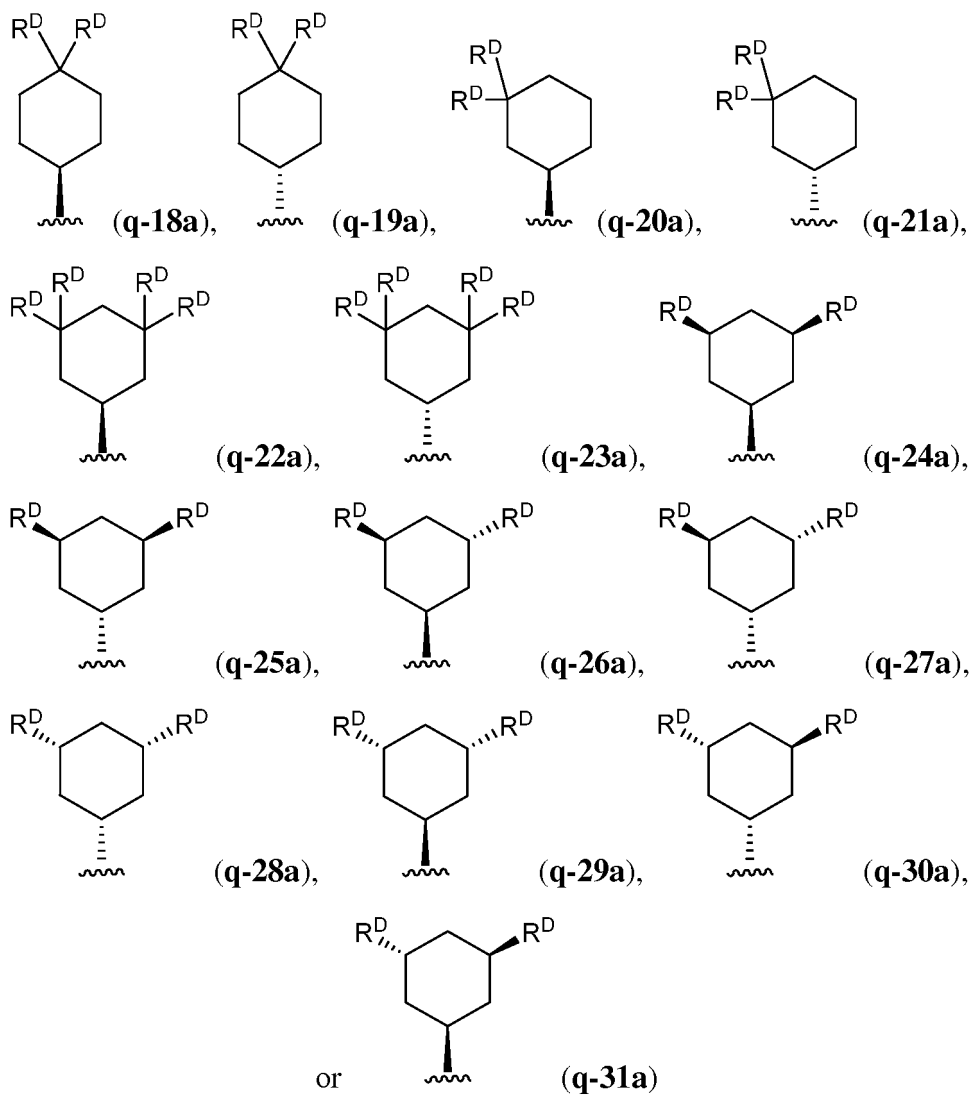
[00132] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-7a) – (q-17a):





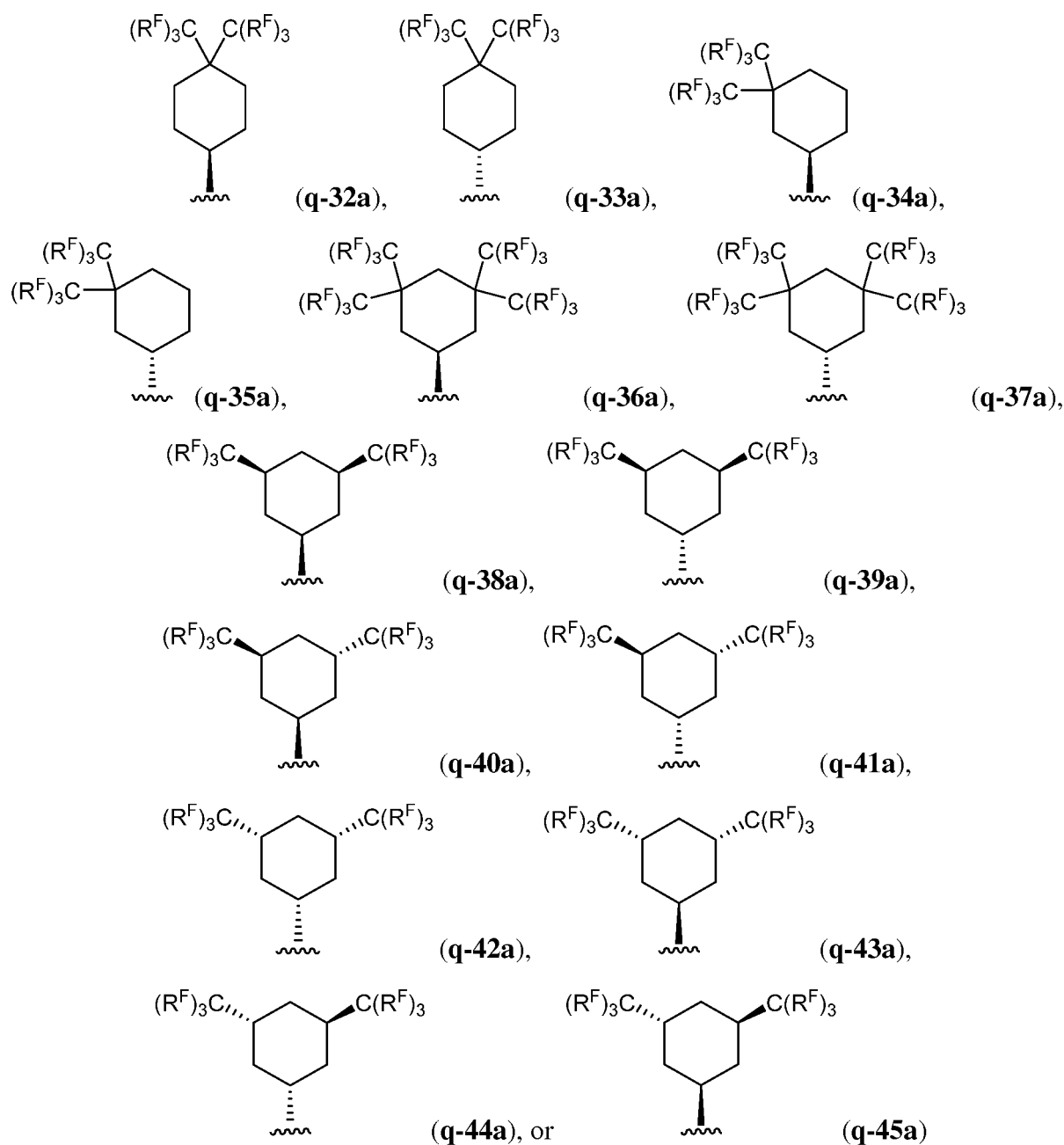
wherein R^D , R^N , and R^F are defined herein.

[00133] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-18a) – (q-31a):



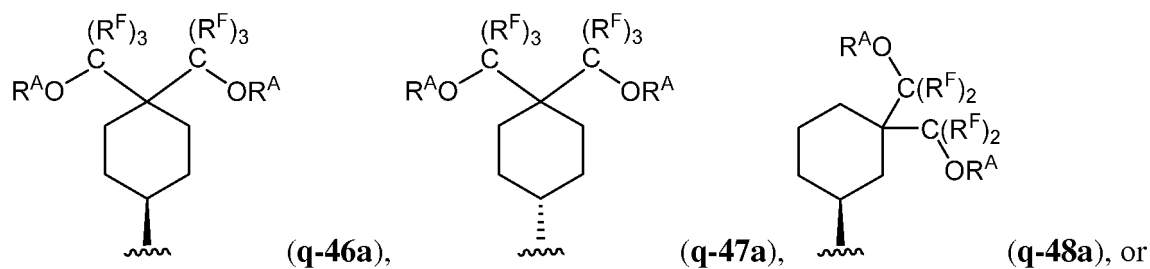
wherein R^D is defined herein.

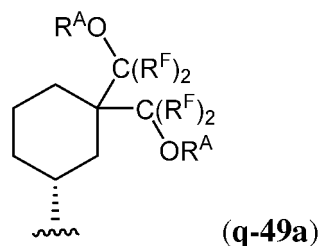
[00134] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-32a) – (q-45a):



wherein R^F is defined herein.

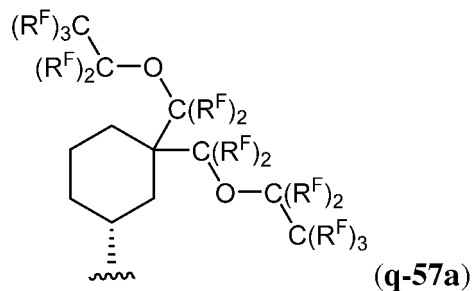
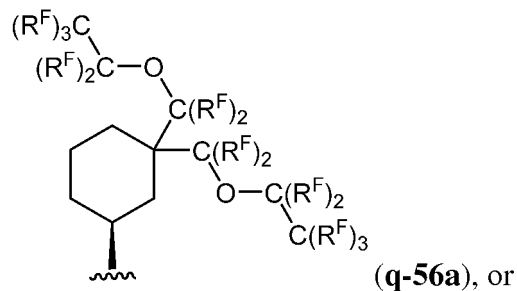
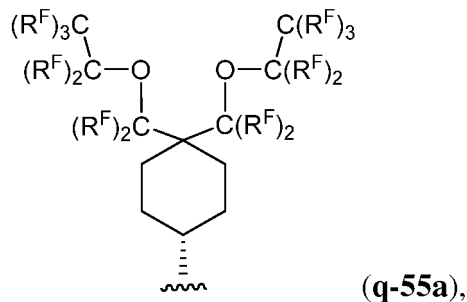
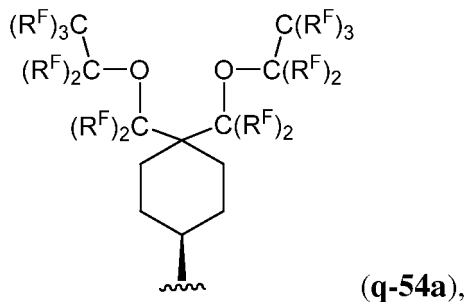
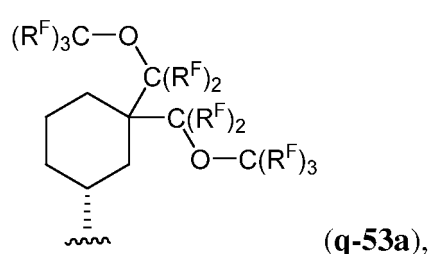
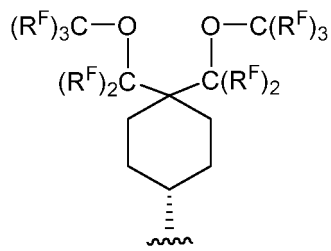
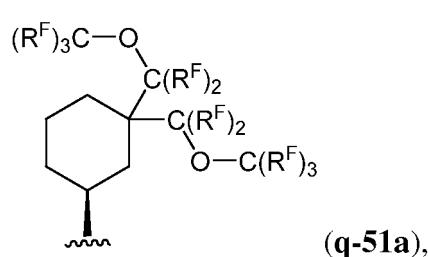
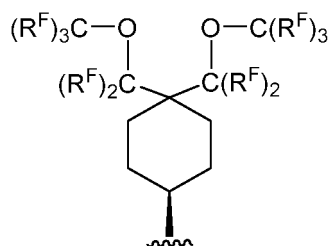
[00135] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-46a) – (q-49a):





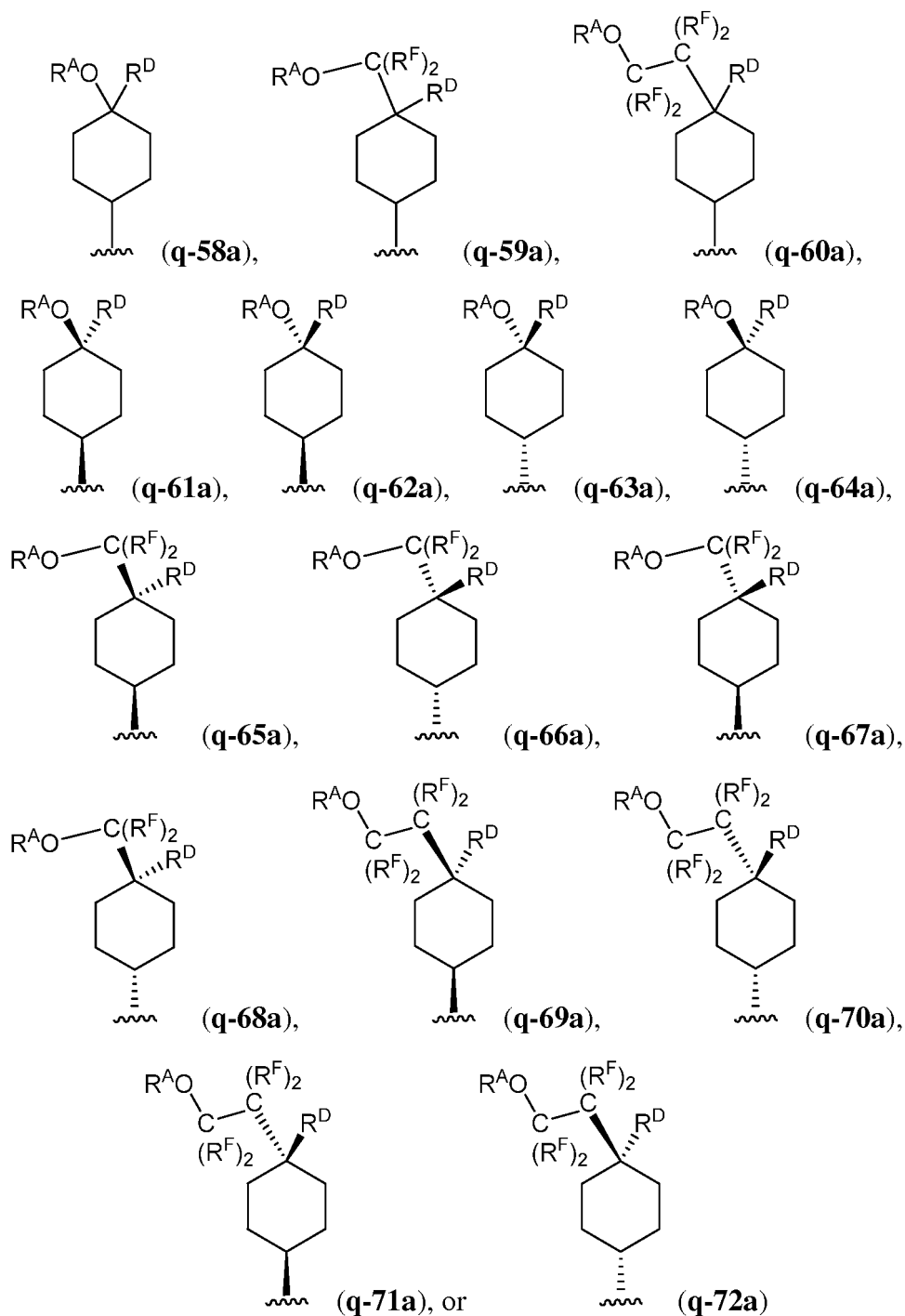
wherein R^A and R^F are defined herein.

[00136] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-50a) – (q-57a):



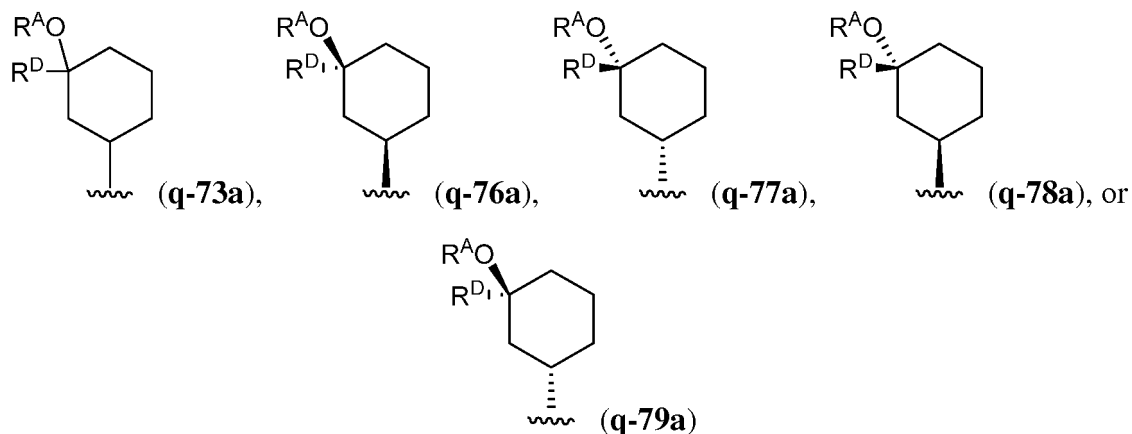
wherein R^F is defined herein.

[00137] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-58a) – (q-72a):



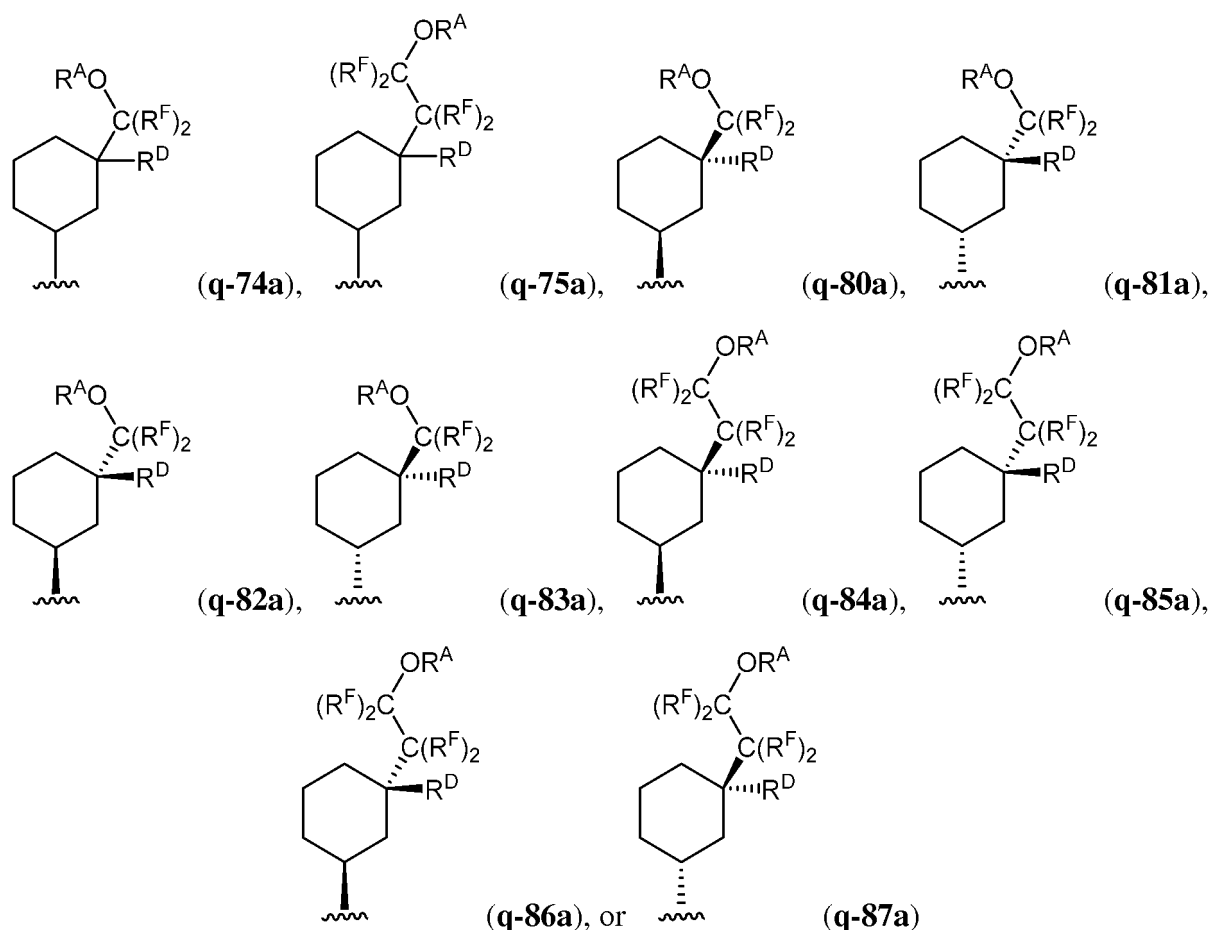
wherein R^A , R^D , and R^F are defined herein.

[00138] In certain embodiments, R^W (or Ring A) or R^4 (as provided in the above recited instance) is of Formula (q-73a), and (q-76a) - (q-79a):



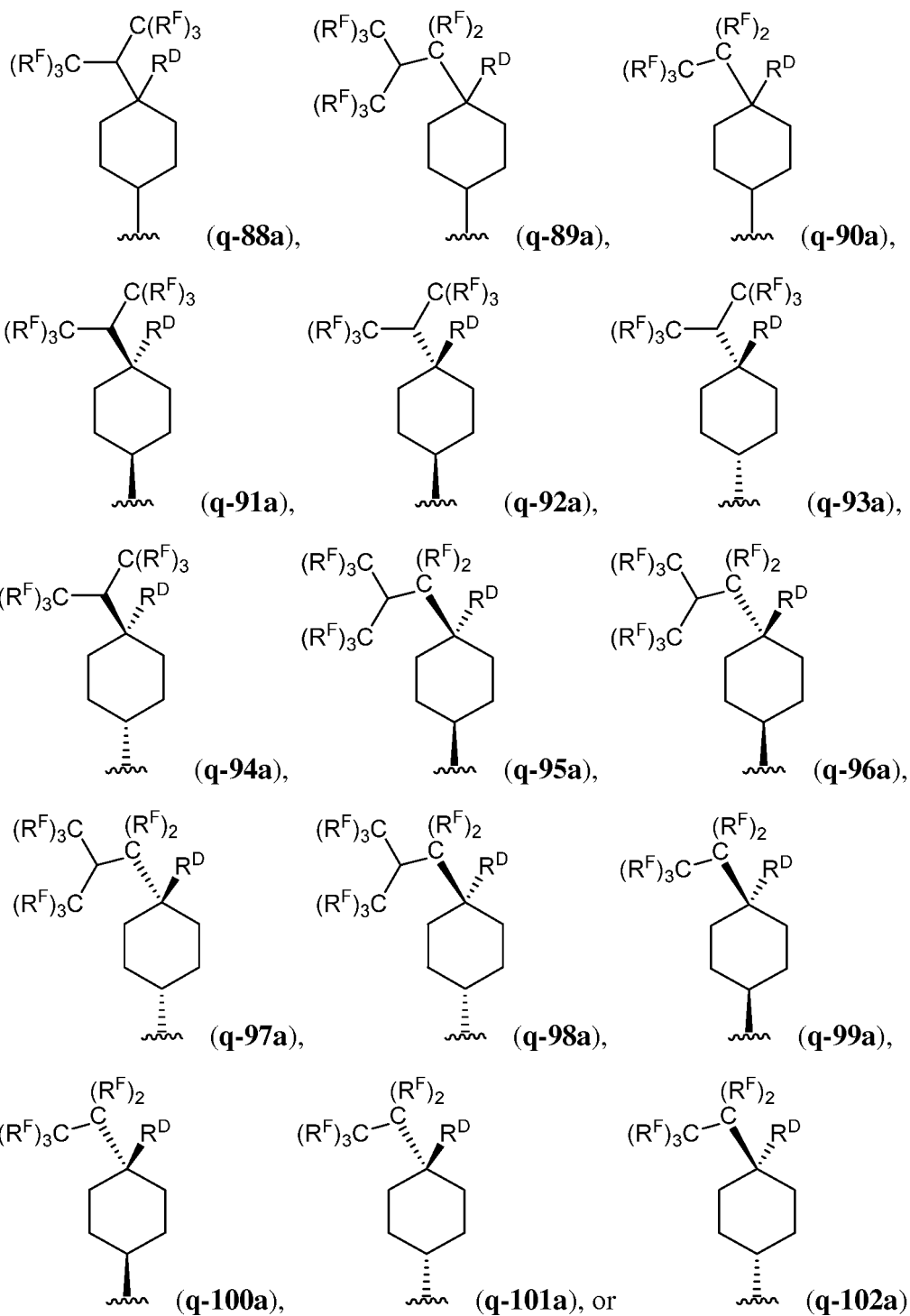
wherein R^A , R^D , and R^F are defined herein.

[00139] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-74a), (q-75a) and (q-80a) – (q-87a):



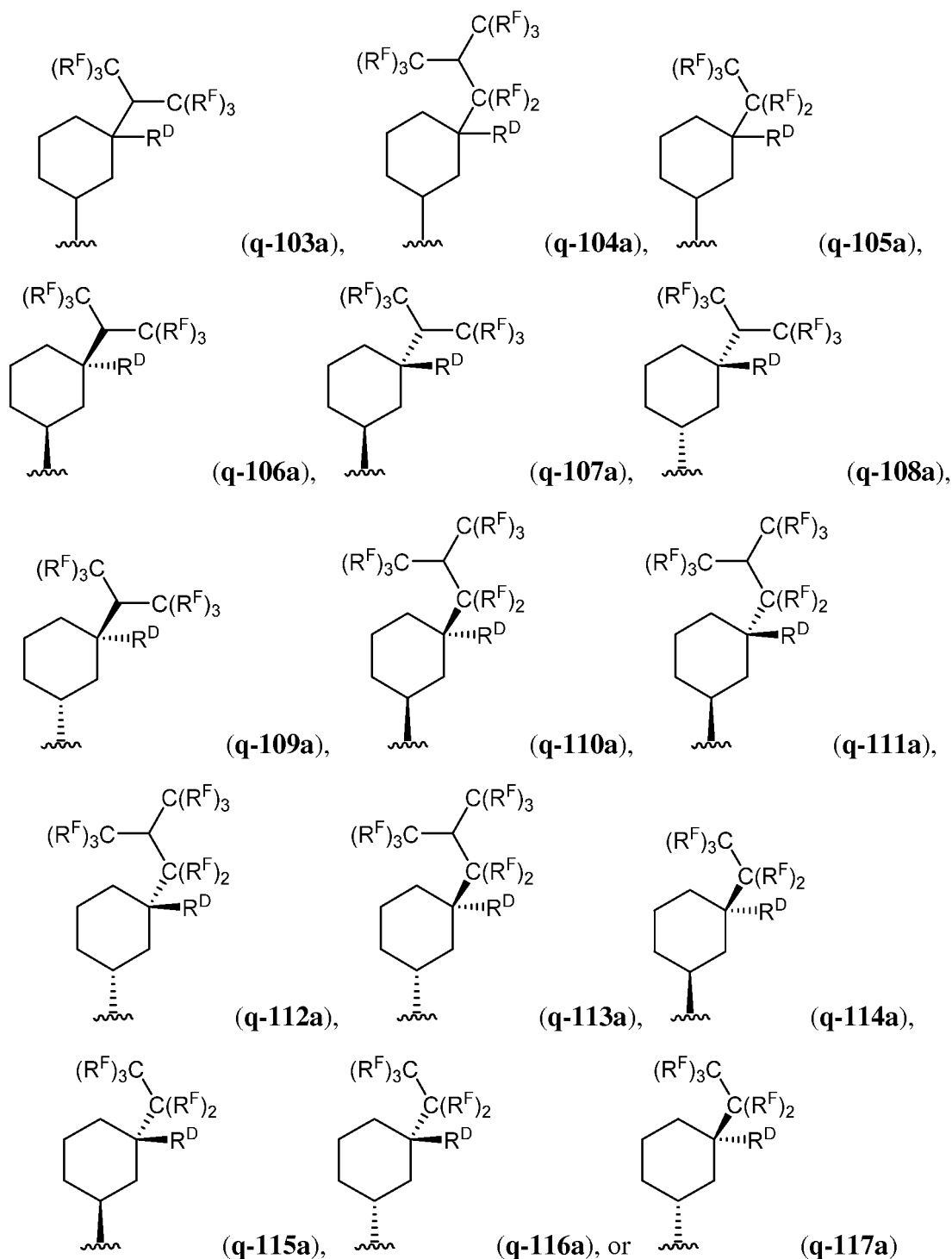
wherein R^A , R^D , and R^F are defined herein.

[00140] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-88a) – (q-102a):



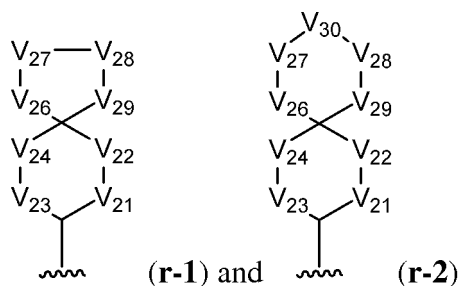
wherein R^D , and R^F are defined herein.

[00141] In certain embodiments, Ring A (R^W or R^4) is of Formula (q-103a) – (q-117a):

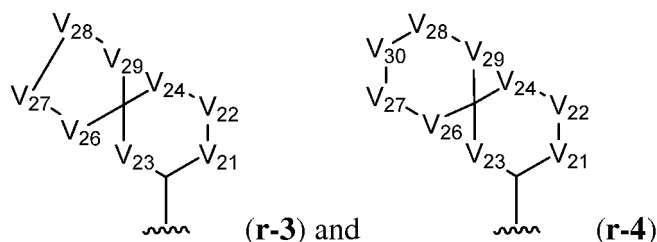


wherein V^{21} , V^{22} , V^{23} , V^{24} , R^D , and R^F are defined herein.

[00142] In certain embodiments, wherein, for example, 2 R^D groups are joined to form a C_{5-6} membered carbocyclic ring, or a 5-6-membered heterocyclic ring, Formula (q-7) is of Formula (r-1) and (r-2):



and Formula (q-9) is of Formula (r-3) and (r-4):



wherein:

V²¹, V²², V²³, and V²⁴ are as defined herein;

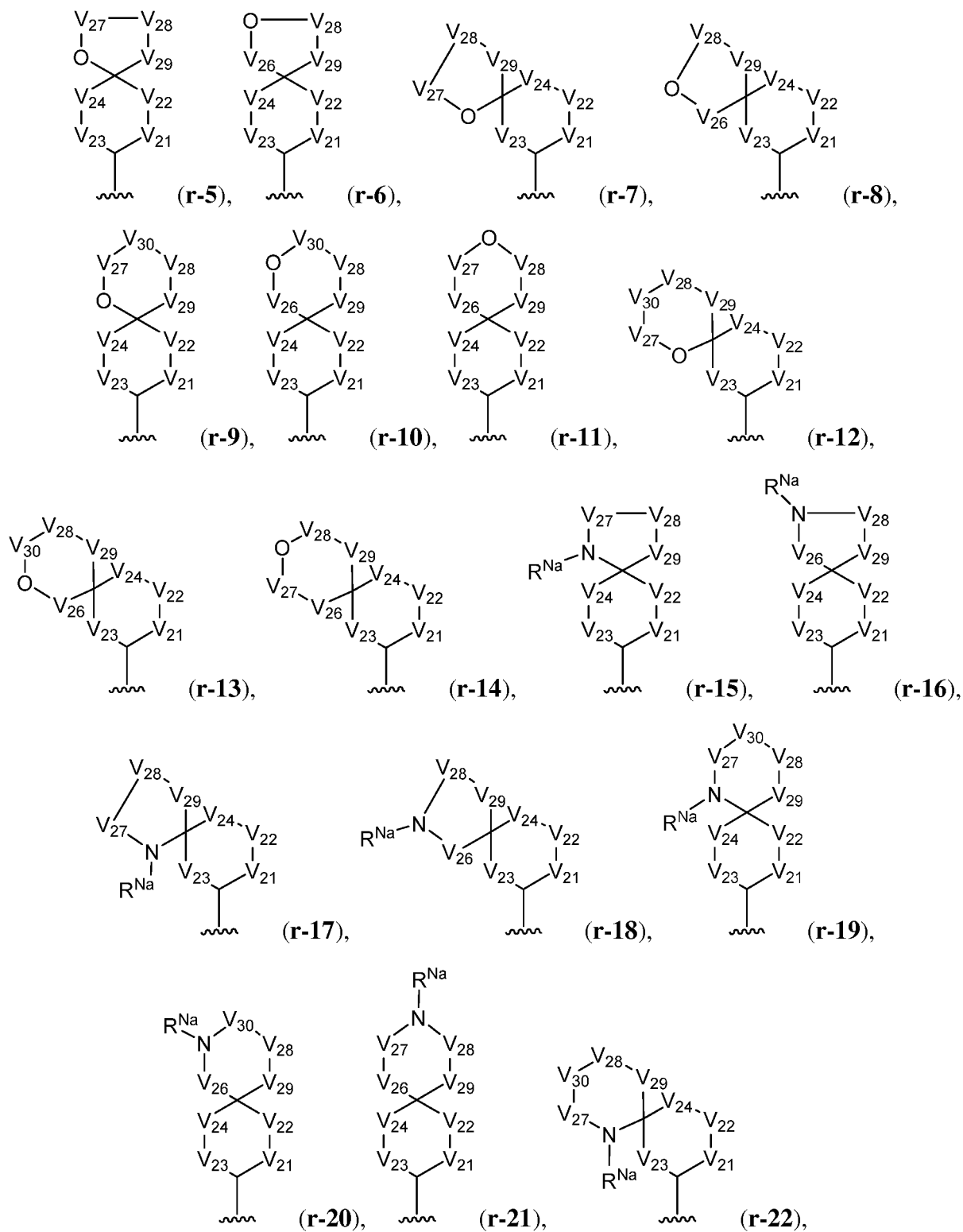
V²⁶, V²⁷, V²⁸, V²⁹, and V³⁰ are each independently O, S, NR^{Na}, C=O, or C(R^E)₂ as valency permits, provided no more than two of V²⁶, V²⁷, V²⁸, V²⁹, and V³⁰ is a heteroatom O, S, and NR^{Na}; alternatively wherein one of V²⁶, V²⁷, V²⁸, V²⁹, and V³⁰ and another of V²⁶, V²⁷, V²⁸, V²⁹, and V³⁰ adjacent to each other are joined to form an N=C(R^E) or C(R^E)=C(R^E) group;

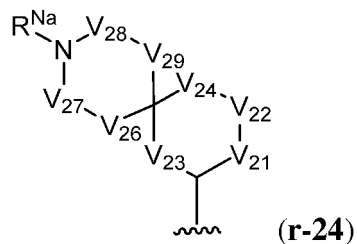
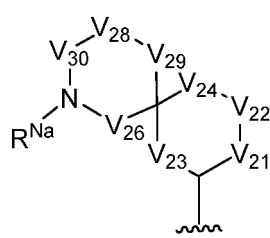
each instance of R^E is independently hydrogen, halo, -CN, -NO₂, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -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, -SO₂R^A, -NR^BSO₂R^A, or -SO₂N(R^B)₂; or two R^E groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring; and

each instance of R^{Na} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, 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, -

$C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-S(=O)R^A$, $-SO_2R^A$, $-SO_2N(R^B)_2$, or a nitrogen protecting group.

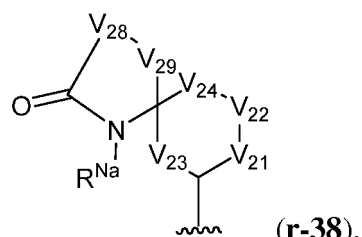
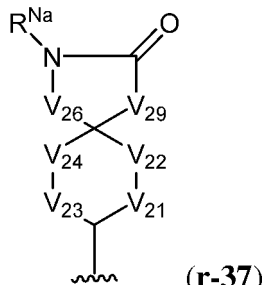
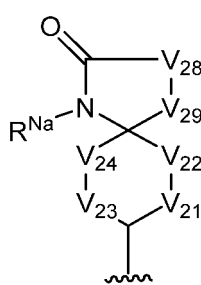
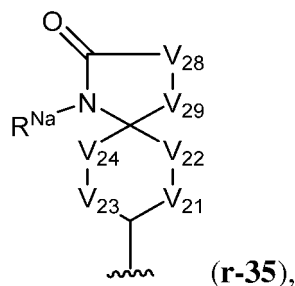
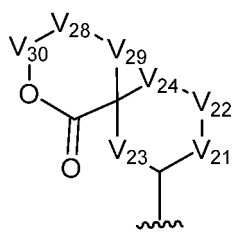
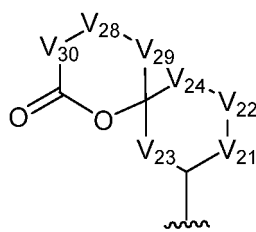
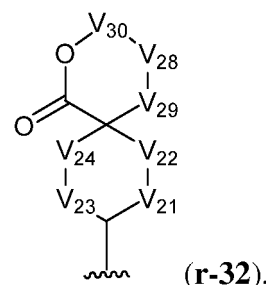
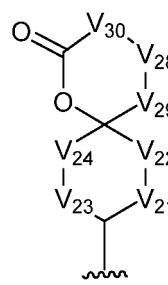
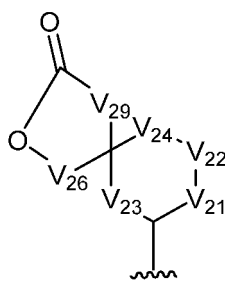
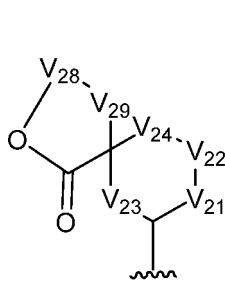
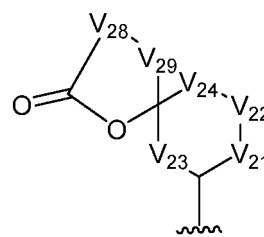
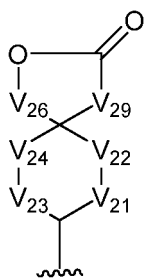
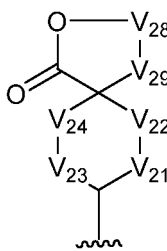
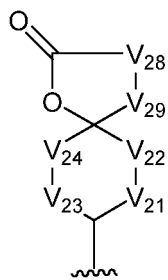
[00143] In certain embodiments, Formula (q-7) or (q-9) is of Formula (r-5) to (r-24):

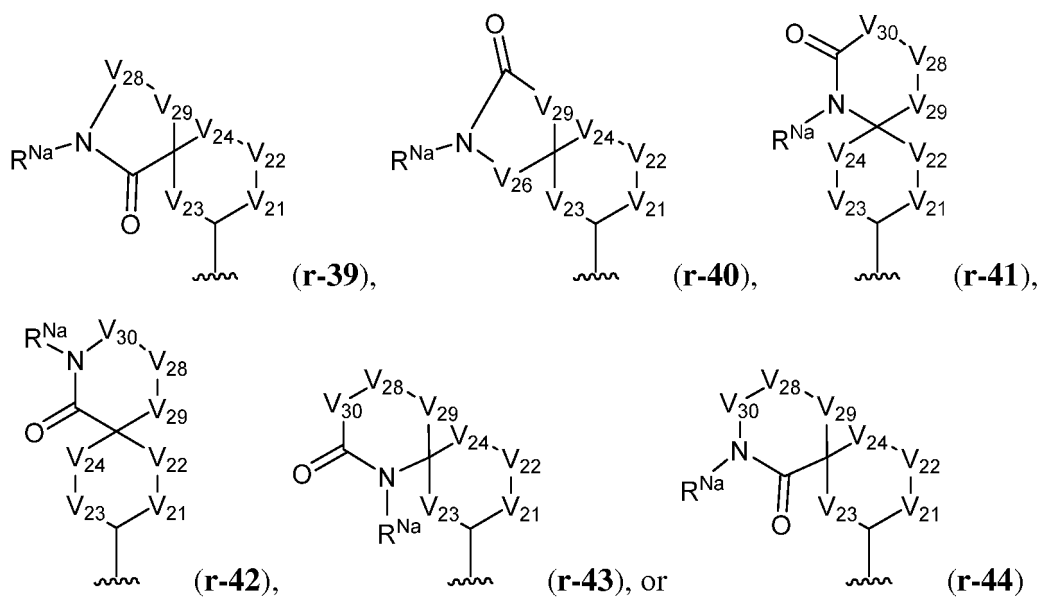




wherein V^{21} , V^{22} , V^{23} , V^{24} , V^{26} , V^{27} , V^{28} , V^{29} , V^{30} , and R^{Na} are defined herein.

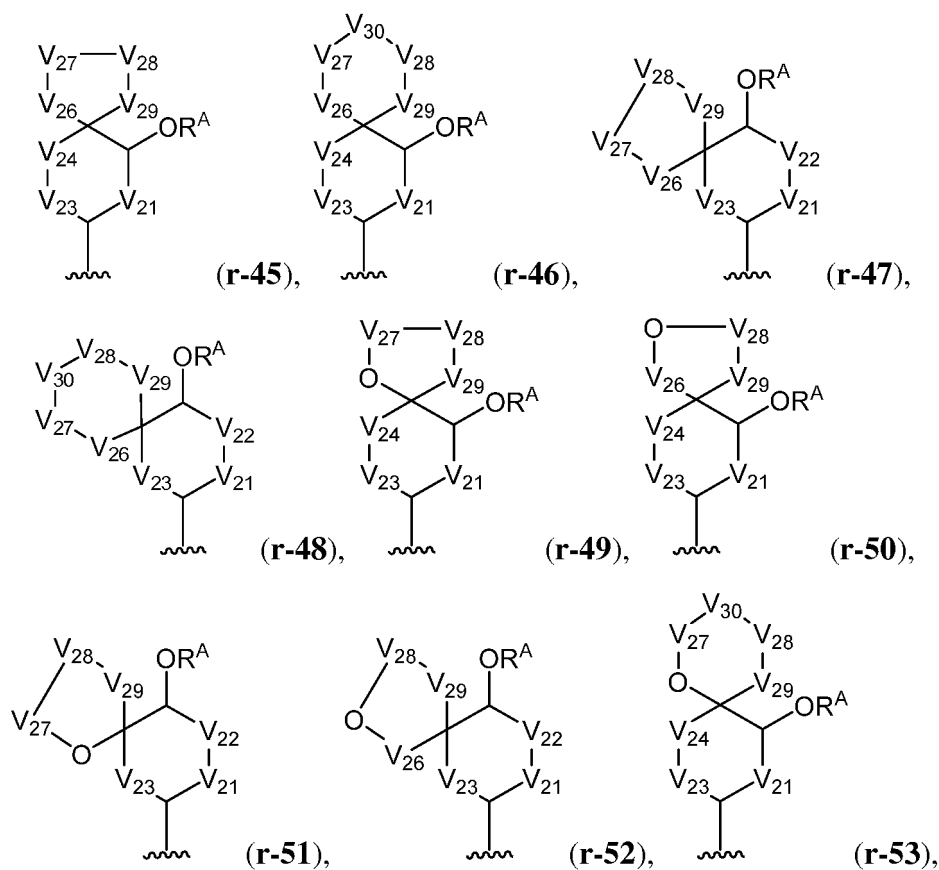
[00144] In certain embodiments, Formula (q-7) or (q-9) is of Formula (r-25) to (r-44):

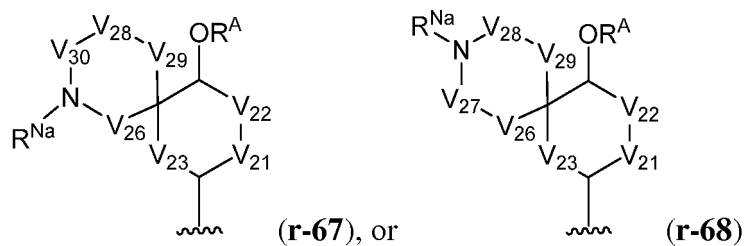
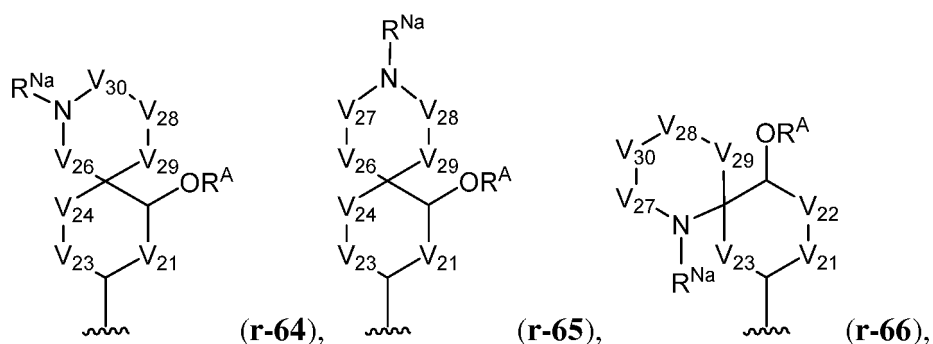
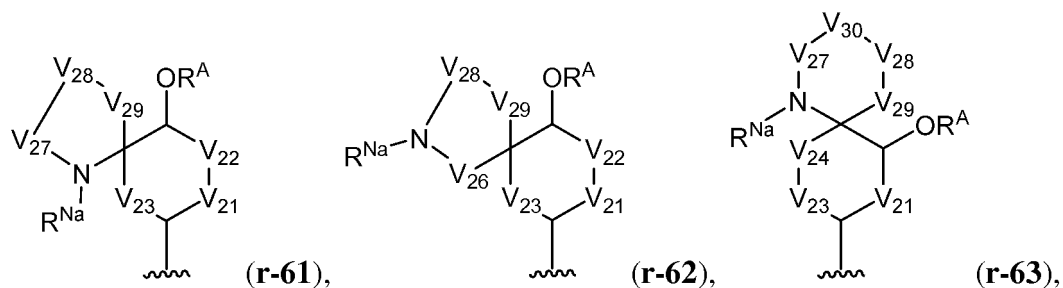
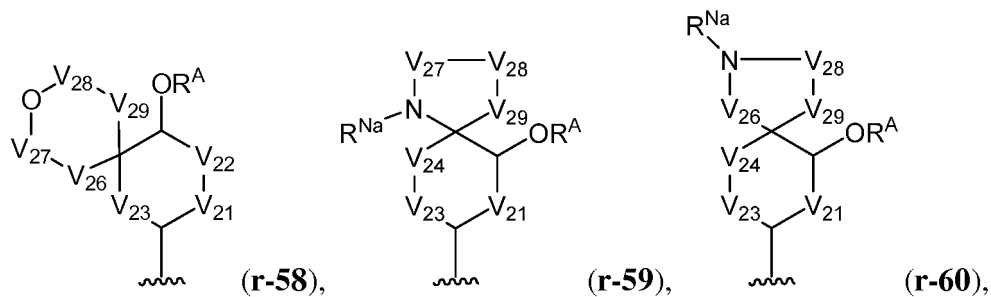
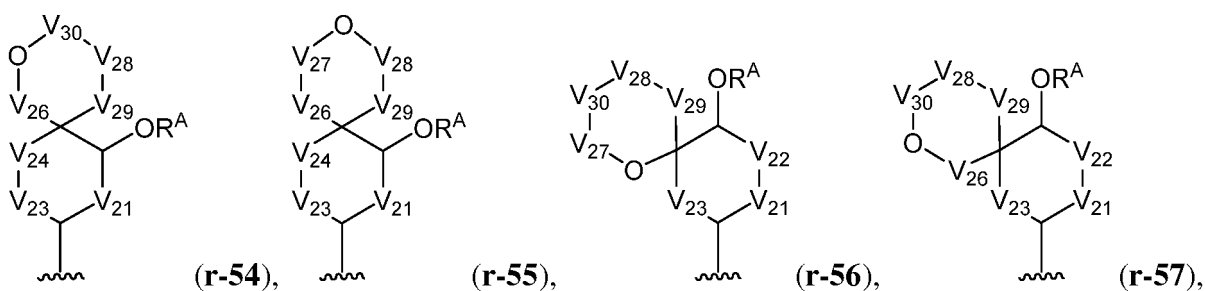




wherein V^{21} , V^{22} , V^{23} , V^{24} , V^{26} , V^{27} , V^{28} , V^{29} , V^{30} , and R^{Na} are defined herein.

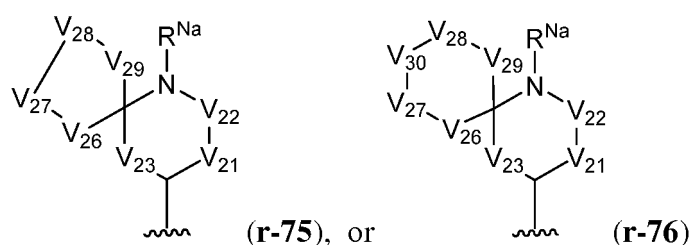
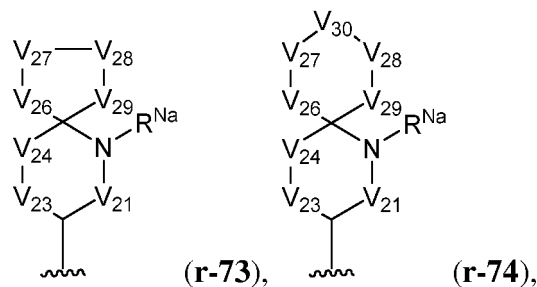
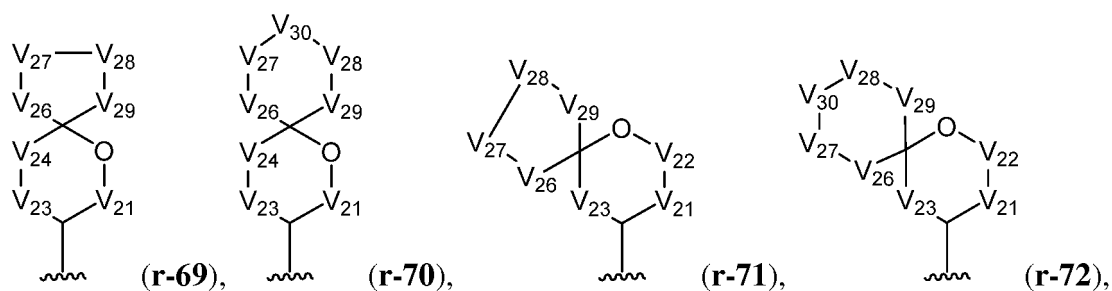
[00145] In certain embodiments, Formula (q-7) or (q-9) is of Formula (r-45) to (r-68):





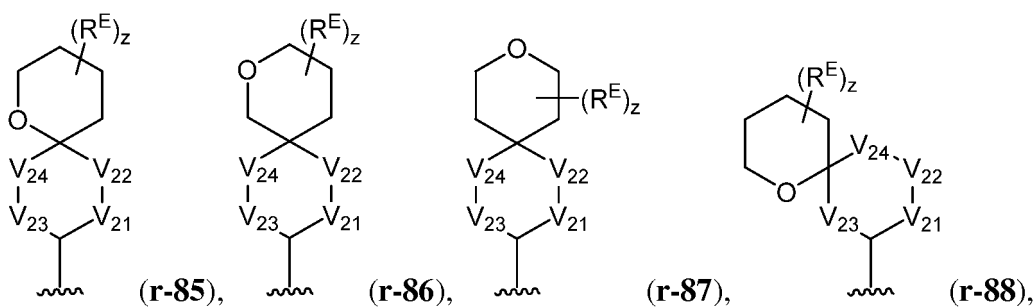
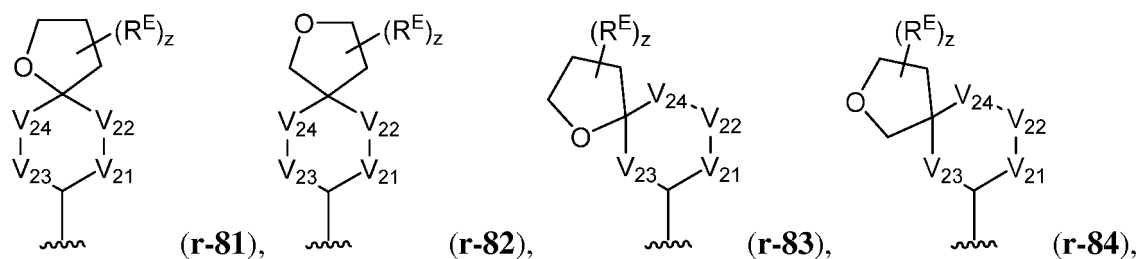
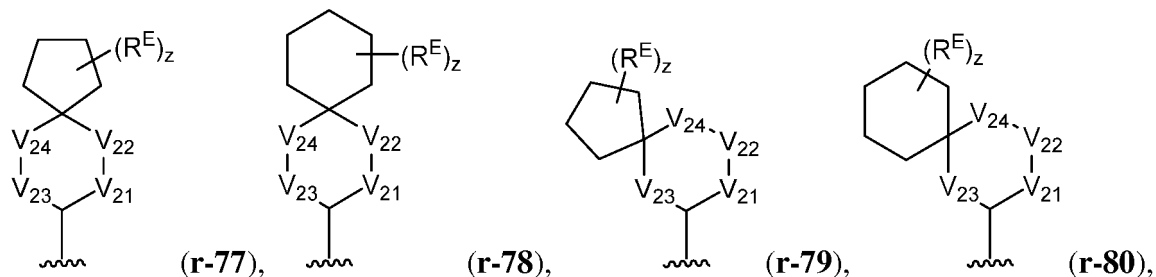
wherein V^{21} , V^{22} , V^{23} , V^{24} , V^{26} , V^{27} , V^{28} , V^{29} , V^{30} , R^{Na} , and R^A are defined herein.

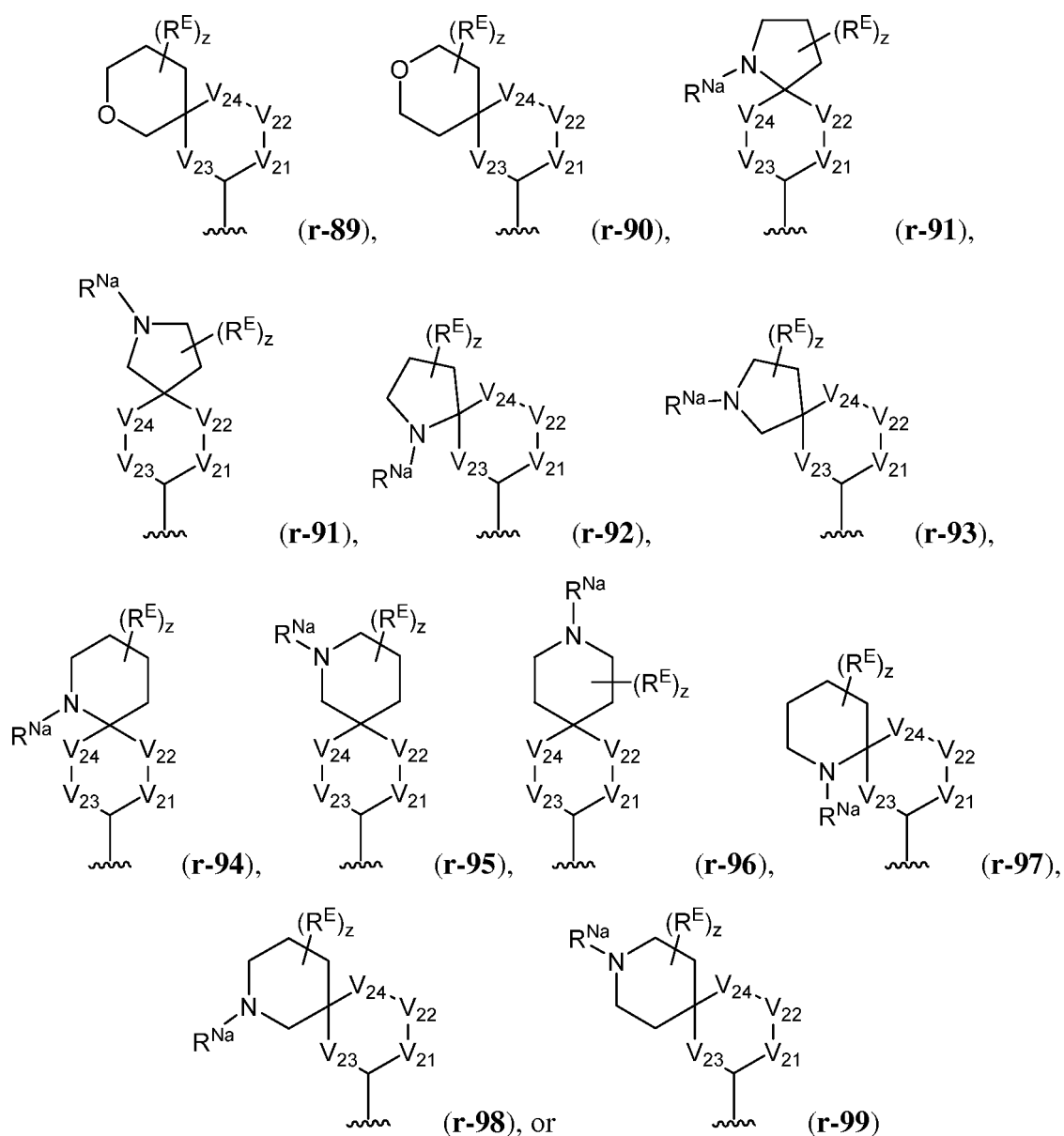
[00146] In certain embodiments, Formula (q-7) or (q-9) is of Formula (r-69) to (r-76):



wherein V^{21} , V^{22} , V^{23} , V^{24} , V^{26} , V^{27} , V^{28} , V^{29} , V^{30} , and R^{Na} are defined herein.

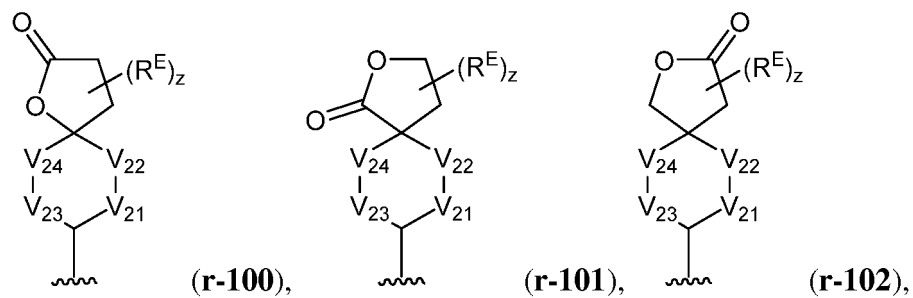
[00147] In certain embodiments, Formula (q-7) or (q-9) is of Formula (r-77) to (r-99):

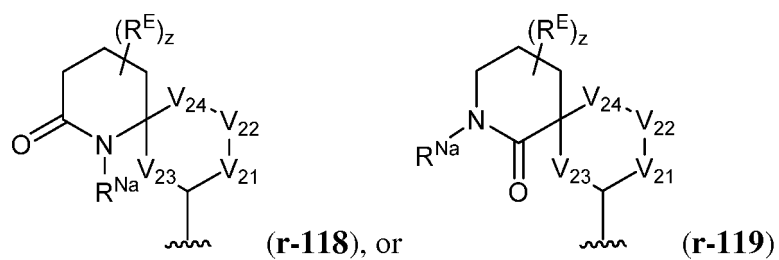




wherein V^{21} , V^{22} , V^{23} , V^{24} , R^E , and R^{Na} are defined herein, and z is 0, 1, 2, 3, or 4.

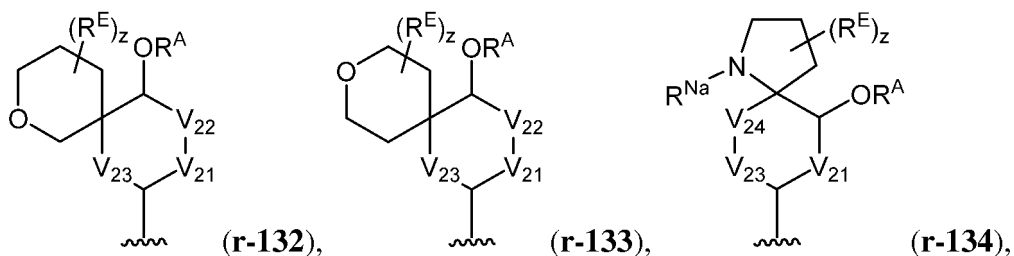
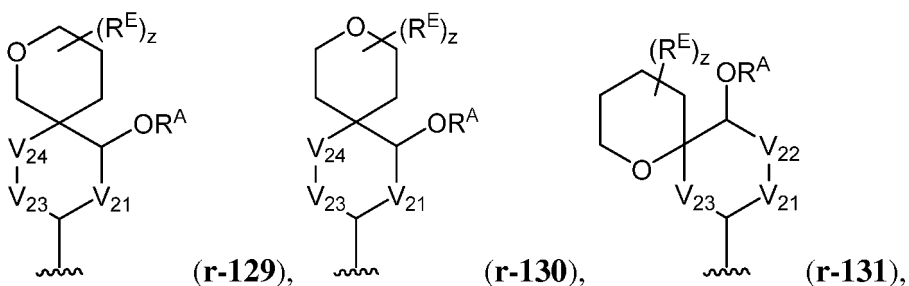
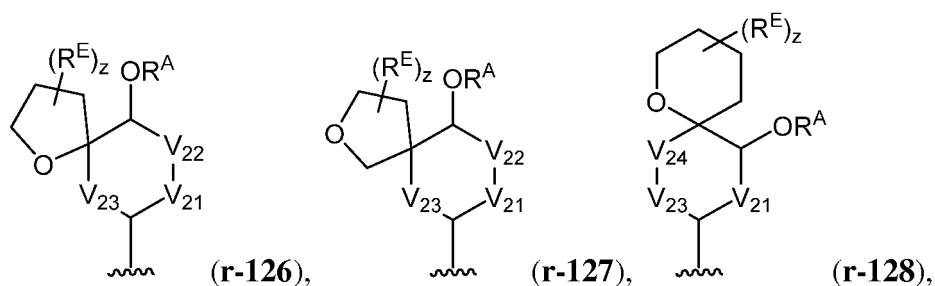
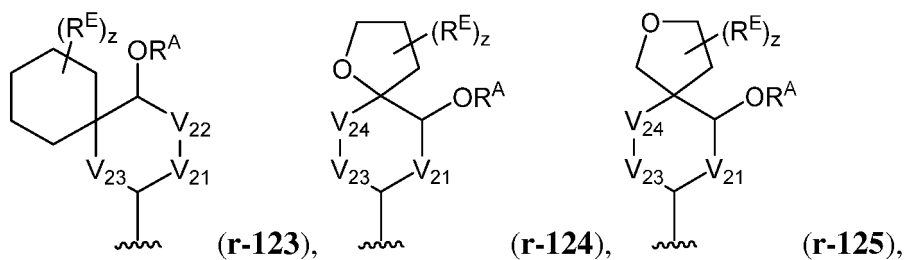
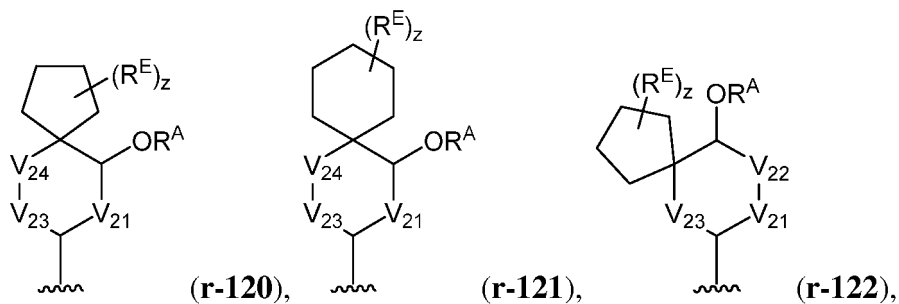
[00148] In certain embodiments, Formula (q-7) or (q-9) is of Formula (r-100) to (r-119):

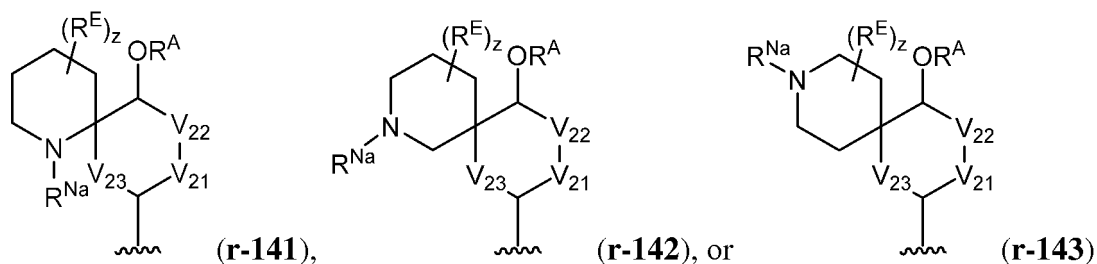
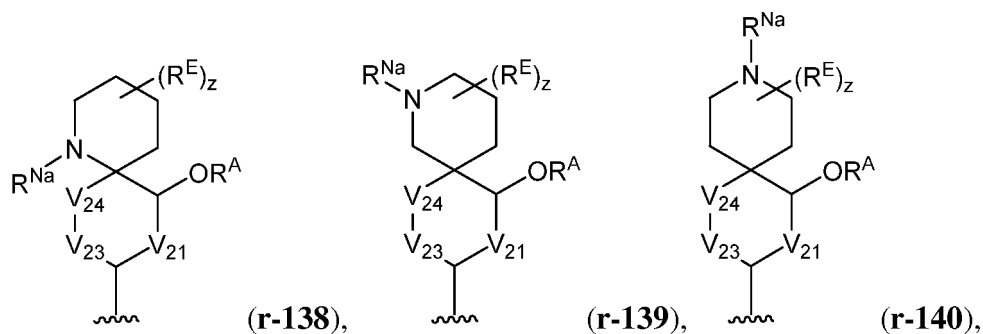
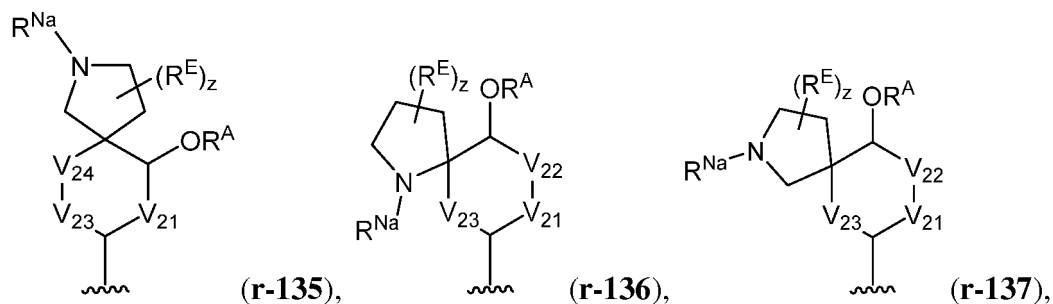




wherein V^{21} , V^{22} , V^{23} , V^{24} , R^E , and R^{Na} are defined herein, and z is 0, 1, 2, 3, or 4.

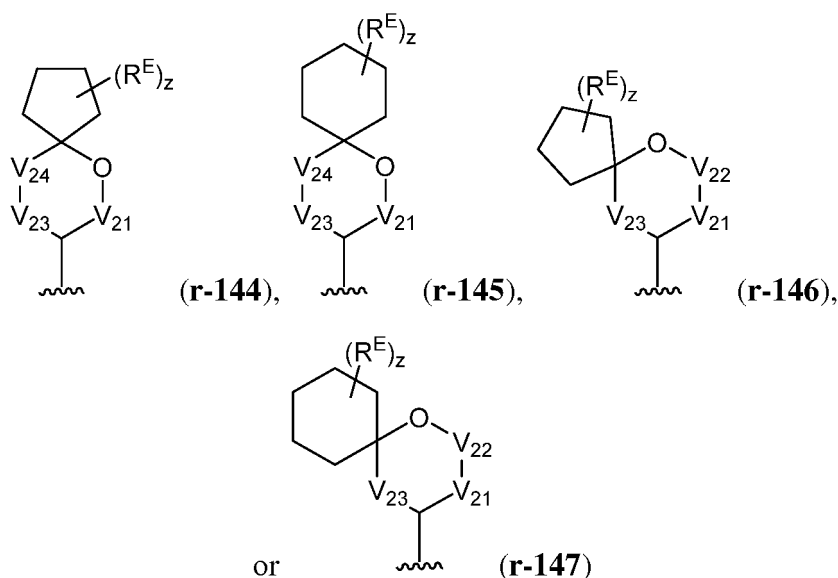
[00149] In certain embodiments, Formula (q-7) is of Formula (r-120) to (r-143):





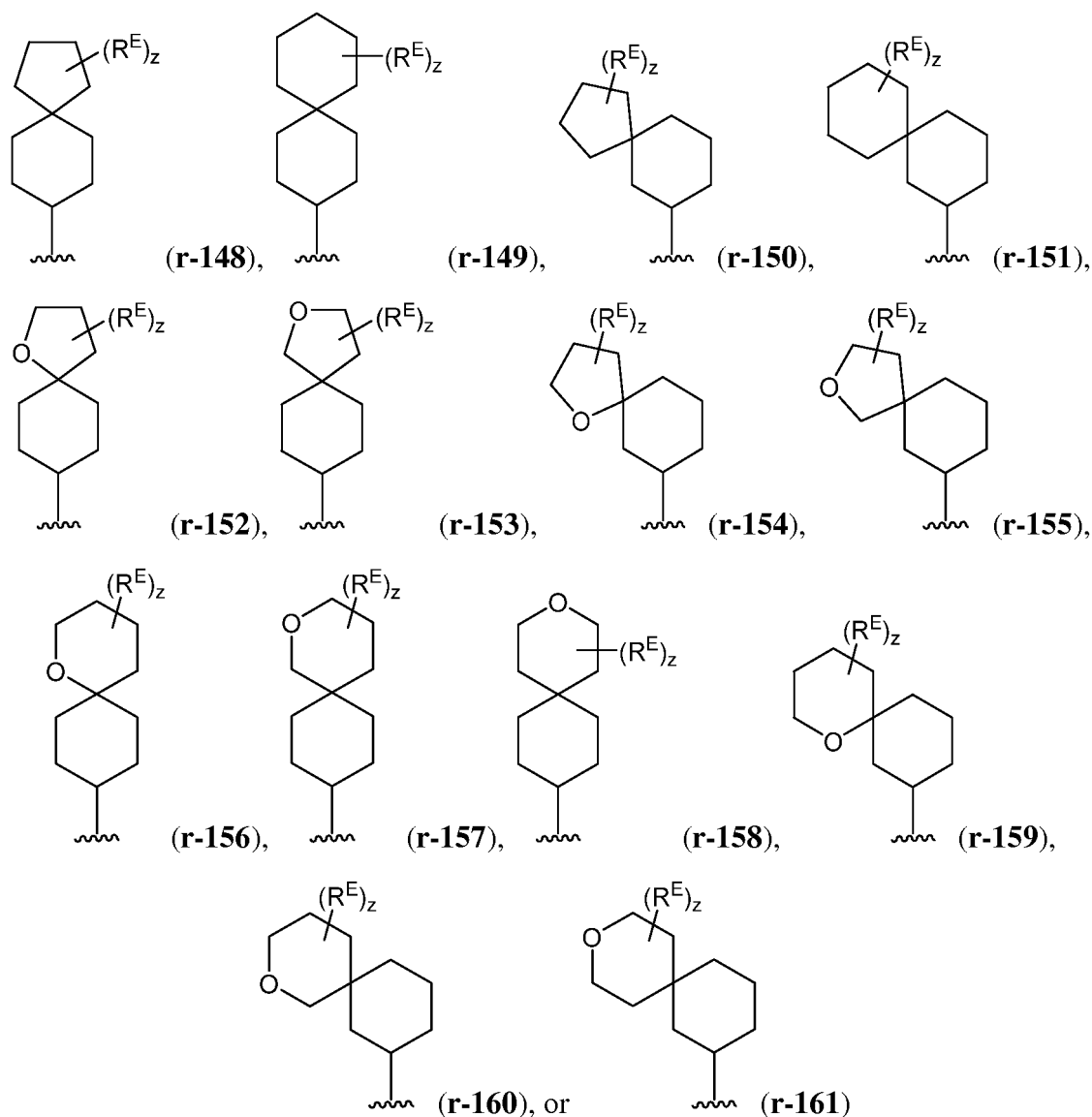
wherein V^{21} , V^{22} , V^{23} , V^{24} , R^A , R^E , and R^{Na} are defined herein, and z is 0, 1, 2, 3, or 4.

[00150] In certain embodiments, Formula (q-7) is of Formula (r-144) to (r-147):



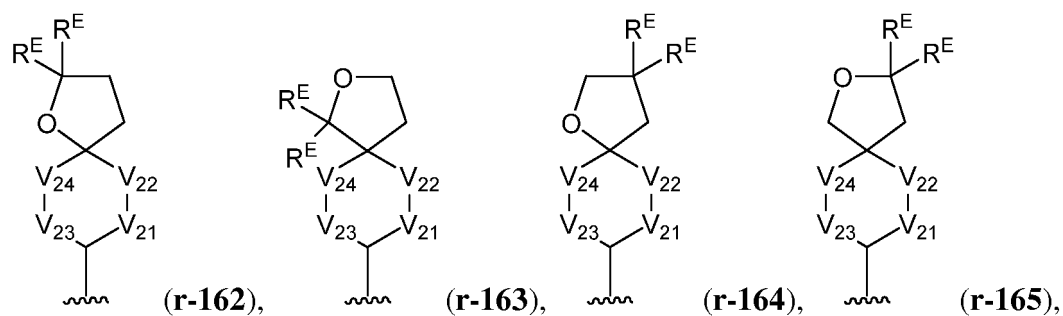
wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^E are defined herein, and z is 0, 1, 2, 3, or 4.

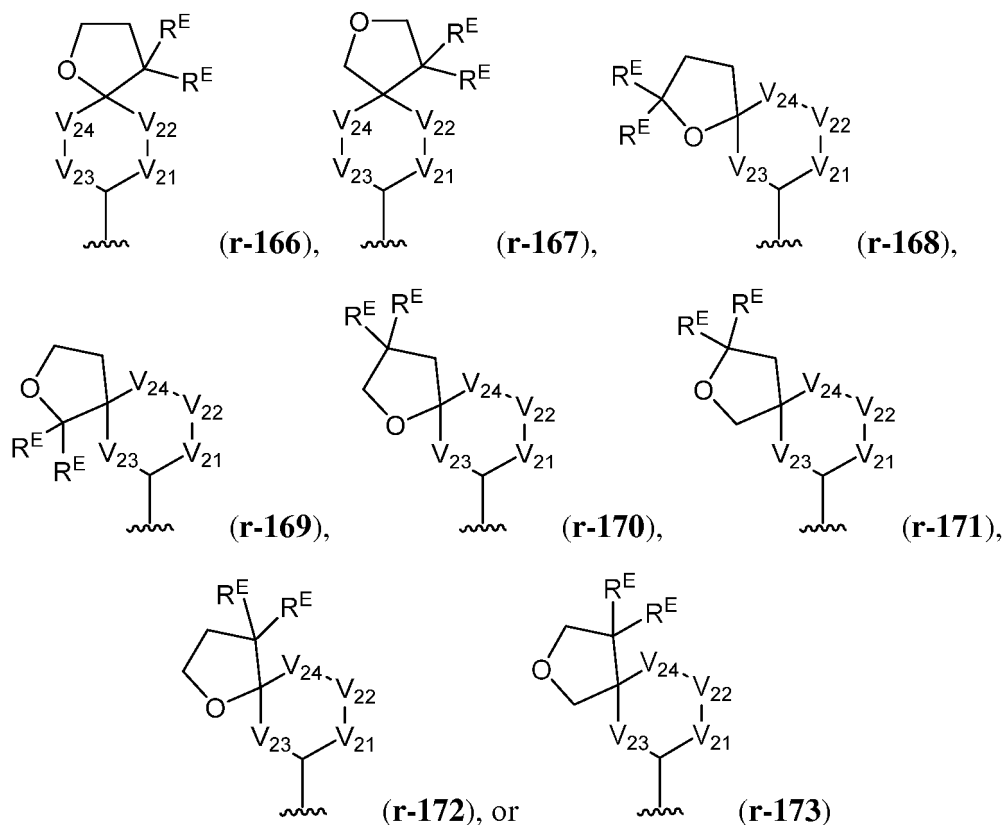
[00151] In certain embodiments, Formula (q-7) is of Formula (r-148) to (r-161):



wherein R^E is as defined herein, and z is 0, 1, 2, 3, or 4.

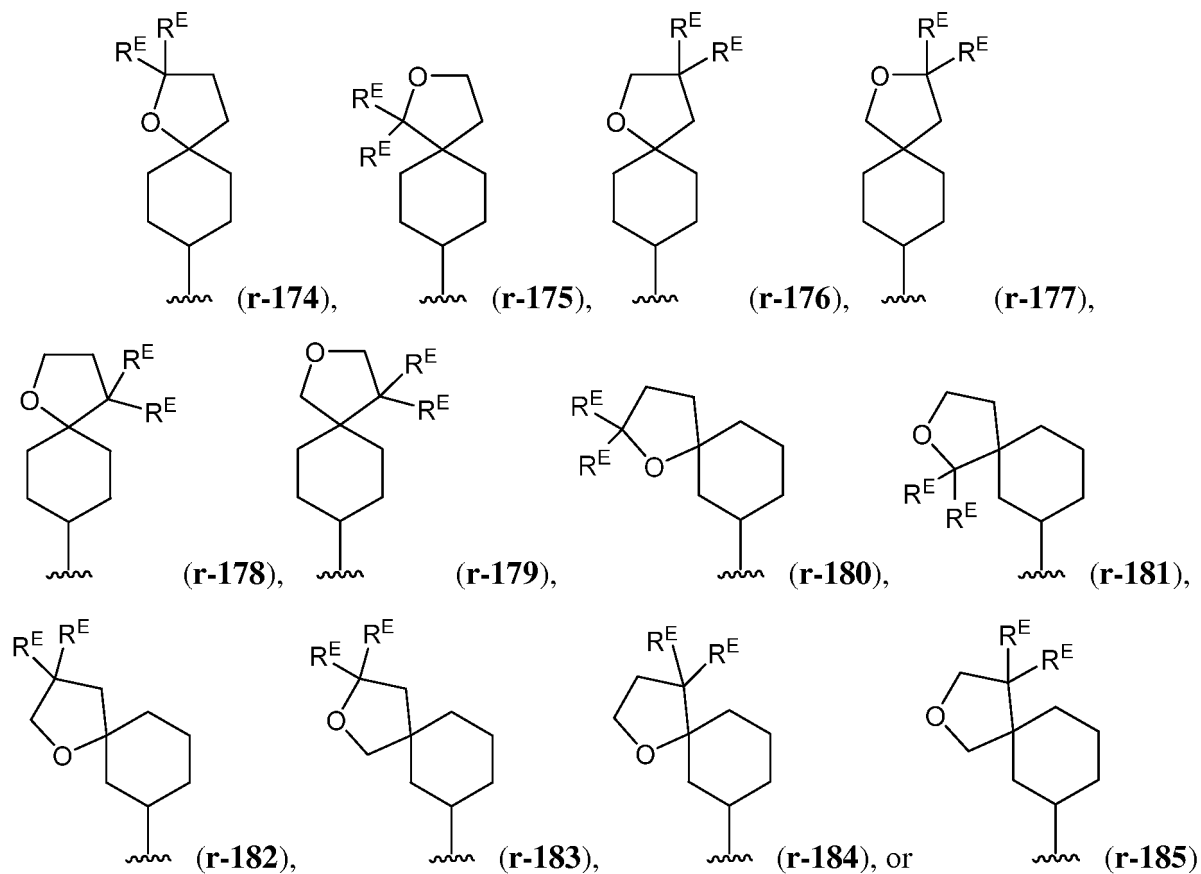
[00152] In certain embodiments, Formula (q-7) is of Formula (r-162) to (r-173):





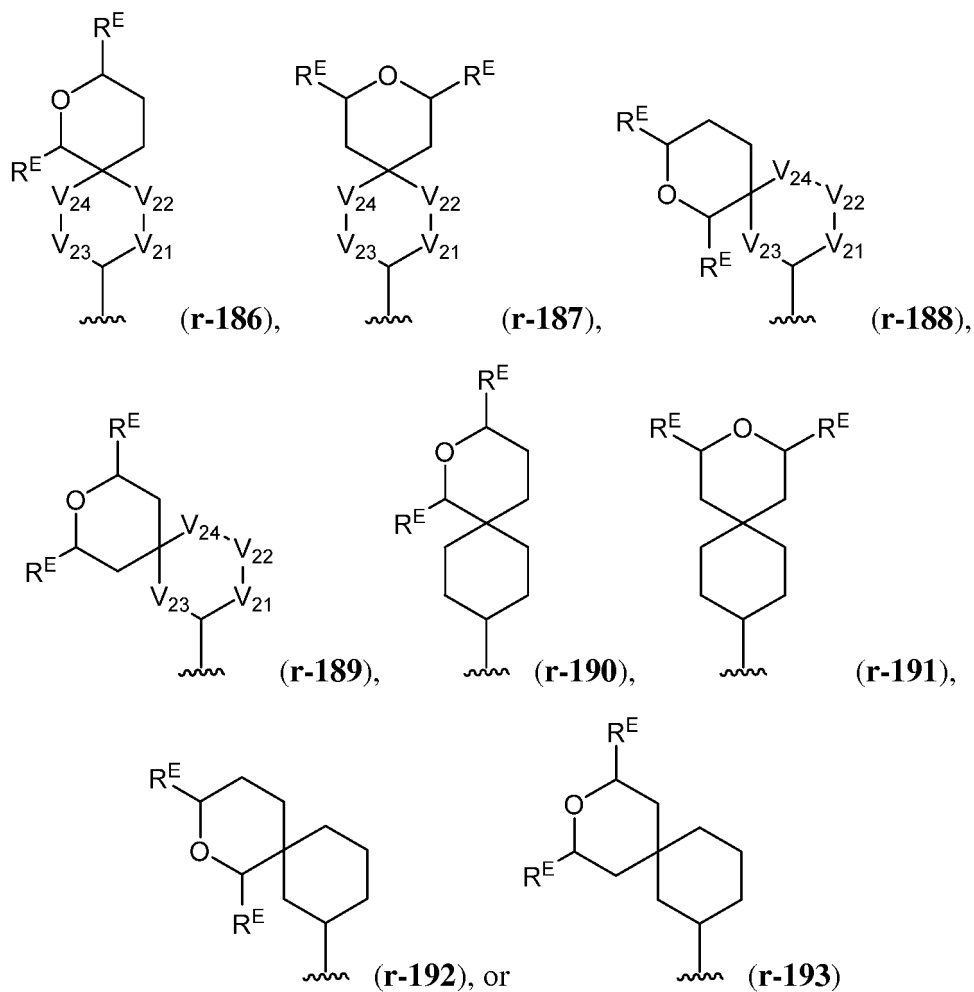
wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^E are defined herein.

[00153] In certain embodiments, Formula (q-7) is of Formula (r-174) to (r-185):



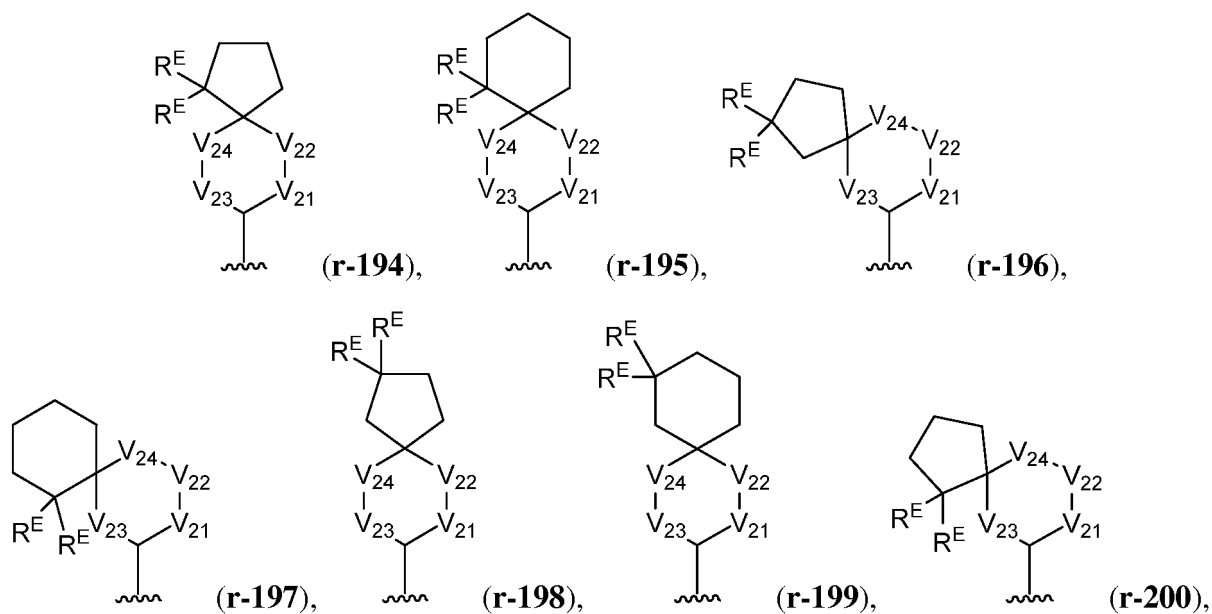
wherein R^E is defined herein.

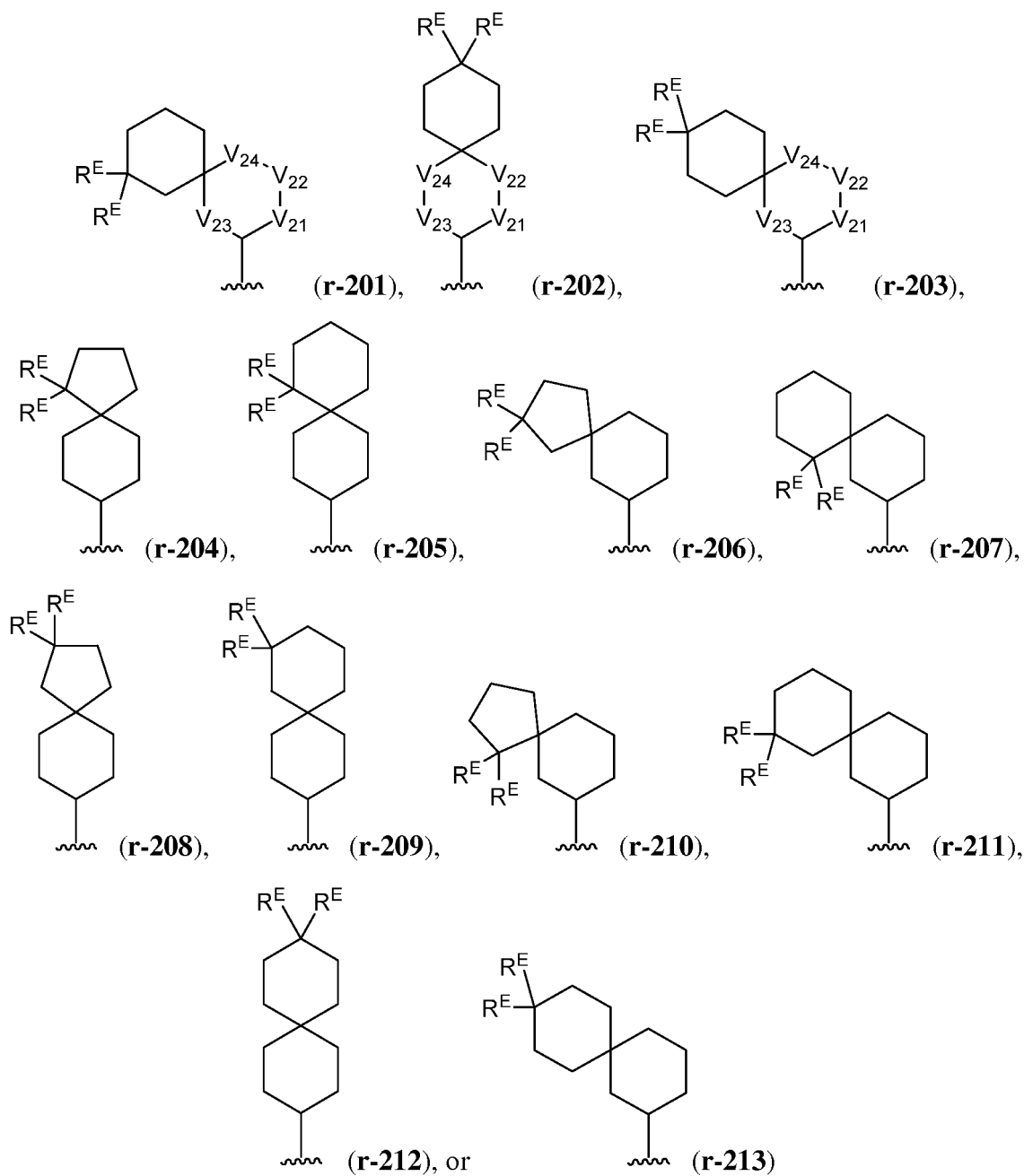
[00154] In certain embodiments, Formula (q-7) is of Formula (r-186) to (r-193):



wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^E are defined herein.

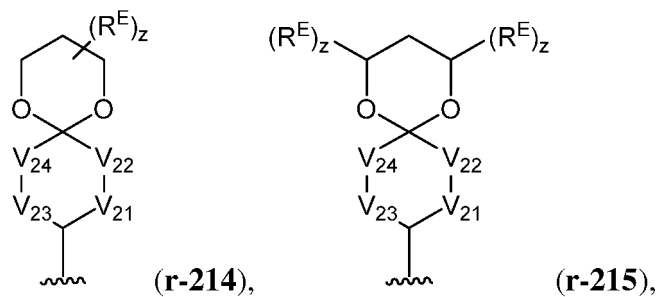
[00155] In certain embodiments, Formula (q-7) is of Formula (r-194) to (r-213):

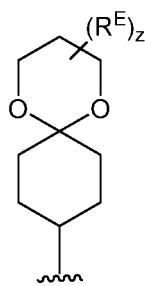




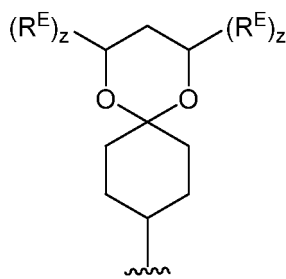
wherein V^{21} , V^{22} , V^{23} , V^{24} , and R^E are defined herein.

[00156] In certain embodiments, Formula (q-7) is of Formula (r-214) to (r-217):





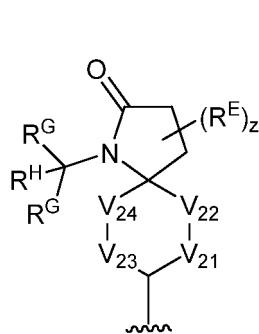
(r-216), or



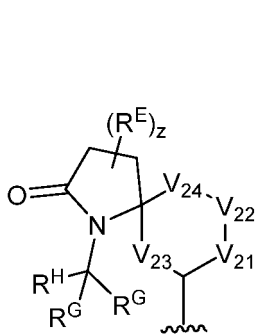
(r-217)

wherein V^{21} , V^{22} , V^{23} , V^{24} , z , and R^E are defined herein.

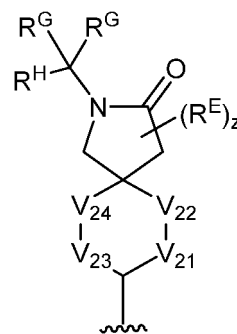
[00157] In certain embodiments, Formula (q-7) is of Formula (r-218) - (r-227):



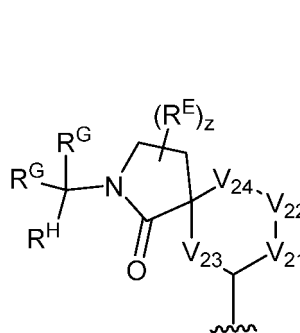
(r-218),



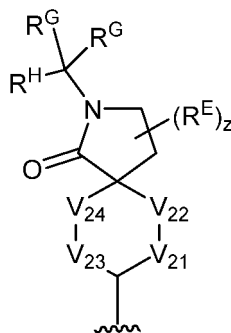
(r-219),



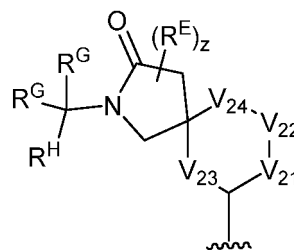
(r-220),



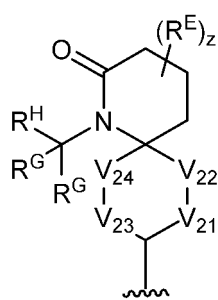
(r-221),



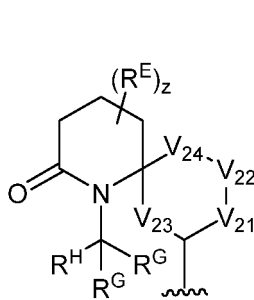
(r-222),



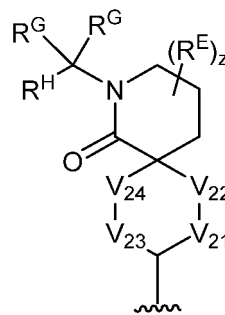
(r-223),



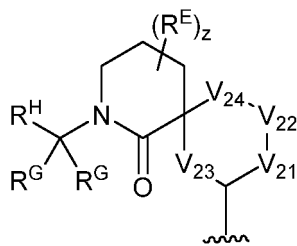
(r-224),



(r-225),



(r-226), or



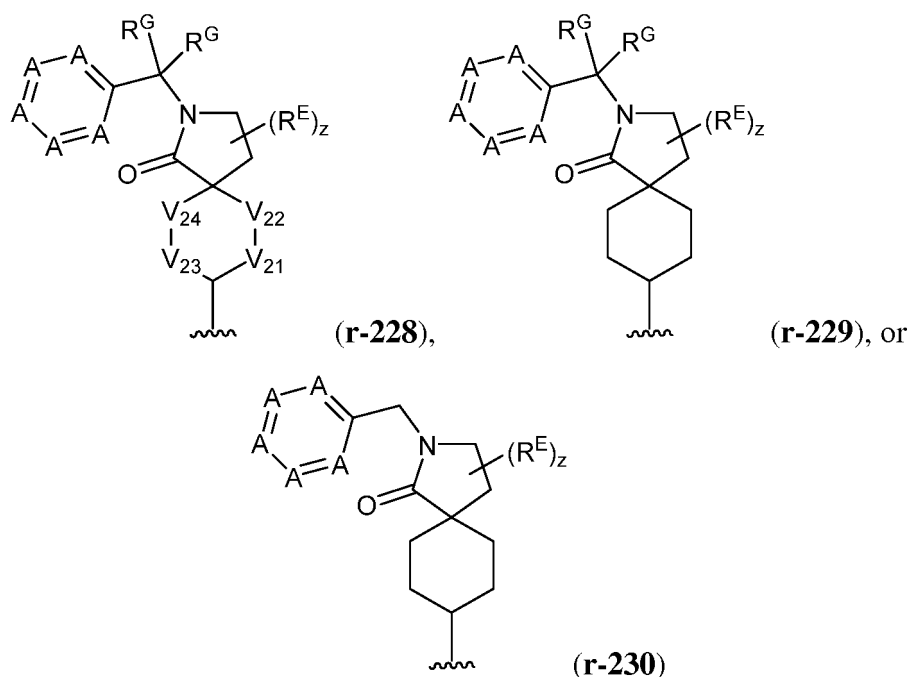
(r-227)

wherein V^{21} , V^{22} , V^{23} , V^{24} , z , and R^E are defined herein;

each instance of R^G is independently hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted carbocyclyl; or two R^G groups can be taken together to form an optionally substituted carbocyclic ring; and

R^H is hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl.

[00158] In certain embodiments, Formula (q-7) is of Formula (r-228) to (r-230):



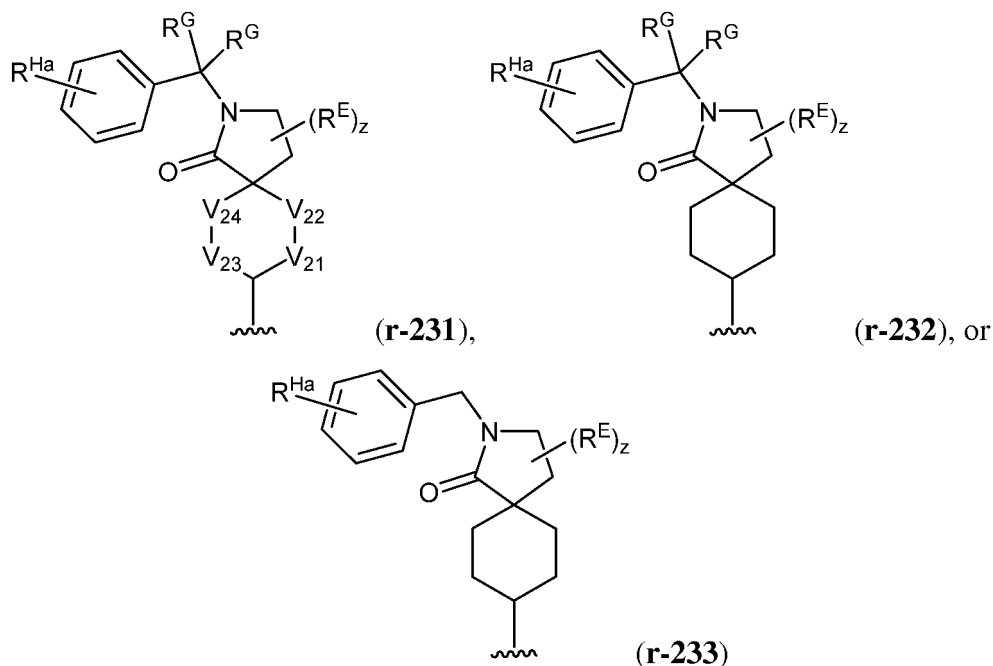
wherein V^{21} , V^{22} , V^{23} , V^{24} , R^E , and R^G are defined herein;

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

each instance of A is independently N or CR^{Ha} provided that no more than 2 instances of A can be N; and

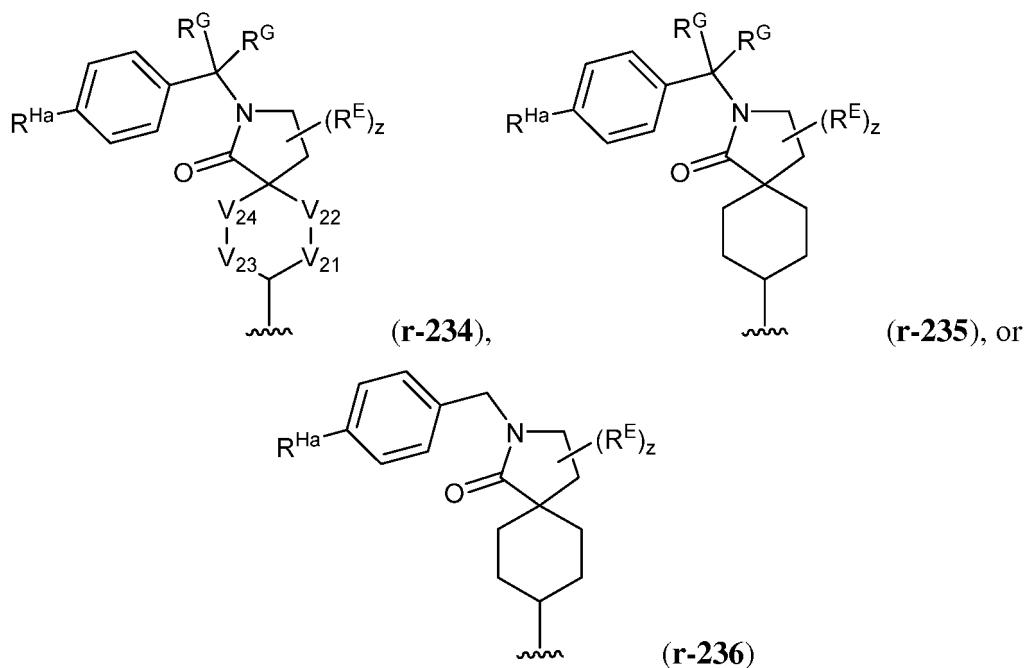
each instance of R^{Ha} is independently hydrogen, halo, -CN, -NO₂, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -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, -SO₂R^A, -NR^BSO₂R^A, or -SO₂N(R^B)₂.

[00159] In certain embodiments, Formula (q-7) is of Formula (r-231) to (r-233):



wherein V^{21} , V^{22} , V^{23} , V^{24} , z , R^E , R^G , and R^{Ha} are defined herein.

[00160] In certain embodiments, Formula (q-7) is of Formula (r-234) to (r-236):



wherein V^{21} , V^{22} , V^{23} , V^{24} , z , R^E , R^G , and R^{Ha} are defined herein.

[00161] In some embodiments, $-L_1-R^W$ is optionally substituted carbocyclyl. In some embodiments, $-L_1-R^W$ is optionally substituted C_{3-6} carbocyclyl. In some embodiments, $-L_1-R^W$ is unsubstituted cyclopropyl. In some embodiments, $-L_1-R^W$ is substituted cyclopropyl. In some embodiments, $-L_1-R^W$ is unsubstituted cyclobutyl. In some embodiments, $-L_1-R^W$ is substituted cyclobutyl. In some embodiments, $-L_1-R^W$ is unsubstituted cyclopentyl. In some embodiments, $-L_1-R^W$ is substituted cyclopentyl. In some embodiments, $-L_1-R^W$ is

unsubstituted cyclohexyl. In some embodiments, $-L_1-R^W$ is substituted cyclohexyl. In some embodiments, $-L_1-R^W$ is optionally substituted cyclopentenyl or optionally substituted cyclohexenyl.

[00162] In some embodiments, $-L_1-R^W$ is optionally substituted heterocyclyl. In some embodiments, $-L_1-R^W$ is an optionally substituted 4- to 7-membered heterocyclyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, $-L_1-R^W$ is azetidiny or oxetanyl. In some embodiments, $-L_1-R^W$ is optionally substituted tetrahydrofuranyl, optionally substituted pyrrolidinyl, optionally substituted dihydropyrrolyl, or optionally substituted pyrrolyl-2,5-dione. In some embodiments, $-L_1-R^W$ is optionally substituted piperidinyl, optionally substituted tetrahydropyranyl, optionally substituted dihydropyranyl, optionally substituted dihydropyridinyl, and optionally substituted thianyl. In certain embodiments, $-L_1-R^W$ is optionally substituted piperidinyl. In some embodiments, $-L_1-R^W$ is optionally substituted piperazinyl, optionally substituted morpholinyl, optionally substituted dithianyl, and optionally substituted dioxanyl. In some embodiments, $-L_1-R^W$ is a 5- or 6-membered heterocyclyl group fused to a C_6 aryl ring. In some embodiments, $-L_1-R^W$ is optionally substituted indolinyl, optionally substituted isoindolinyl, optionally substituted dihydrobenzofuranyl, optionally substituted dihydrobenzothienyl, or optionally substituted benzoxazolinonyl. In some embodiments, $-L_1-R^W$ is optionally substituted tetrahydroquinolinyl or optionally substituted tetrahydroisoquinolinyl.

[00163] In some embodiments, $-L_1-R^W$ is optionally substituted alkyl. In some embodiments, $-L_1-R^W$ is optionally substituted alkenyl. In some embodiments, $-L_1-R^W$ is optionally substituted alkynyl. In some embodiments, $-L_1-R^W$ is optionally substituted C_{1-6} alkyl. In some embodiments, $-L_1-R^W$ is unsubstituted C_{1-6} alkyl. In some embodiments, $-L_1-R^W$ is methyl, ethyl, propyl, or butyl. In some embodiments, $-L_1-R^W$ is isopropyl, isobutyl, or isoamyl. In some embodiments, $-L_1-R^W$ is optionally substituted C_{2-6} alkenyl. In some embodiments, $-L_1-R^W$ is C_{2-6} alkynyl.

[00164] As defined generally above, R^3 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl. In certain embodiments, R^3 is ethyl. In certain embodiments, R^3 is propyl or butyl. In certain embodiments, R^3 is cyclopropyl. In certain embodiment, R^3 is cyclobutyl.

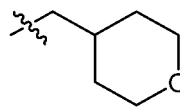
[00165] As defined generally above, R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted

C₃₋₇ cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl; or optionally substituted C₁₋₄ alkyl-Cy, wherein Cy is optionally substituted C₃₋₇ cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. Alternatively, when L₁ is a bond and R^W is hydrogen, then X is CR⁵, Z is N, and Y is NR⁴, then R⁴ is optionally substituted carbocyclyl or optionally substituted heterocyclyl as defined above and herein.

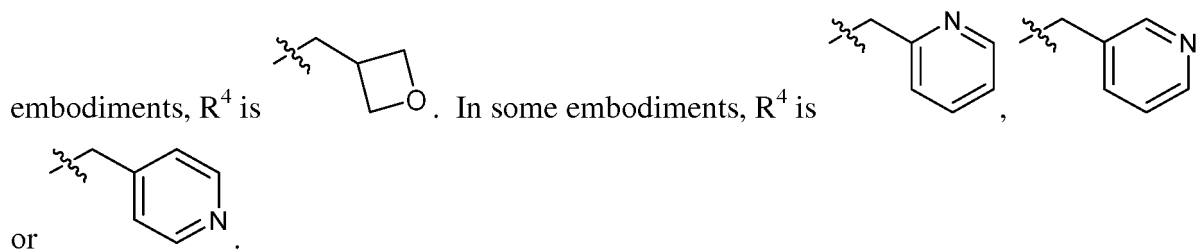
[00166] In certain embodiments, R⁴ is hydrogen. In certain embodiments, R⁴ is optionally substituted C₁₋₆ alkyl. In certain embodiments, R⁴ is unsubstituted C₁₋₆ alkyl. In certain embodiments, R⁴ is methyl, ethyl, or isopropyl. In certain embodiments, R⁴ is substituted C₁₋₆ alkyl. In certain embodiments, R⁴ is methoxyethyl. In certain embodiments, R⁴ is hydroxyethyl or propane-1,2-diol. In certain embodiments, R⁴ is optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, R⁴ is unsubstituted C₃₋₇ cycloalkyl. In certain embodiments, R⁴ is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R⁴ is optionally substituted 4- to 7-membered heterocyclyl. In certain embodiments, R⁴ is optionally substituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, R⁴ is oxetane, tetrahydrofuran, or tetrahydropyran.

[00167] In certain embodiments, R⁴ is optionally substituted C₁₋₄ alkyl-Cy, wherein Cy is optionally substituted C₃₋₇ cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, Cy is optionally substituted C₃₋₇ cycloalkyl. In some embodiments, Cy is optionally substituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Cy is oxetane, tetrahydrofuran, or tetrahydropyran. In some embodiments, Cy is optionally substituted aryl. In some embodiments, Cy is optionally substituted phenyl. In some embodiments, Cy is unsubstituted phenyl. In some embodiments, Cy is optionally substituted heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Cy is optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some

embodiments, Cy is pyridyl. In some embodiments, R⁴ is



. In some



[00168] As defined generally above, R^5 is hydrogen, halo, -CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{3-4} cycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is halo. In certain embodiments, R^5 is chloro. In certain embodiments, R^5 is fluoro. In certain embodiments, R^5 is -CN. In certain embodiments, R^5 is optionally substituted C_{1-4} alkyl. In certain embodiments, R^5 is unsubstituted C_{1-4} alkyl. In certain embodiments, R^5 is methyl. In certain embodiments, R^5 is ethyl. In certain embodiments, R^5 is propyl or butyl. In certain embodiments, R^5 is C_{1-4} alkyl substituted with one or more fluoro groups. In certain embodiments, R^5 is -CF₃. In certain embodiments, R^5 is -CHF₂. In certain embodiments, R^5 is optionally substituted C_{3-4} cycloalkyl. In certain embodiments, R^5 is cyclopropyl or cyclobutyl.

[00169] As defined generally above, R^x is optionally substituted C_{1-4} alkyl or optionally substituted C_{3-4} cycloalkyl. In certain embodiments, R^x is optionally substituted C_{1-4} alkyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl. In certain embodiments, R^x is methyl. In certain embodiments, R^x is ethyl. In certain embodiments, R^x is isopropyl. In certain embodiments, R^x is propyl or butyl. In certain embodiments, R^x is substituted C_{1-4} alkyl. In certain embodiments, R^x is C_{1-4} alkyl substituted with hydroxyl or alkoxy. In certain embodiments, R^x is hydroxyethyl or methoxyethyl. In certain embodiments, R^x is optionally substituted C_{3-4} cycloalkyl. In certain embodiments, R^x is unsubstituted C_{3-4} cycloalkyl. In certain embodiments, R^x is cyclopropyl. In certain embodiments, R^x is cyclobutyl.

[00170] As defined generally above, each R^A is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom. In some embodiments, R^A is hydrogen. In some embodiments, R^A is optionally substituted alkyl. In some embodiments, R^A is optionally substituted alkyl substituted with a Cy group to form optionally substituted alkyl-Cy, wherein Cy is described herein. In some embodiments, R^A is optionally substituted alkenyl or optionally substituted alkynyl. In some embodiments, R^A is optionally substituted carbocyclyl, optionally substituted heterocyclyl,

optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, R^A is an oxygen protecting group when attached to an oxygen atom. In some embodiments, R^A is not an oxygen protecting group. In some embodiments, R^A is sulfur protecting group when attached to a sulfur atom. In some embodiments, R^A is not a sulfur protecting group.

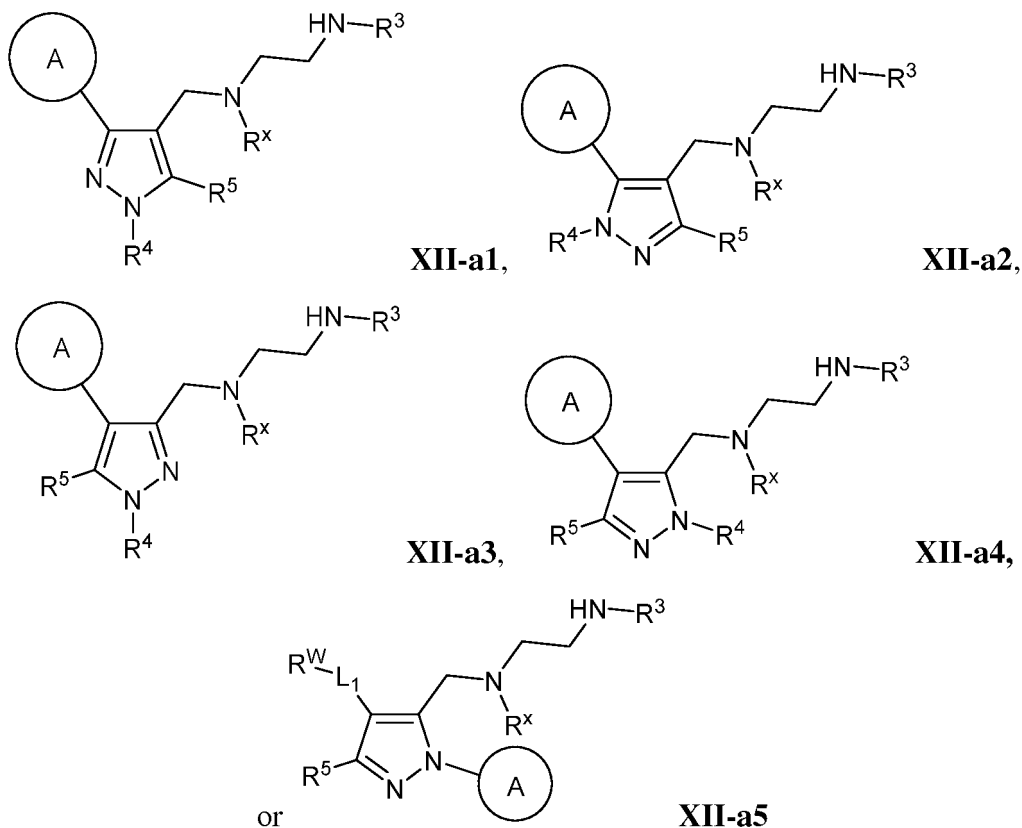
[00171] As defined generally above, each R^B is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, and a nitrogen protecting group, or two R^B groups or an R^B group and an R^W group on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic ring. In some embodiments, R^B is hydrogen. In some embodiments, R^B is optionally substituted alkyl. In some embodiments, R^B is optionally alkyl substituted with a Cy group to form optionally substituted alkyl-Cy, wherein Cy is described herein. In some embodiments, R^B is optionally substituted alkenyl or optionally substituted alkynyl. In some embodiments, R^B is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, R^B is a nitrogen protecting group. In some embodiments, R^B is not a nitrogen protecting group. In some embodiments, two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring. In some embodiments, an R^B group and an R^W group on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.

[00172] As defined generally above, each instance of R^E is independently hydrogen, halo, -CN, -NO₂, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, 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, -SO₂R^A, -NR^BSO₂R^A, or -SO₂N(R^B)₂; or two R^E groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring. In certain embodiments, R^E is hydrogen. In certain embodiments, R^E is not hydrogen. In certain embodiments, R^E is halo (e.g., fluoro, chloro, bromo, or iodo). In certain embodiments, R^E is optionally substituted alkyl. In certain embodiments, R^E is optionally substituted C₁₋₆ alkyl. In certain embodiments, R^E is

unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain R^E is unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, R^E is methyl. In certain embodiments, R^E is C₁₋₆ haloalkyl (*e.g.*, -CF₃, -CF₂H, or -CF₂CH₃). In certain embodiments, R^E is -CF₃. In certain embodiments, R^E is alkoxyalkyl (*e.g.*, -CH₂OR^A or -CH₂CH₂OR^A). In certain embodiments, R^E is an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclopropyl). In certain embodiments, R^E is an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclopropyl). In certain embodiments, R^E is substituted phenyl. In certain embodiments, R^E is unsubstituted phenyl. In certain embodiments, R^E is an optionally substituted heterocyclic ring (*e.g.*, azetidine, oxetane, furan, pyrrolidine, piperidine, piperazine, or morpholine). In certain embodiments, R^E is an unsubstituted heterocyclic ring (*e.g.*, azetidine, oxetane, furan, pyrrolidine, piperidine, piperazine, or morpholine). In certain embodiments, R^E is an optionally substituted heteroaryl ring (*e.g.*, pyrazole, imidazole, triazole, pyridine, pyrimidine, or pyridizine). In certain embodiments, R^E is an unsubstituted heteroaryl ring (*e.g.*, pyrazole, imidazole, triazole, pyridine, pyrimidine, or pyridizine). In certain embodiments, R^E is alkoxy. In certain embodiments, R^E is -OR^A; and R^A is optionally substituted C₁₋₆ alkyl. In certain embodiments, R^E is -OR^A; and R^A is unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, or propyl). In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring.

[00173] Various combinations of certain above-described embodiments are further envisioned herein.

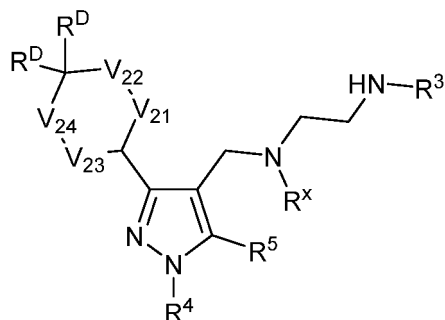
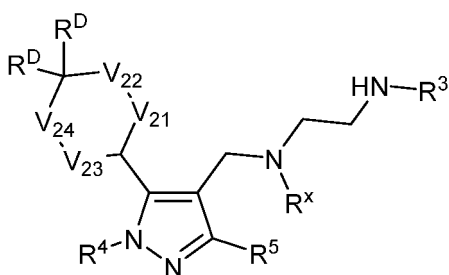
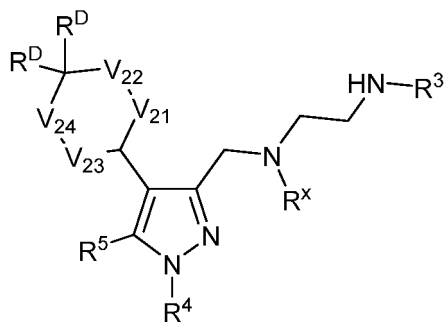
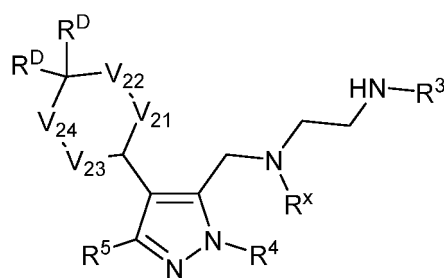
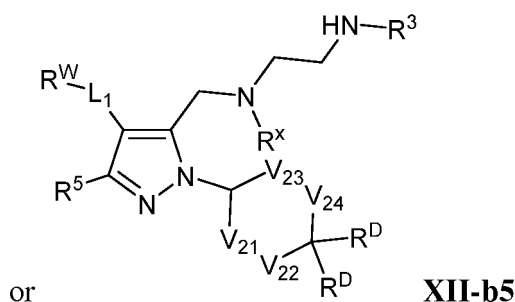
[00174] For example, in certain embodiments, provided are compounds of Formulae **XII-a1** to **XII-a5**:



or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , and R^x are defined herein; and Ring A is any of Formulae (**q-7**) to (**q-117**), (**q-7a**) to (**q-117a**), or (**r-1**) to (**r-236**).

In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00175] In certain embodiments, when Ring A is of Formula (q-7), provided are compounds of Formulae **XII-b1** to **XII-b5**:

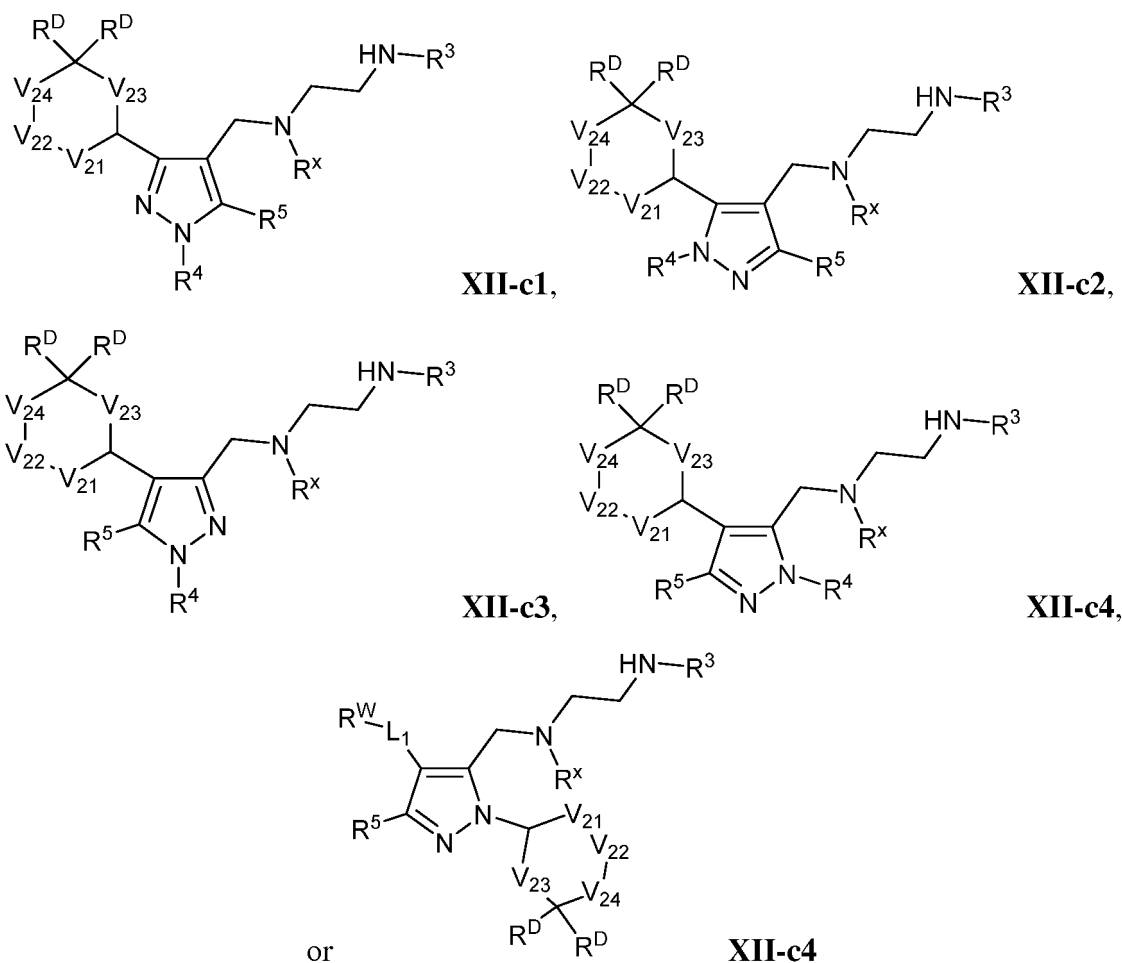
**XII-b1,****XII-b2,****XII-b3,****XII-b4,****XII-b5**

or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , and R^D are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, at least one

instance of R^D is hydrogen. In certain embodiments, at least one instance of R^D is halo (*e.g.*, fluoro, chloro, or bromo). In certain embodiments, at least one instance of R^D is optionally substituted alkyl. In certain embodiments, at least one instance of R^D is optionally substituted C_{1-4} alkyl. In certain embodiments, at least one instance of R^D is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, at least one instance of R^D is unsubstituted branched C_{3-4} alkyl (*e.g.*, isopropyl, isobutyl, *sec*-butyl, or *tert*-butyl). In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is optionally substituted alkyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is optionally substituted C_{1-4} alkyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is branched C_{3-4} alkyl (*e.g.*, isopropyl, isobutyl, *sec*-butyl, or *tert*-butyl). In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is methyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is ethyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is isopropyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is isobutyl. In certain embodiments, both instances of R^D are optionally substituted C_{1-4} alkyl. In certain embodiments, both instances of R^D are methyl. In certain embodiments, one instance of R^D is hydrogen; and one instance of R^D is $-OR^A$. In certain embodiments, at least one instance of R^D is optionally substituted alkoxyalkyl (*e.g.*, $-CH_2OR^A$, $-CH_2CH_2OR^A$, or $-CH_2CH_2CH_2OR^A$). In certain embodiments, both instances of R^D are optionally substituted alkoxyalkyl (*e.g.*, $-CH_2OR^A$, $-CH_2CH_2OR^A$, or $-CH_2CH_2CH_2OR^A$). In certain embodiments, two R^D groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring. In certain embodiments, two R^D groups are joined to form an optionally substituted cyclopentane. In certain embodiments, two R^D groups are joined to form an optionally substituted cyclohexane. In certain embodiments, two R^D groups are joined to form an optionally substituted furan. In certain embodiments, two R^D groups are joined to form an optionally substituted pyran. In certain embodiments, two R^D groups are joined to form an optionally substituted pyrrolidinone. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two

R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00176] In certain embodiments, when Ring A is of Formula (q-9), provided are compounds of Formulae **XII-c1** to **XII-c5**:

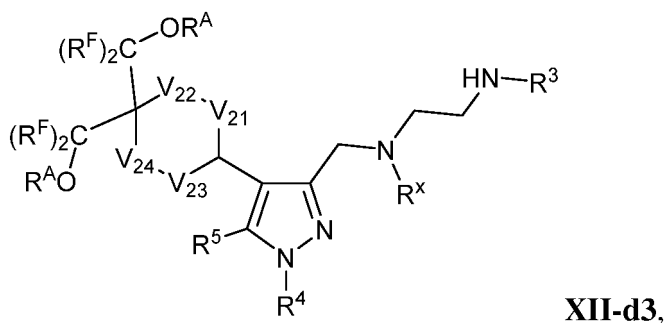
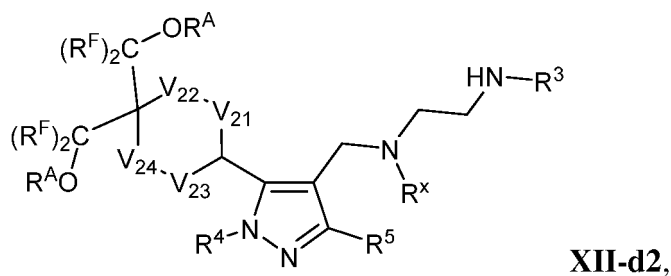
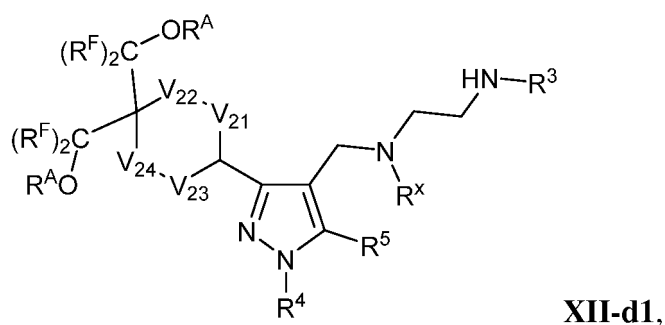


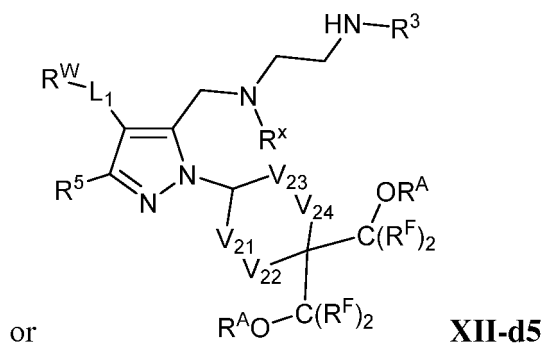
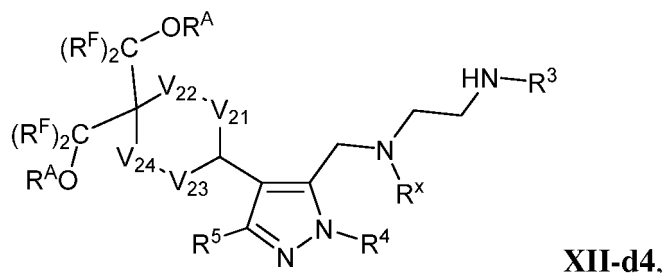
or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , and R^D are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least

two of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, at least one of V_{21} and V_{22} is O or $-\text{CH}(\text{OR}^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-\text{CH}(\text{OR}^A)-$. In certain embodiments, V_{21} is O. In certain embodiments, V_{21} is $-\text{CH}(\text{OR}^A)-$. In certain embodiments, at least one instance of R^D is hydrogen. In certain embodiments, at least one instance of R^D is halo (*e.g.*, fluoro, chloro, or bromo). In certain embodiments, at least one instance of R^D is optionally substituted alkyl. In certain embodiments, at least one instance of R^D is optionally substituted C_{1-4} alkyl. In certain embodiments, at least one instance of R^D is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, at least one instance of R^D is unsubstituted branched C_{3-4} alkyl (*e.g.*, isopropyl, isobutyl, *sec*-butyl, or *tert*-butyl). In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is optionally substituted alkyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is optionally substituted C_{1-4} alkyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is branched C_{3-4} alkyl (*e.g.*, isopropyl, isobutyl, *sec*-butyl, or *tert*-butyl). In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is methyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is ethyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is isopropyl. In certain embodiments, one instance of R^D is hydrogen; and the second instance of R^D is isobutyl. In certain embodiments, both instances of R^D are optionally substituted C_{1-4} alkyl. In certain embodiments, both instances of R^D are methyl. In certain embodiments, one instance of R^D is hydrogen; and one instance of R^D is $-\text{OR}^A$. In certain embodiments, at least one instance of R^D is optionally substituted alkoxyalkyl (*e.g.*, $-\text{CH}_2\text{OR}^A$, $-\text{CH}_2\text{CH}_2\text{OR}^A$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OR}^A$). In certain embodiments, both instances of R^D is optionally substituted alkoxyalkyl (*e.g.*, $-\text{CH}_2\text{OR}^A$, $-\text{CH}_2\text{CH}_2\text{OR}^A$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OR}^A$). In certain embodiments, two R^D groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring. In certain embodiments, two R^D groups are joined to form an optionally substituted cyclopentane. In certain embodiments, two R^D groups are joined to form an optionally substituted cyclohexane. In certain embodiments, two R^D groups are joined to form an optionally substituted furan. In certain embodiments, two R^D groups are joined to form an optionally substituted pyran. In certain embodiments, two R^D groups are joined to form an optionally substituted

pyrrolidinone. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00177] In certain embodiments, when Ring A is of Formula (q-46) or (q-47), provided are compounds of Formulae **XII-d1** to **XII-d5**:

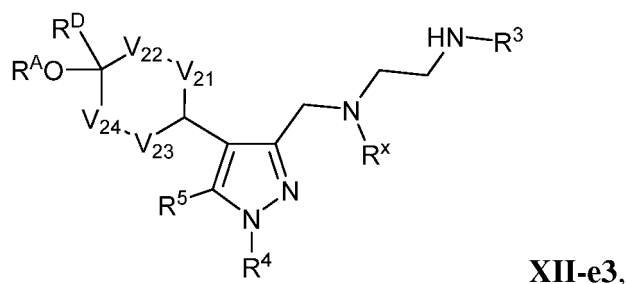
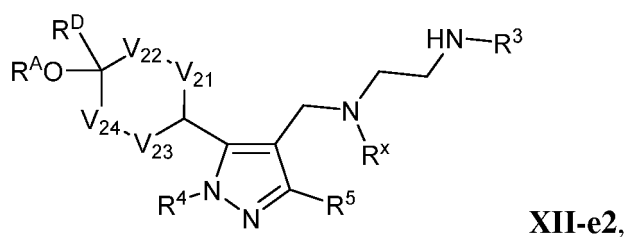
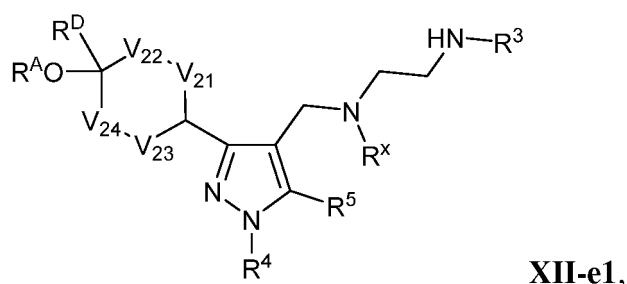


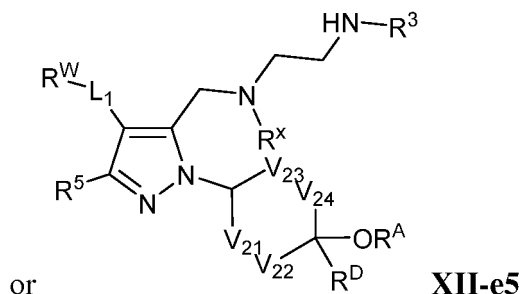
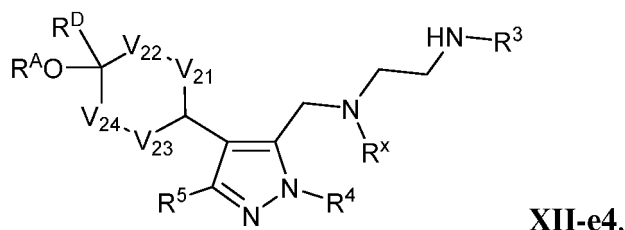


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , R^A , and R^F are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, at least two instances of R^F are hydrogen. In certain embodiments, all four instances of R^F are hydrogen. In certain embodiments, each instance of R^A is independently hydrogen. In certain embodiments, both instances of R^A are hydrogen. In certain embodiments, neither instance of R^A is hydrogen. In certain embodiments, at least one instance of R^A is optionally substituted alkyl. In certain embodiments, both instances of R^A are independently optionally substituted alkyl. In certain embodiments, at least one instance of R^A is optionally substituted C_{1-4} alkyl. In certain embodiments, both instances of R^A are independently optionally substituted C_{1-4} alkyl. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, both instances of R^A are

independently unsubstituted alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, at least one instance of R^A is methyl. In certain embodiments, both instances of R^A are methyl. In certain embodiments, at least one instance of R^A is ethyl. In certain embodiments, both instances of R^A are ethyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00178] In certain embodiments, when Ring A is of Formula (q-58), provided are compounds of Formulae **XII-e1** to **XII-e5**:

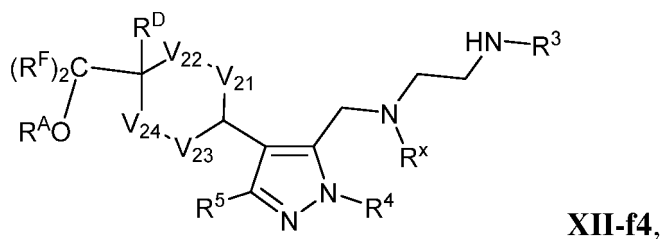
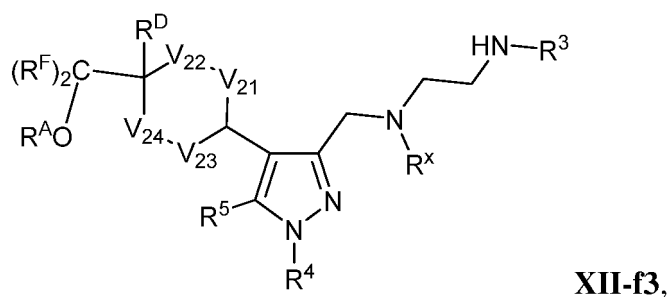
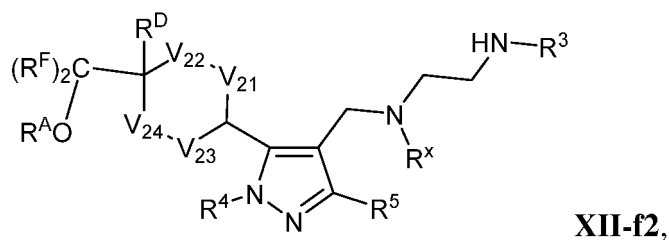
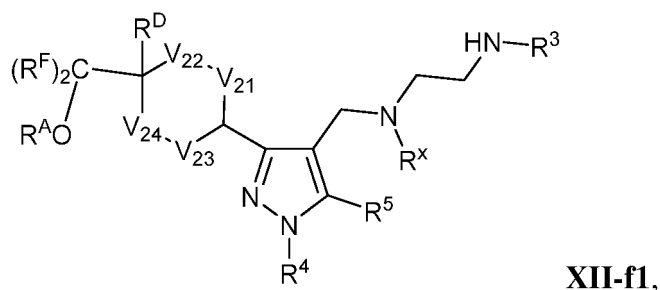


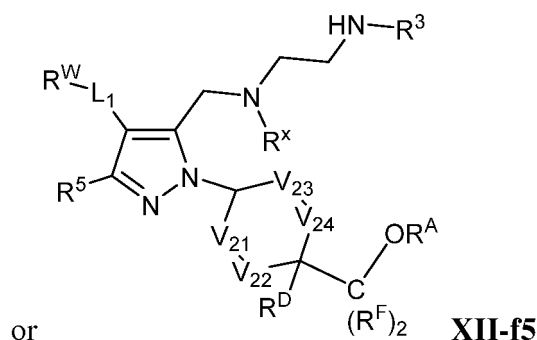


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , R^A , and R^D are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, R^D is hydrogen. In certain embodiments, R^A is hydrogen. In certain embodiments, R^A is not hydrogen. In certain embodiments, R^A is optionally substituted alkyl. In certain embodiments, R^A is optionally substituted C_{1-6} alkyl. In certain embodiments, R^A is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, R^A is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, R^A is methyl. In certain embodiments, R^A is ethyl. In certain embodiments, R^A is 3-pentyl. In certain embodiments, R^D is hydrogen; and R^A is methyl. In certain embodiments, R^D is hydrogen; and R^A is ethyl. In certain embodiments, R^D is hydrogen; and R^A is 3-pentyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl,

cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00179] In certain embodiments, when Ring A is of Formula (q-59), provided are compounds of Formulae **XII-f1** to **XII-f5**:

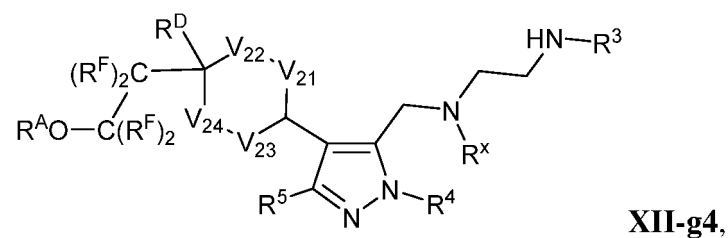
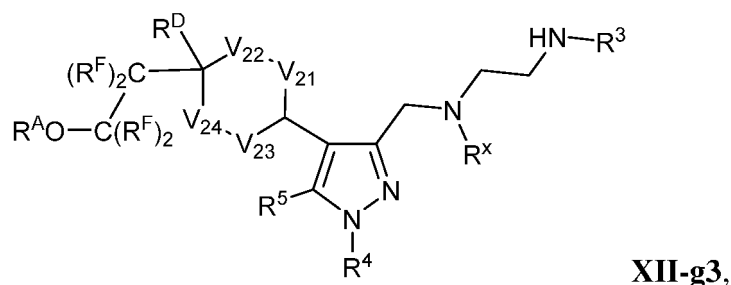
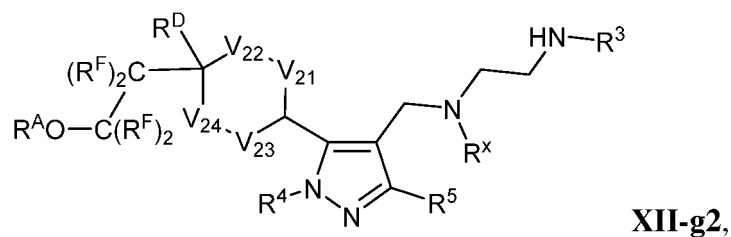
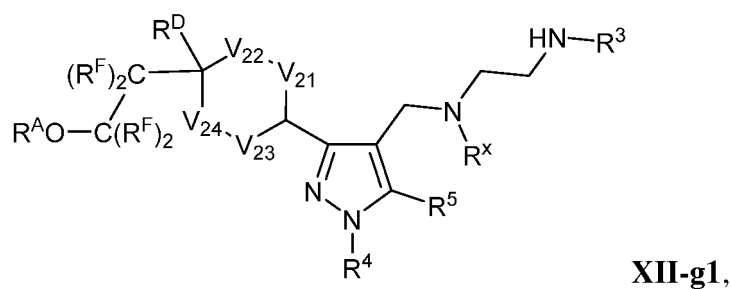


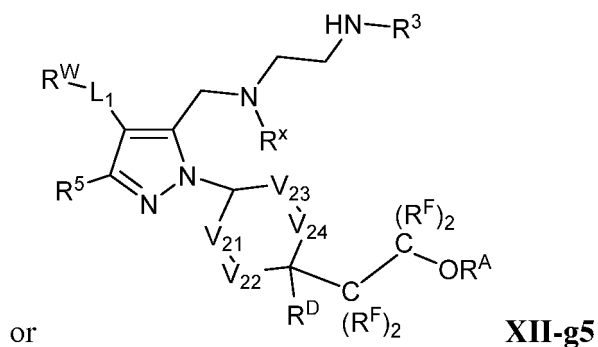


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , R^A , R^D , and R^F are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, both instances of R^F are hydrogen. In certain embodiments, R^D is hydrogen. In certain embodiments, R^A is hydrogen. In certain embodiments, R^A is not hydrogen. In certain embodiments, R^A is optionally substituted alkyl. In certain embodiments, R^A is optionally substituted C_{1-6} alkyl. In certain embodiments, R^A is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, R^A is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, R^A is methyl. In certain embodiments, R^A is ethyl. In certain embodiments, R^A is 3-pentyl. In certain embodiments, R^D is hydrogen; and R^A is methyl. In certain embodiments, R^D is hydrogen; and R^A is ethyl. In certain embodiments, R^D is hydrogen; and R^A is 3-pentyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two

R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00180] In certain embodiments, when Ring A is of Formula (q-60), provided are compounds of Formulae **XII-g1** to **XII-g5**:

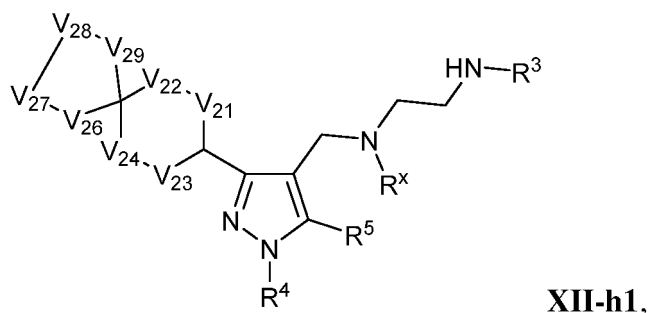




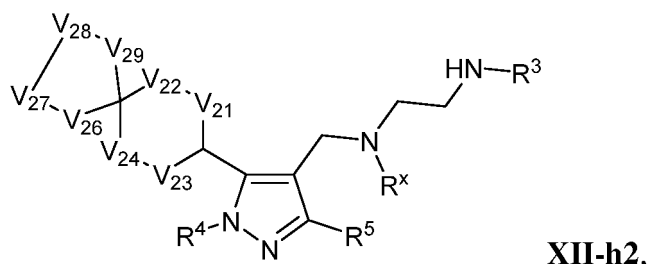
or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , R^A , R^D , and R^F are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, at least two instances of R^F are hydrogen. In certain embodiments, all four instances of R^F are hydrogen. In certain embodiments, R^D is hydrogen. In certain embodiments, R^A is hydrogen. In certain embodiments, R^A is not hydrogen. In certain embodiments, R^A is optionally substituted alkyl. In certain embodiments, R^A is optionally substituted C_{1-6} alkyl. In certain embodiments, R^A is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, R^A is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, R^A is methyl. In certain embodiments, R^A is ethyl. In certain embodiments, R^A is 3-pentyl. In certain embodiments, R^D is hydrogen; and R^A is methyl. In certain embodiments, R^D is hydrogen; and R^A is ethyl. In certain embodiments, R^D is hydrogen; and R^A is 3-pentyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic

ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L₁ is a bond and R^W is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R⁵ is hydrogen. In certain embodiments, L₁ is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L₁ is a bond and R^W is optionally substituted C₁₋₆alkyl, *e.g.*, unsubstituted C₁₋₄alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

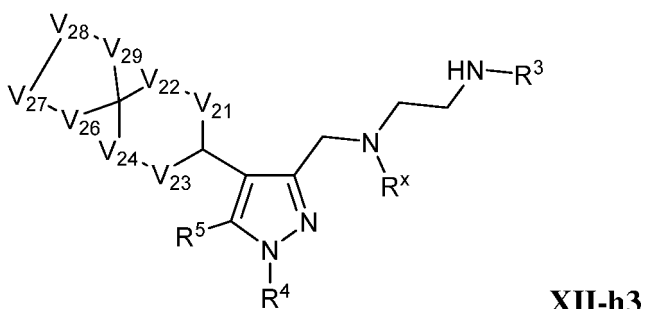
[00181] In certain embodiments, when Ring A is of Formula (r-1), provided are compounds of Formulae **XII-h1** to **XII-h5**:



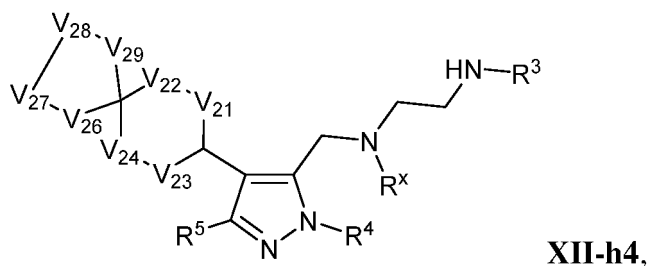
XII-h1.



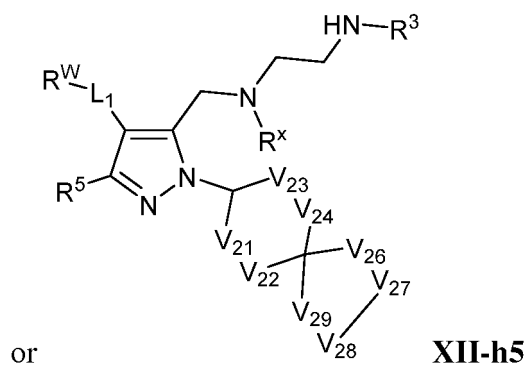
XII-h2,



XII-h3.



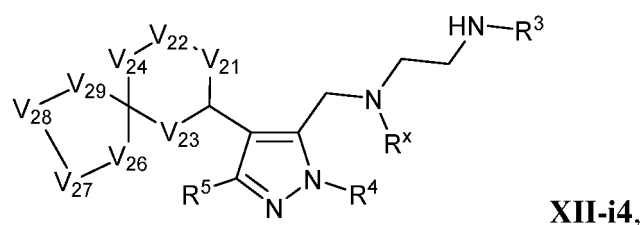
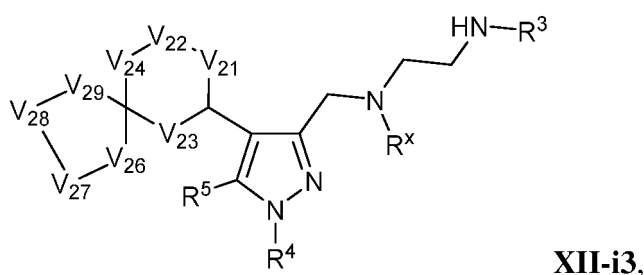
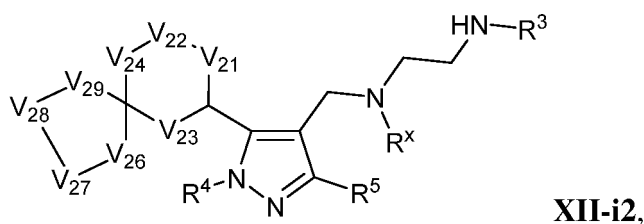
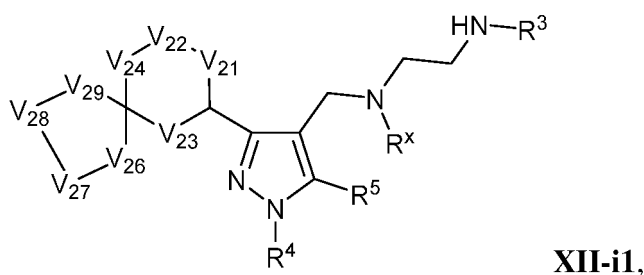
XII-h4.

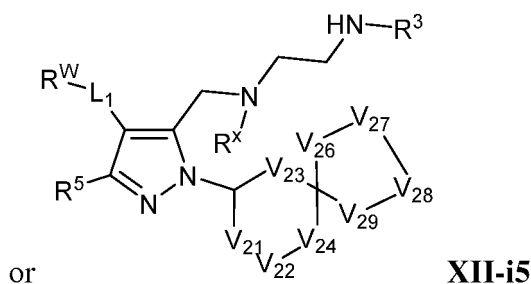


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , and V_{29} are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O. In certain embodiments, exactly two instances of V_{26} , V_{27} , V_{28} , or V_{29} are O. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O; and all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O; and a second instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(R^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O; and a second instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(Me)_2-$. In certain embodiments, all four of V_{26} , V_{27} , V_{28} , and V_{29} are $-CH_2-$. In certain embodiments, all eight of V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , and V_{29} are $-CH_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is NR^{Na} ; and a second instance of V_{26} , V_{27} , V_{28} , or V_{29} is $C=O$. In certain embodiments, at least one instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(R^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(R^E)_2-$; and each instance of R^E is independently halogen (*e.g.*, fluoro, chloro, or bromo). In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E

groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00182] In certain embodiments, when Ring A is of Formula (**r-3**), provided are compounds of Formulae **XII-i1** to **XII-i5**:

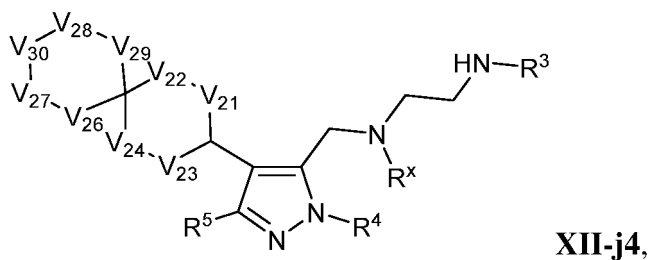
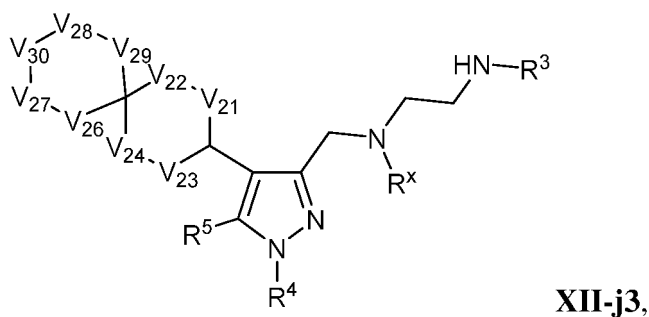
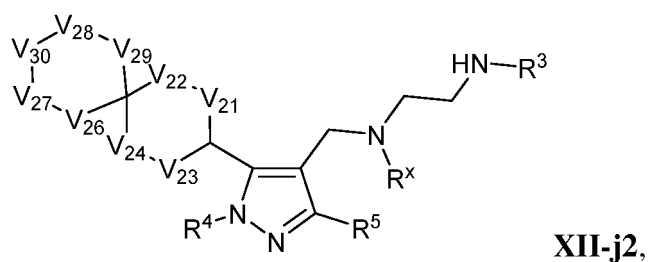
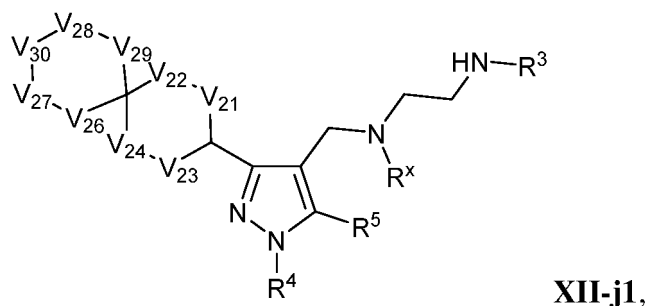


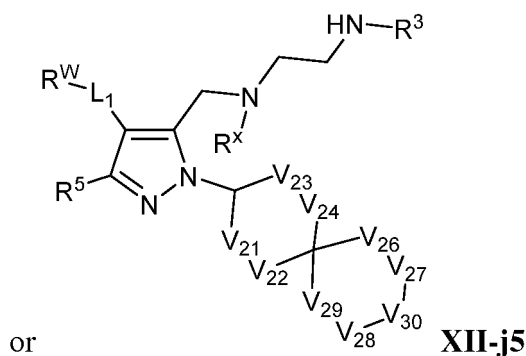


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , and V_{29} are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O. In certain embodiments, exactly two instances of V_{26} , V_{27} , V_{28} , or V_{29} are O. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O; and all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O; and a second instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(R^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is O; and a second instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(Me)_2-$. In certain embodiments, all four of V_{26} , V_{27} , V_{28} , and V_{29} are $-CH_2-$. In certain embodiments, all eight of V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , and V_{29} are $-CH_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is NR^{Na} ; and a second instance of V_{26} , V_{27} , V_{28} , or V_{29} is $C=O$. In certain embodiments, at least one instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(R^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , or V_{29} is $-C(R^E)_2-$; and each instance of R^E is independently halogen (*e.g.*, fluoro, chloro, or bromo). In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments,

two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00183] In certain embodiments, when Ring A is of Formula (**r-2**), provided are compounds of Formulae **XII-j1** to **XII-j5**:

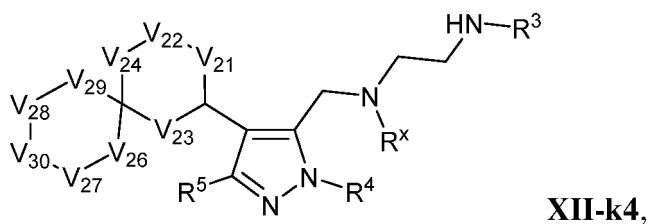
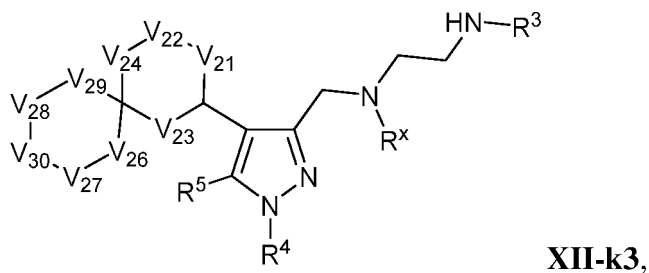
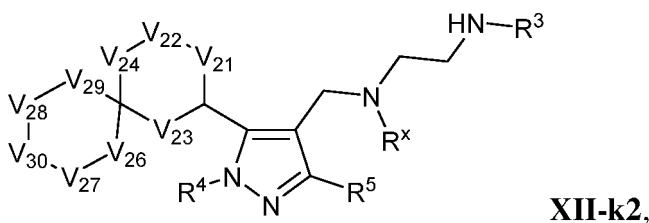
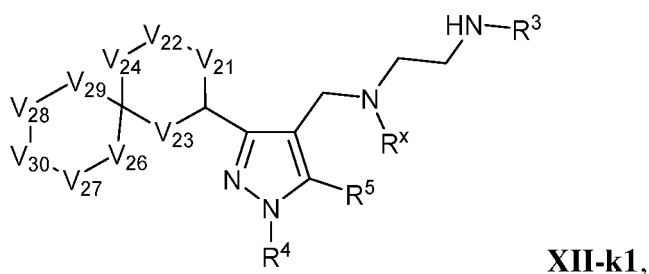


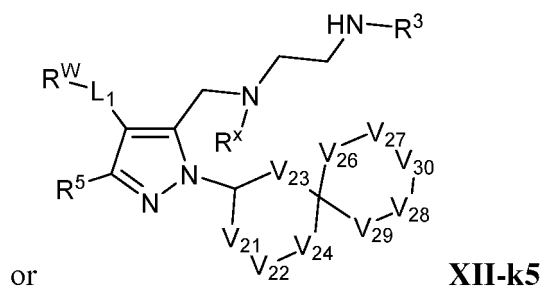


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , V_{29} , and V_{30} are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{22} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{22} is O. In certain embodiments, V_{22} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O. In certain embodiments, exactly two instances of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} are O. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O; and all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O; and a second instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-C(R^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O; and a second instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-C(Me)_2-$. In certain embodiments, all five of V_{26} , V_{27} , V_{28} , V_{29} , and V_{30} are $-CH_2-$. In certain embodiments, all nine of V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , V_{29} , and V_{30} are $-CH_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is NR^{Na} ; and a second instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $C=O$. In certain embodiments, at least one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-C(R^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-C(R^E)_2-$; and each instance of R^E is independently halogen (*e.g.*, fluoro, chloro, or bromo). In certain embodiments, V_{30} is $-CF_2-$; and V_{26} , V_{27} , V_{28} , and V_{29} are $-CH_2-$. In certain embodiments, V_{30} is $-CF_2-$; and V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , and

V₂₉ are -CH₂-. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L₁ is a bond and R^W is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R⁵ is hydrogen. In certain embodiments, L₁ is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L₁ is a bond and R^W is optionally substituted C₁₋₆alkyl, *e.g.*, unsubstituted C₁₋₄alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00184] In certain embodiments, when Ring A is of Formula (**r-4**), provided are compounds of Formulae **XII-k1** to **XII-k5**:

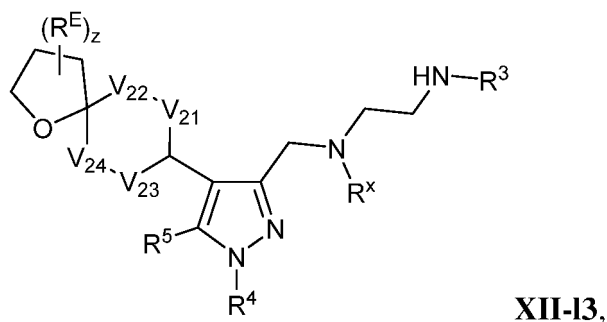
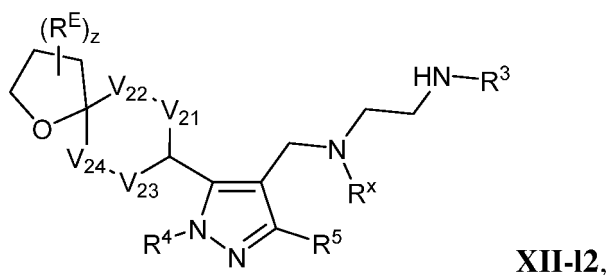
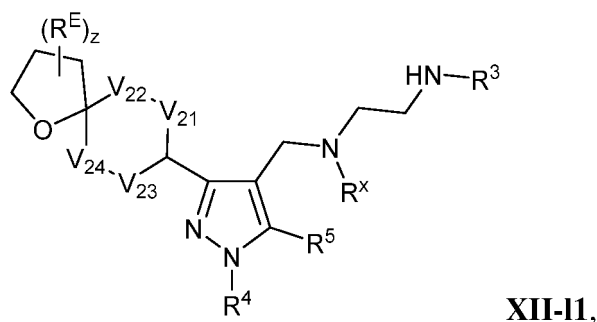


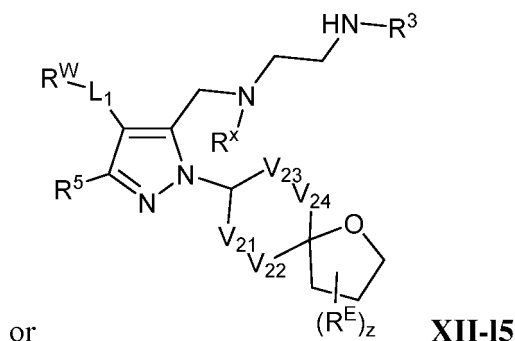
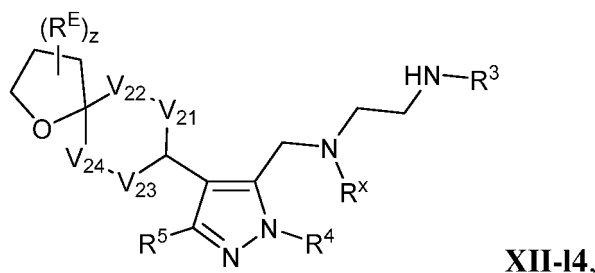


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , V_{29} , and V_{30} are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-\text{CH}_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-\text{CH}(\text{OR}^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-\text{CH}(\text{OR}^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-\text{CH}(\text{OR}^A)-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O. In certain embodiments, exactly two instances of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} are O. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O; and all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O; and a second instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-\text{C}(\text{R}^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is O; and a second instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-\text{C}(\text{Me})_2-$. In certain embodiments, all five of V_{26} , V_{27} , V_{28} , V_{29} , and V_{30} are $-\text{CH}_2-$. In certain embodiments, all nine of V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , V_{29} , and V_{30} are $-\text{CH}_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is NR^{Na} ; and a second instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $\text{C}=\text{O}$. In certain embodiments, at least one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-\text{C}(\text{R}^E)_2-$. In certain embodiments, exactly one instance of V_{26} , V_{27} , V_{28} , V_{29} , or V_{30} is $-\text{C}(\text{R}^E)_2-$; and each instance of R^E is independently halogen (*e.g.*, fluoro, chloro, or bromo). In certain embodiments, V_{30} is $-\text{CF}_2-$; and V_{26} , V_{27} , V_{28} , and V_{29} are $-\text{CH}_2-$. In certain embodiments, V_{30} is $-\text{CF}_2-$; and V_{21} , V_{22} , V_{23} , V_{24} , V_{26} , V_{27} , V_{28} , and V_{29} are $-\text{CH}_2-$. In certain embodiments, two R^E groups are joined to form an optionally

substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00185] In certain embodiments, when Ring A is of Formula (**r-81**), provided are compounds of Formulae **XII-11** to **XII-15**:

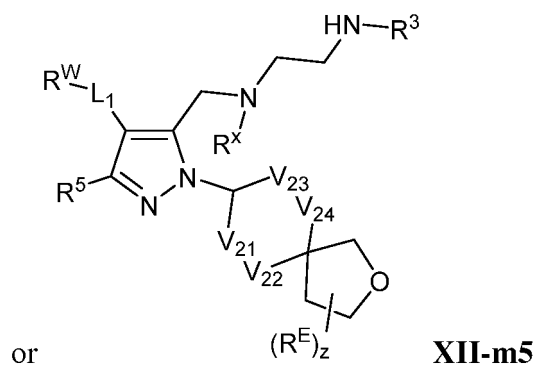
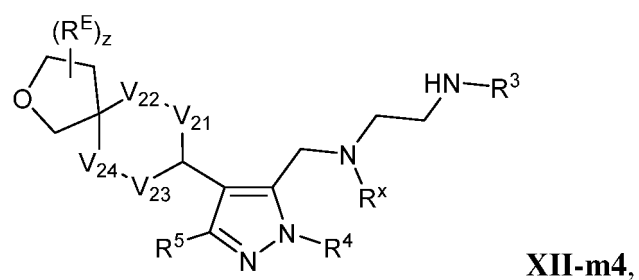
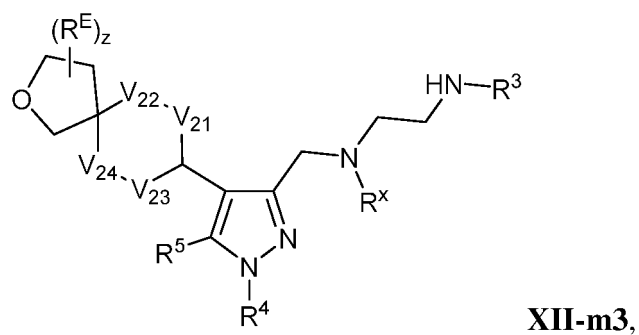
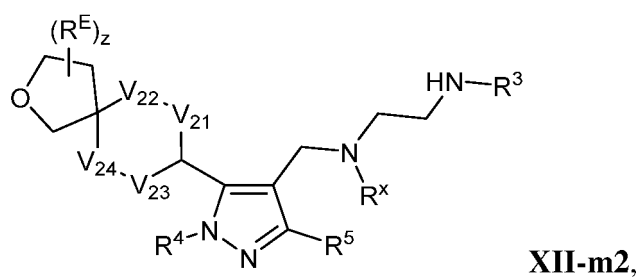
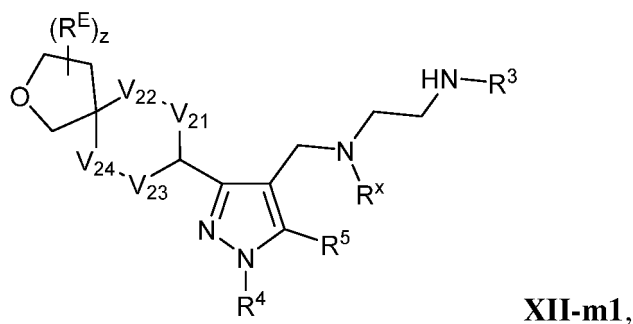




or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z and R^E are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-\text{CH}_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-\text{CH}_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-\text{CH}(\text{OR}^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-\text{CH}(\text{OR}^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-\text{CH}(\text{OR}^A)-$. In certain embodiments, z is 2. In certain embodiments, at least one instance of R^E is optionally substituted alkyl. In certain embodiments, at least one instance of R^E is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^E is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least one instance of R^E is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least one instance of R^E is methyl. In certain embodiments, at least two instances of R^E are independently optionally substituted alkyl. In certain embodiments, at least two instances of R^E are independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least two instances of R^E are independently unsubstituted

C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least two instances of R^E are independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least two instances of R^E are methyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted C₁₋₆ alkyl. In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; and each instance of R^E is methyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted C₁₋₆ alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is methyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L₁ is a bond and R^W is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R^S is hydrogen. In certain embodiments, L₁ is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L₁ is a bond and R^W is optionally substituted C₁₋₆alkyl, *e.g.*, unsubstituted C₁₋₄alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

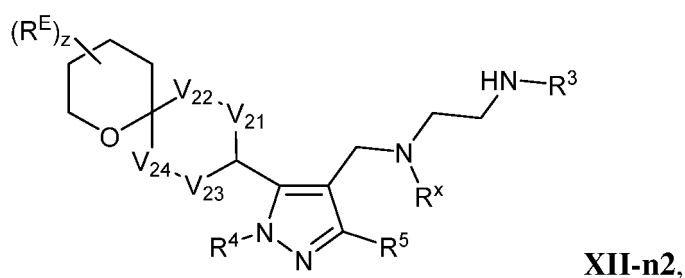
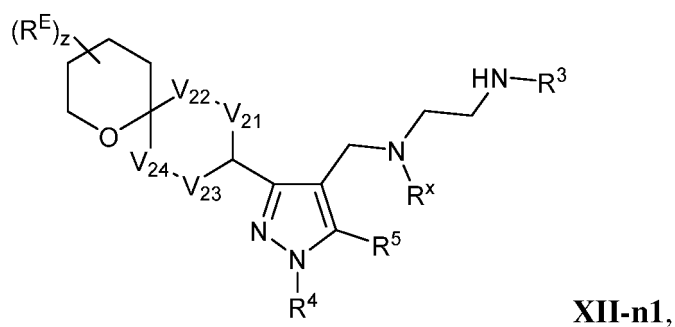
[00186] In certain embodiments, when Ring A is of Formula (**r-82**), provided are compounds of Formulae **XII-m1** to **XII-m5**:



or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z and R^E are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, z is 2. In certain embodiments, at least one instance of R^E is optionally substituted alkyl. In certain embodiments, at least one instance of R^E is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^E is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least one instance of R^E is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least one instance of R^E is methyl. In certain embodiments, at least two instances of R^E are independently optionally substituted alkyl. In certain embodiments, at least two instances of R^E are independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least two instances of R^E are independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least two instances of R^E are independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least two instances of R^E are methyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; and each instance of R^E is methyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted alkyl. In certain

embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is methyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

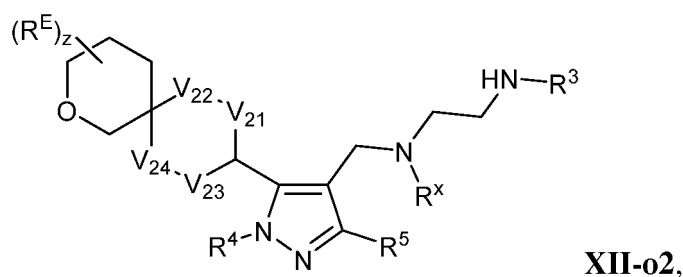
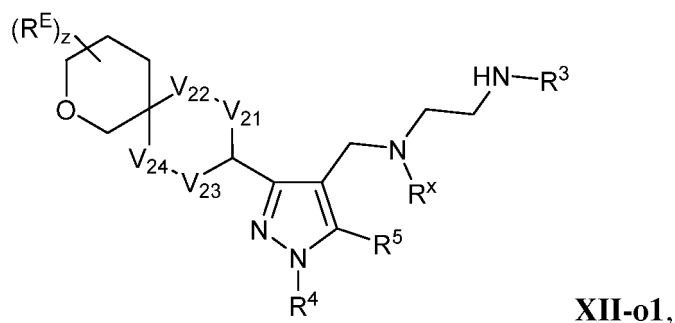
[00187] In certain embodiments, when Ring A is of Formula (**r-85**), provided are compounds of Formulae **XII-n1** to **XII-n5**:

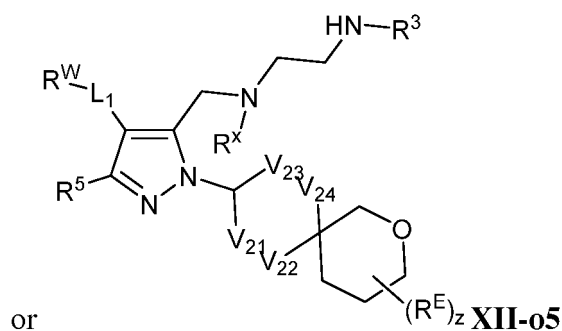
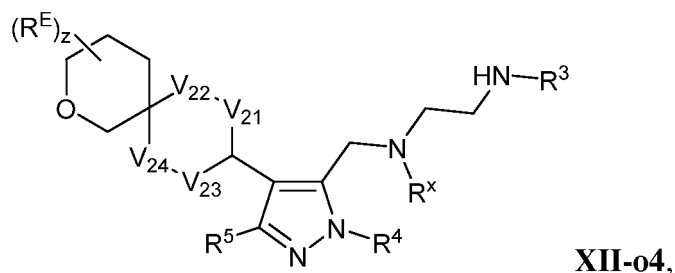
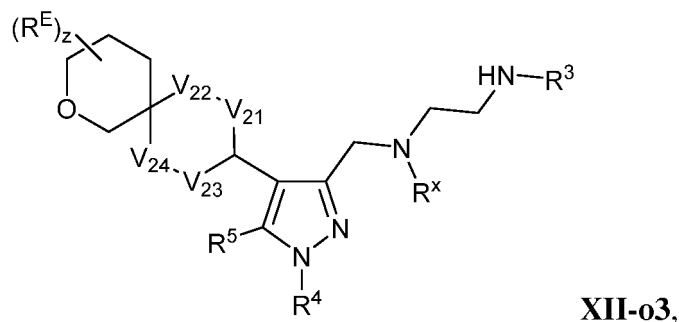


embodiments, at least one instance of R^E is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least one instance of R^E is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least one instance of R^E is methyl. In certain embodiments, at least two instances of R^E are independently optionally substituted alkyl. In certain embodiments, at least two instances of R^E are independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least two instances of R^E are independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least two instances of R^E are independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least two instances of R^E are methyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; and each instance of R^E is methyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is methyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted

branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, *z* is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is methyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L₁ is a bond and R^W is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R⁵ is hydrogen. In certain embodiments, L₁ is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L₁ is a bond and R^W is optionally substituted C₁₋₆alkyl, *e.g.*, unsubstituted C₁₋₄alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00188] In certain embodiments, when Ring A is of Formula (**r-86**), provided are compounds of Formulae **XII-o1** to **XII-o5**:





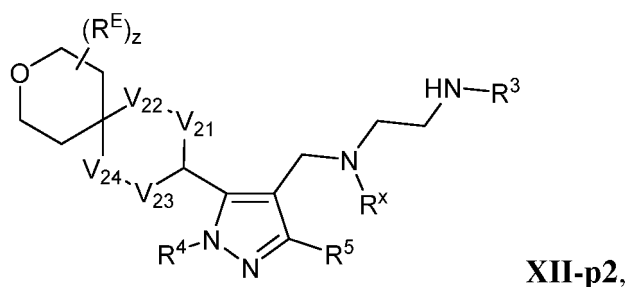
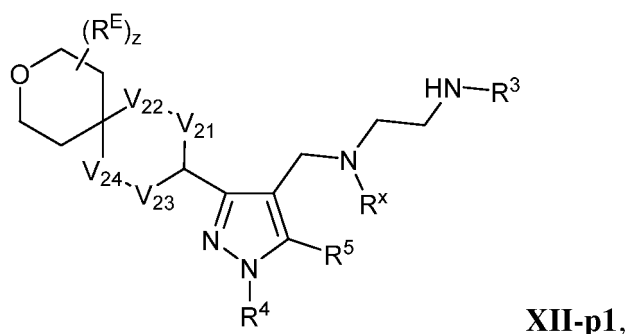
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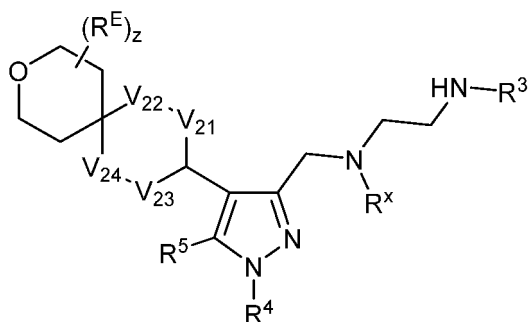
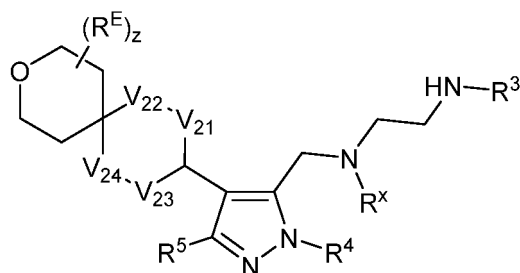
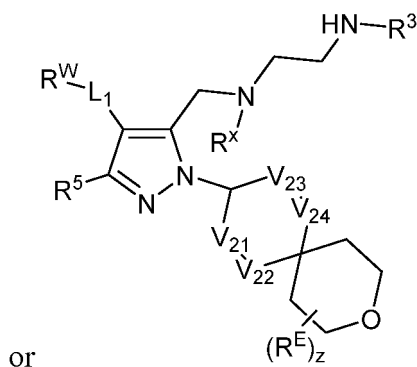
or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z and R^E are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, z is 2. In certain embodiments, at least one instance of R^E is optionally substituted alkyl. In certain embodiments, at least one instance of R^E is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^E is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl,

propyl, butyl, pentyl, or hexyl). In certain embodiments, at least one instance of R^E is unsubstituted branched C_{3-6} alkyl (e.g., isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least one instance of R^E is methyl. In certain embodiments, at least two instances of R^E are independently optionally substituted alkyl. In certain embodiments, at least two instances of R^E are independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least two instances of R^E are independently unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least two instances of R^E are independently unsubstituted branched C_{3-6} alkyl (e.g., isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least two instances of R^E are methyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (e.g., isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; and each instance of R^E is methyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (e.g., isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is methyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (e.g., isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl).

In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is methyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00189] In certain embodiments, when Ring A is of Formula (r-87), provided are compounds of Formulae **XII-p1 to XII-p5**:



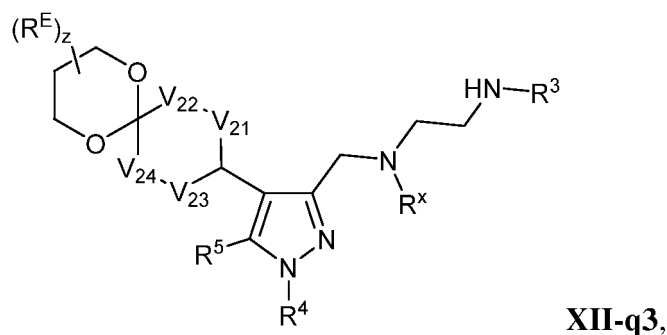
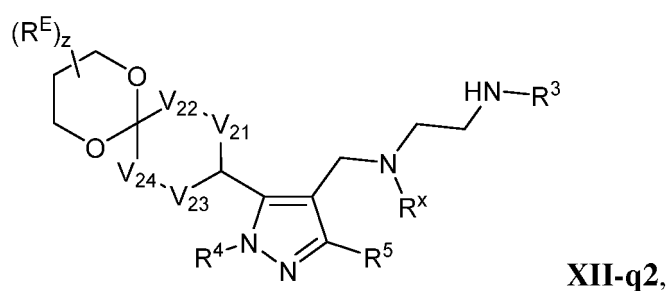
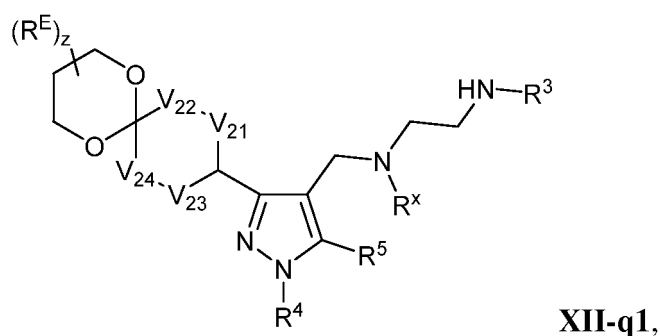
**XII-p3,****XII-p4,****XII-p5**

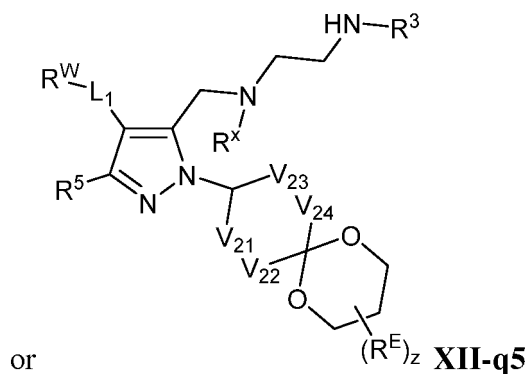
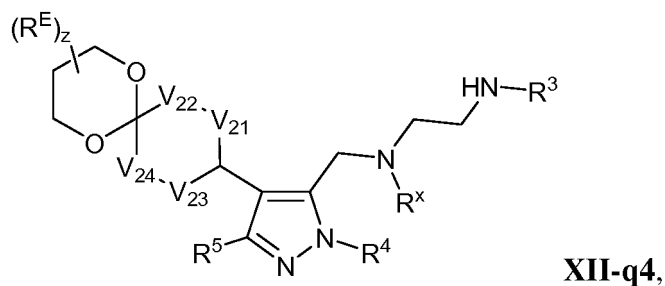
or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z and R^E are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, z is 2. In certain embodiments, at least one instance of R^E is optionally substituted alkyl. In certain embodiments, at least one instance of R^E is optionally substituted C_{1-6} alkyl. In certain

embodiments, at least one instance of R^E is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least one instance of R^E is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least one instance of R^E is methyl. In certain embodiments, at least two instances of R^E are independently optionally substituted alkyl. In certain embodiments, at least two instances of R^E are independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least two instances of R^E are independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least two instances of R^E are independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least two instances of R^E are methyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; and each instance of R^E is methyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is methyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted C_{1-6} alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted

branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, *z* is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is methyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L₁ is a bond and R^W is hydrogen. In certain embodiments, L₁ is a bond, R^W is hydrogen, and R⁵ is hydrogen. In certain embodiments, L₁ is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L₁ is a bond and R^W is optionally substituted C₁₋₆alkyl, *e.g.*, unsubstituted C₁₋₄alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00190] In certain embodiments, when Ring A is of Formula (**r-214**), provided are compounds of Formulae **XII-q1** to **XII-q5**:





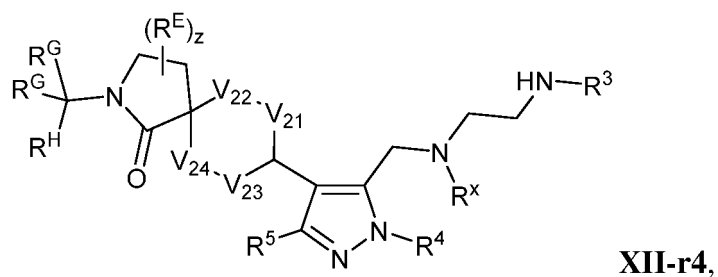
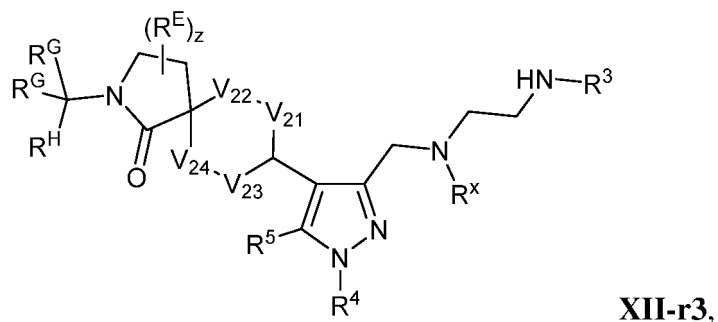
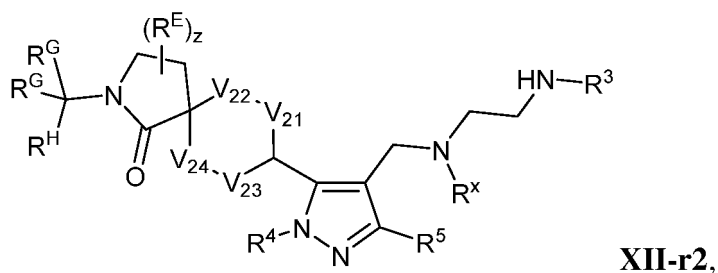
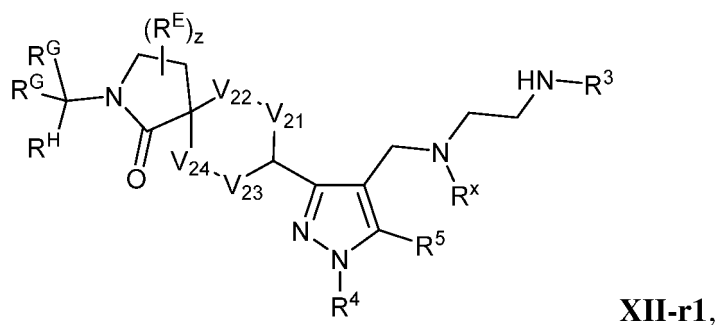
or

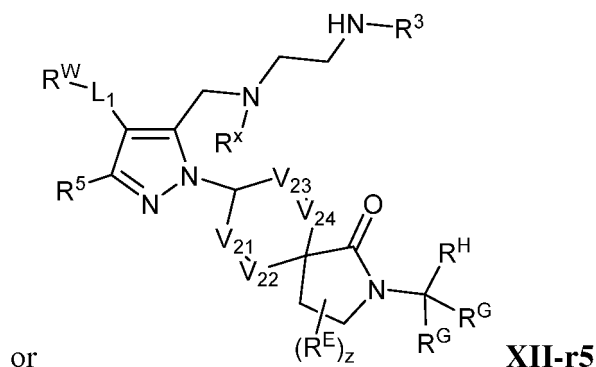
or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z and R^E are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, z is 2. In certain embodiments, at least one instance of R^E is optionally substituted alkyl. In certain embodiments, at least one instance of R^E is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^E is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least one instance of R^E is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least one instance of R^E is methyl. In certain embodiments, at least two instances of R^E are independently optionally substituted alkyl. In certain embodiments, at least two instances of R^E are independently optionally substituted C_1 .

₆ alkyl. In certain embodiments, at least two instances of R^E are independently unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, at least two instances of R^E are independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, at least two instances of R^E are methyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; and each instance of R^E is independently optionally substituted C₁₋₆ alkyl. In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; and each instance of R^E is independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; and each instance of R^E is methyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently optionally substituted C₁₋₆ alkyl. In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; both instances of R^E are attached to the same carbon; and each instance of R^E is methyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently optionally substituted C₁₋₆ alkyl. In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is independently unsubstituted branched C₃₋₆ alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, z is 2; each instance of R^E is attached to a different carbon; and each instance of R^E is methyl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an

unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00191] In certain embodiments, when Ring A is of Formula (r-222), provided are compounds of Formulae **XII-r1 to XII-r5**:

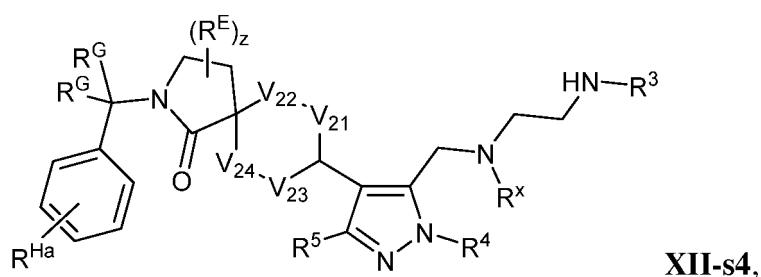
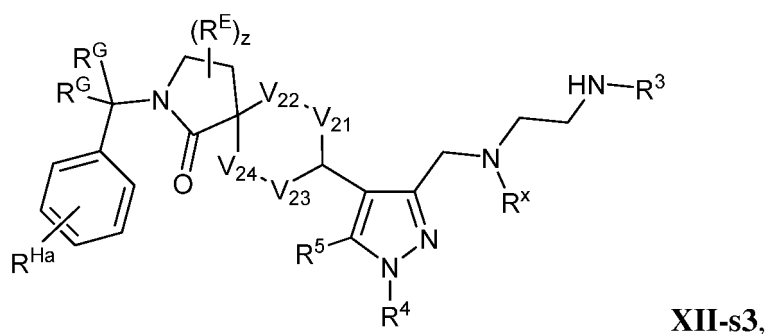
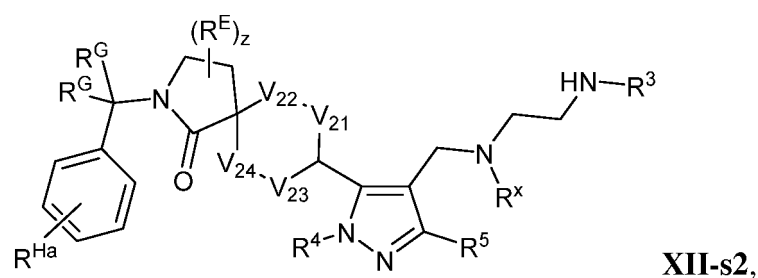
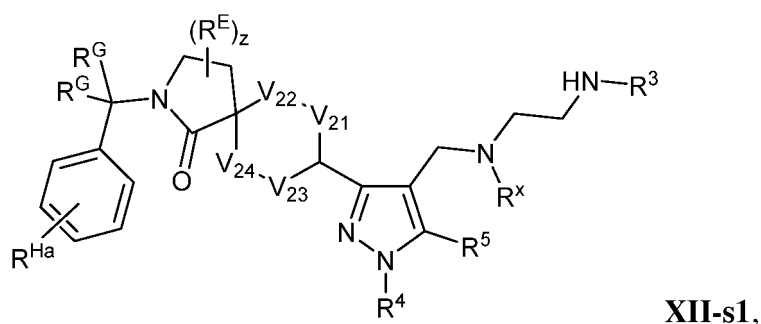


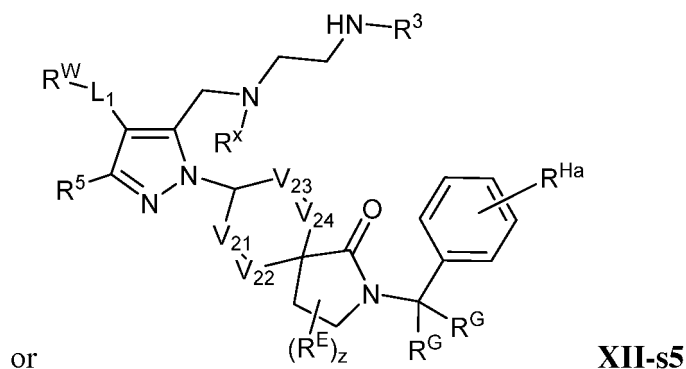


or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z , R^E , R^G , and R^H are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, z is 0. In certain embodiments, at least one instance of R^G is hydrogen. In certain embodiments, both instances of R^G are hydrogen. In certain embodiments, R^H is hydrogen. In certain embodiments, R^H is optionally substituted alkyl. In certain embodiments, R^H is optionally substituted C_{1-6} alkyl. In certain embodiments, R^H is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, or hexyl). In certain embodiments, R^H is unsubstituted branched C_{3-6} alkyl (*e.g.*, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, or 3-pentyl). In certain embodiments, R^H is methyl. In certain embodiments, R^H is ethyl. In certain embodiments, R^H is isopropyl. In certain embodiments, R^H is *tert*-butyl. In certain embodiments, R^H is optionally substituted carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, R^H is optionally substituted aryl. In certain embodiments, R^H is optionally substituted heterocyclyl. In certain embodiments, R^H is optionally substituted heteroaryl. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to

form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00192] In certain embodiments, when Ring A is of Formula (**r-231**), provided are compounds of Formulae **XII-s1** to **XII-s5**:





or pharmaceutically acceptable salt thereof; wherein R^3 , R^4 , R^5 , R^x , V_{21} , V_{22} , V_{23} , V_{24} , z , R^E , R^G , and R^{Ha} are defined herein. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^3 is methyl. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or butyl). In certain embodiments, R^4 is methyl. In certain embodiments, R^x is unsubstituted C_{1-4} alkyl (*e.g.*, methyl, ethyl, propyl or butyl). In certain embodiments, R^x is methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, at least one of V_{21} , V_{22} , V_{23} , and V_{24} is $-CH_2-$. In certain embodiments, at least two of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least three of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, all four of V_{21} , V_{22} , V_{23} , and V_{24} are $-CH_2-$. In certain embodiments, at least one of V_{23} and V_{24} is O or $-CH(OR^A)-$. In certain embodiments, V_{23} is O. In certain embodiments, V_{23} is $-CH(OR^A)-$. In certain embodiments, V_{24} is O. In certain embodiments, V_{24} is $-CH(OR^A)-$. In certain embodiments, z is 0. In certain embodiments, at least one instance of R^G is hydrogen. In certain embodiments, both instances of R^G are hydrogen. In certain embodiments, R^{Ha} is halogen (*e.g.*, fluorine, chlorine, or bromine). In certain embodiments, R^{Ha} is fluorine. In certain embodiments, two R^E groups are joined to form an optionally substituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an optionally substituted cyclopropyl ring. In certain embodiments, two R^E groups are joined to form an unsubstituted carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl). In certain embodiments, two R^E groups are joined to form an unsubstituted cyclopropyl ring. In certain embodiments, L_1 is a bond and R^W is hydrogen. In certain embodiments, L_1 is a bond, R^W is hydrogen, and R^5 is hydrogen. In certain embodiments, L_1 is a bond and R^W is halogen, *e.g.*, fluoro, chloro, bromo, or iodo. In certain embodiments, L_1 is a bond and R^W is optionally substituted C_{1-6} alkyl, *e.g.*, unsubstituted C_{1-4} alkyl, *e.g.*, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or isoamyl.

[00193] In certain embodiments, a provided compound is a compound listed in Table 1A, Table 1B, or a pharmaceutically acceptable salt thereof.

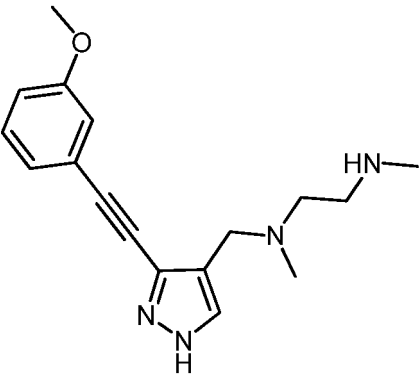
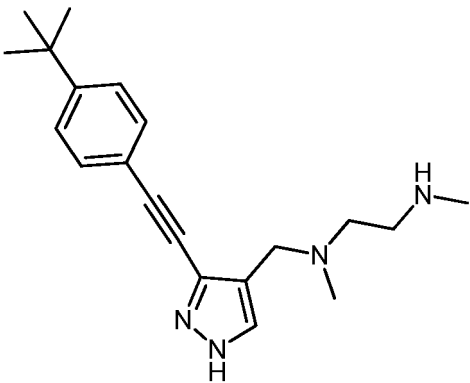
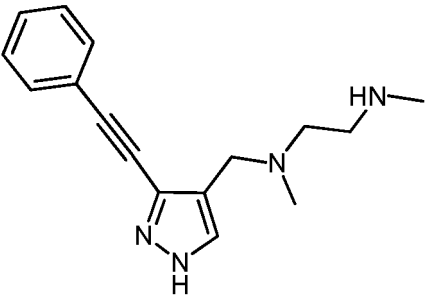
Table 1A. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
1		299.30
2		325.30
3		269.30

Table 1A. Exemplary Compounds

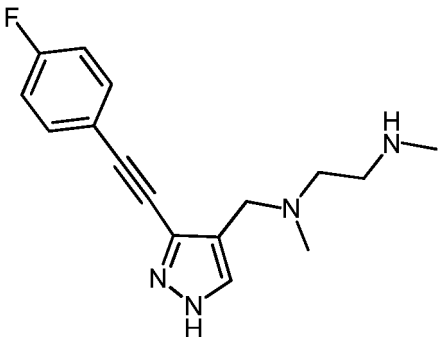
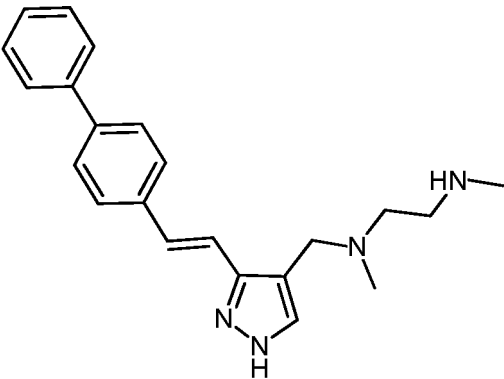
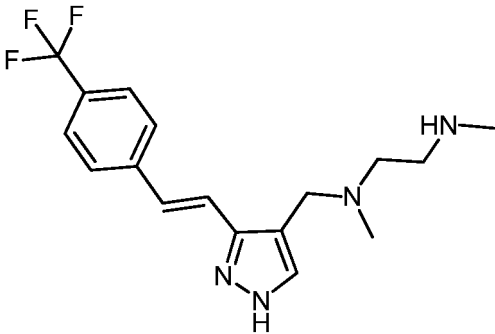
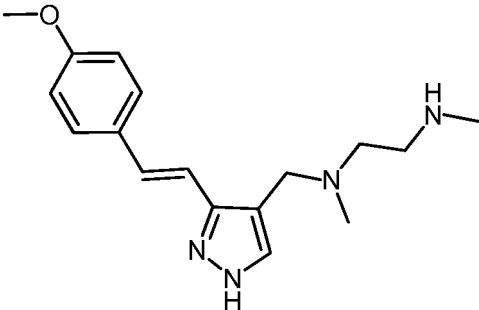
Cmpd No	Structure	LC-MS m/z (M+H)
4		287.20
5		347.00
6		339.20
7		301.20

Table 1A. Exemplary Compounds

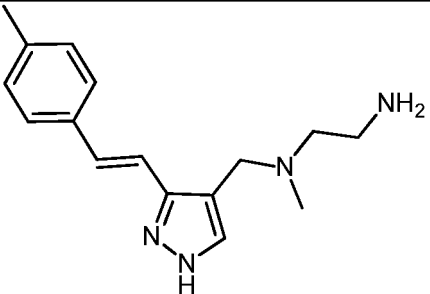
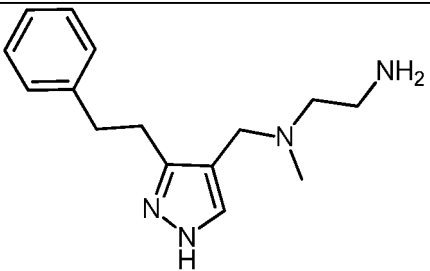
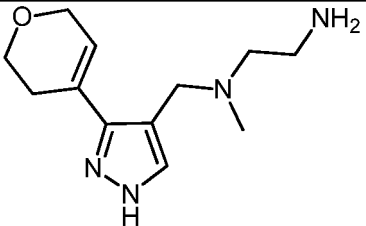
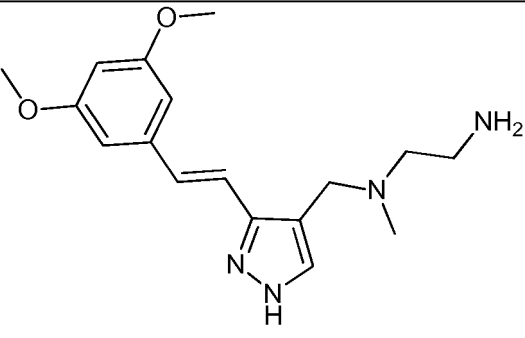
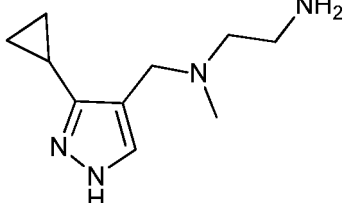
Cmpd No	Structure	LC-MS m/z (M+H)
8		271.20
9		259.10
10		237.10
11		317.30
12		195.10

Table 1A. Exemplary Compounds

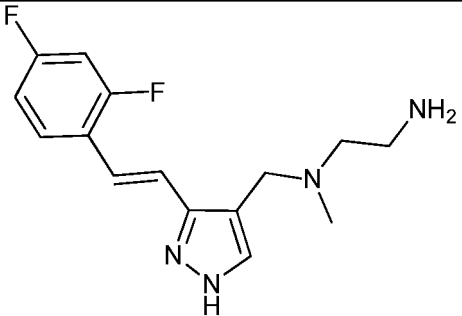
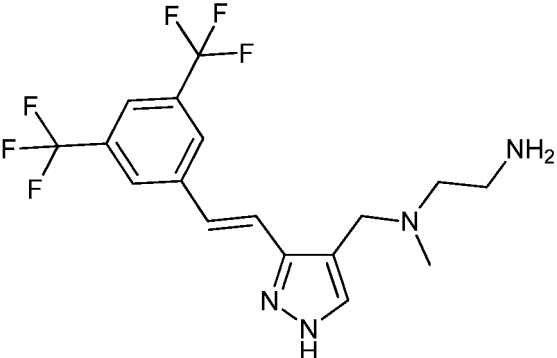
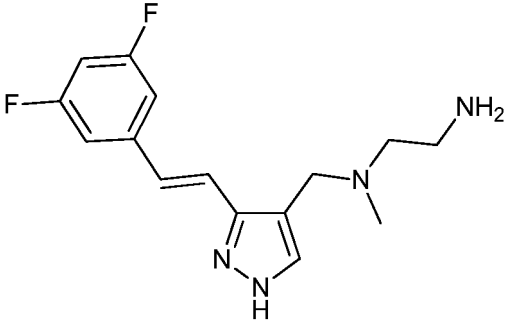
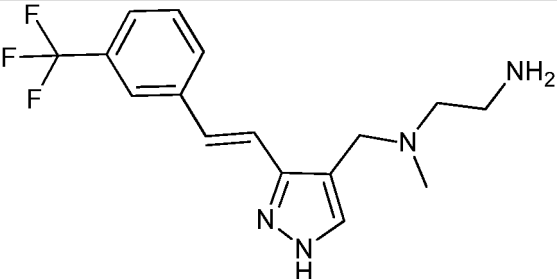
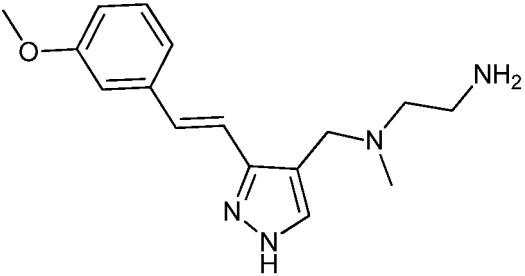
Cmpd No	Structure	LC-MS m/z (M+H)
13		293.10
14		393.10
15		293.10
16		325.10
17		287.30

Table 1A. Exemplary Compounds

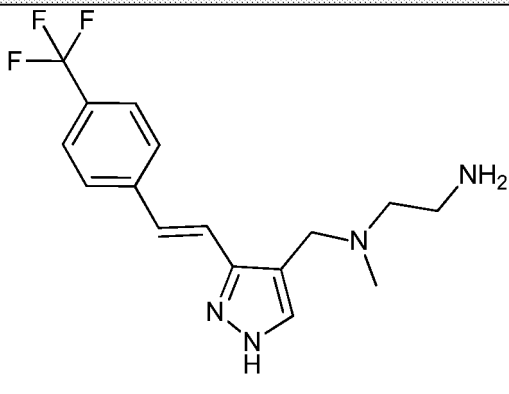
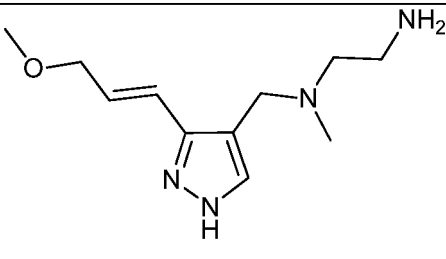
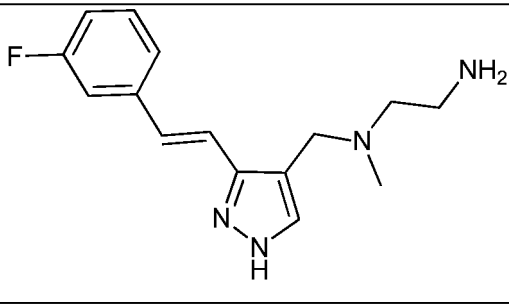
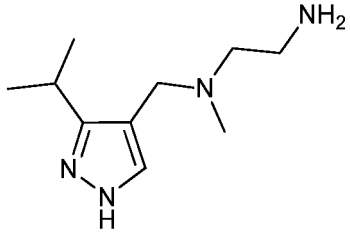
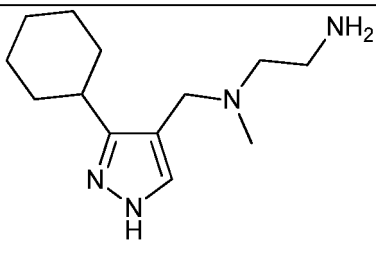
Cmpd No	Structure	LC-MS m/z (M+H)
18		325.10
19		225.20
20		-
21		197.30
22		237.10

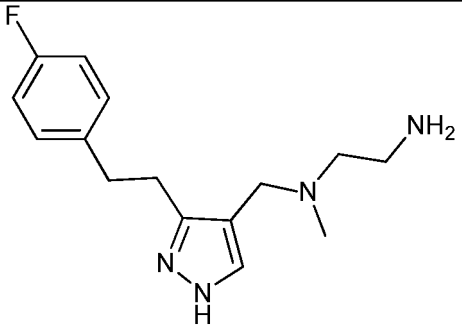
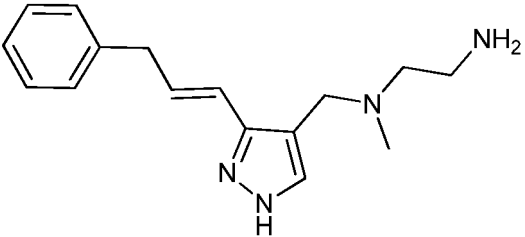
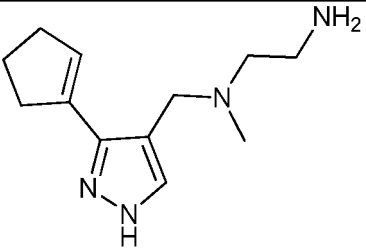
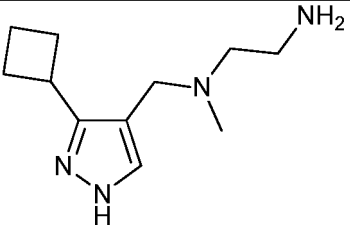
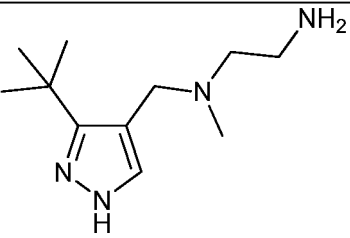
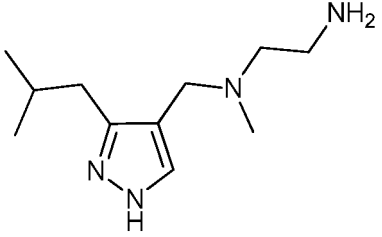
Table 1A. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
23		277.05
24		271.40
25		221.30
26		209.50
27		211.40
28		211.70

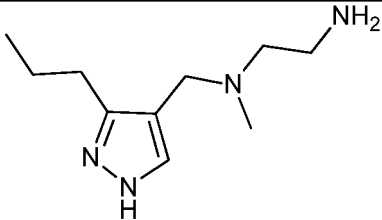
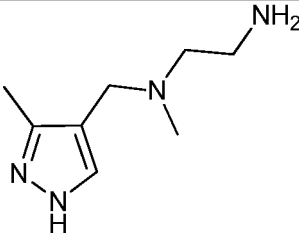
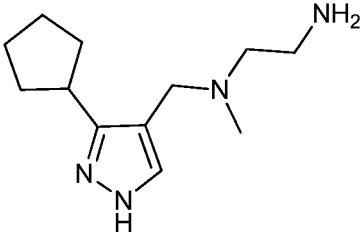
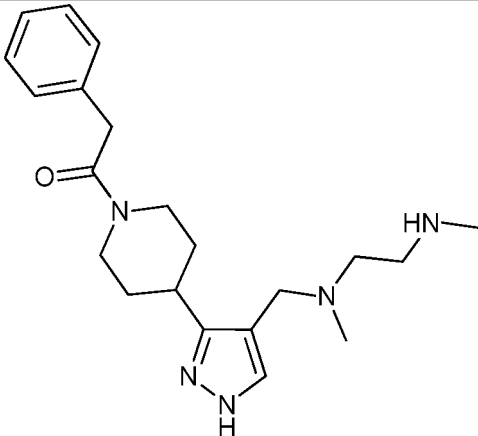
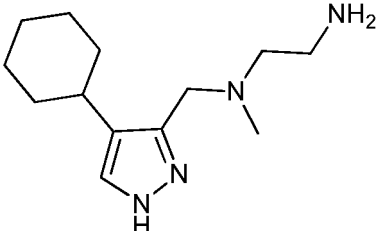
Table 1A. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
29		197.30
30		169.80
31		223.30
32		370.00
33		237.05

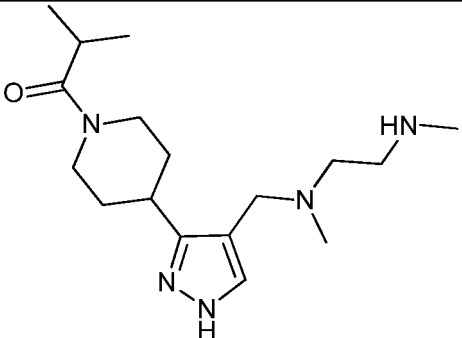
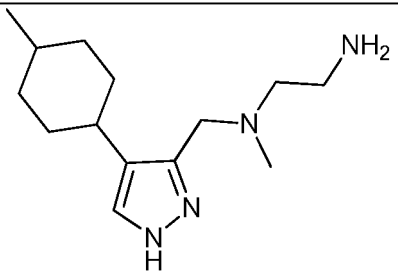
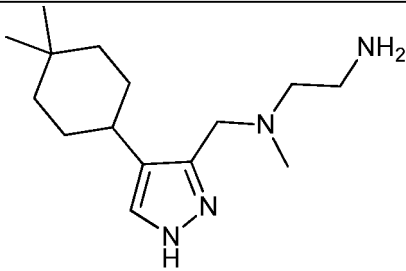
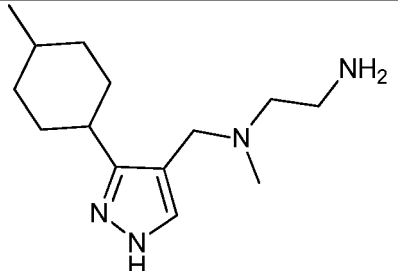
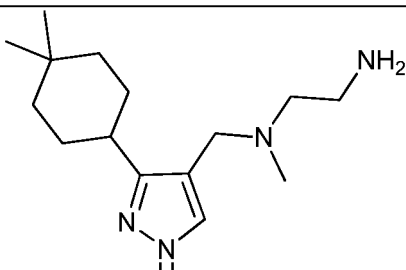
Table 1A. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
34		322.15
35		251.00
36		265.05
37		251.10
38		265.10

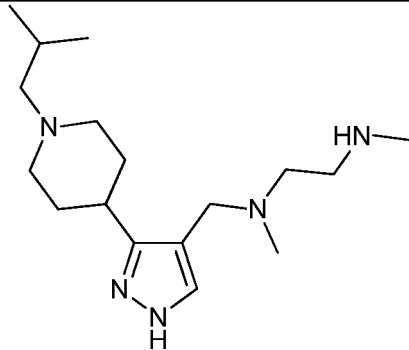
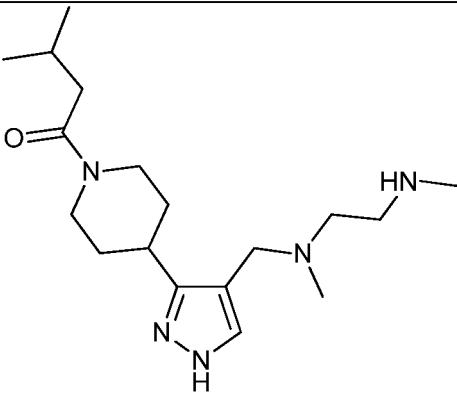
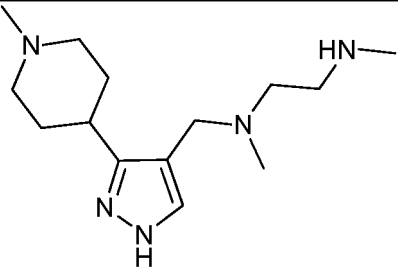
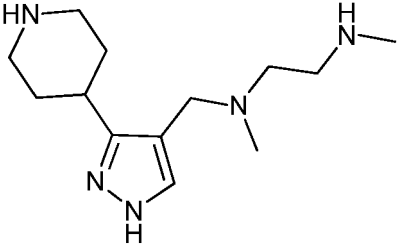
Table 1A. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
39		308.20
40		336.15
41		266.15
42		252.10

Table 1A. Exemplary Compounds

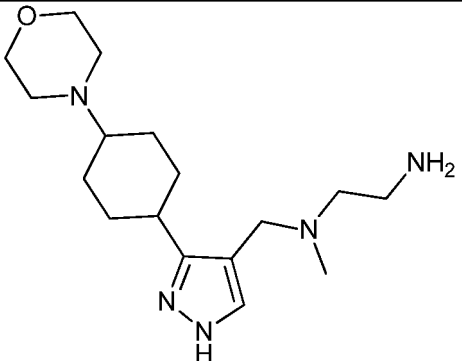
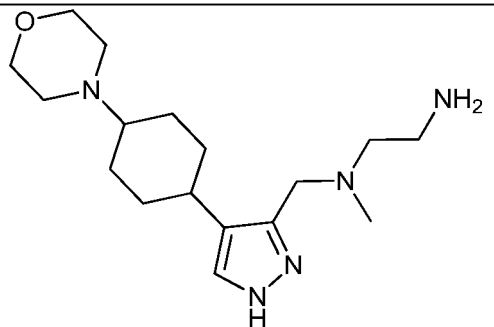
Cmpd No	Structure	LC-MS m/z (M+H)
43		322.15
44		322.15

Table 1B. Exemplary Compounds

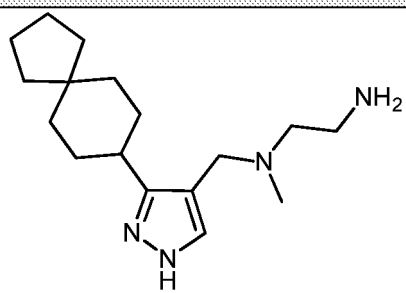
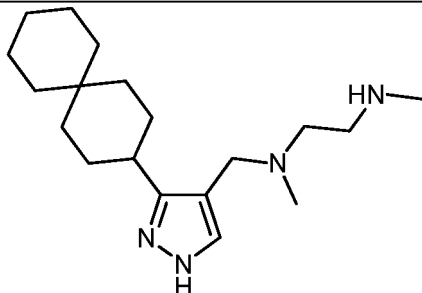
Cmpd No	Structure	LC-MS m/z (M+H)
45		291.15
46		319.15

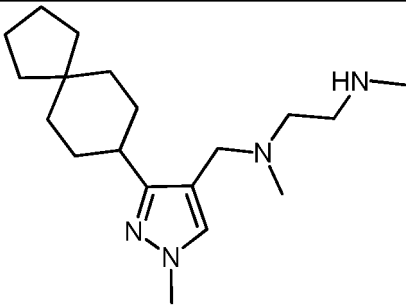
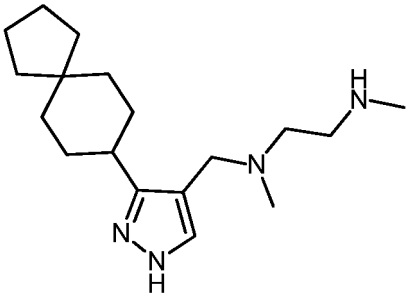
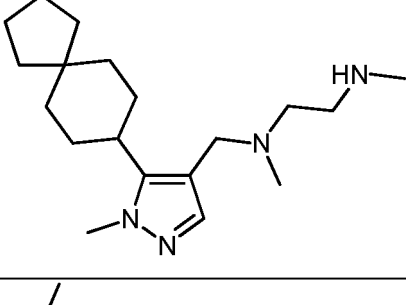
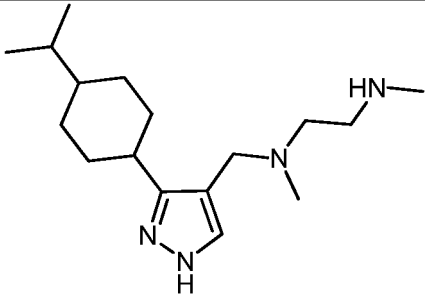
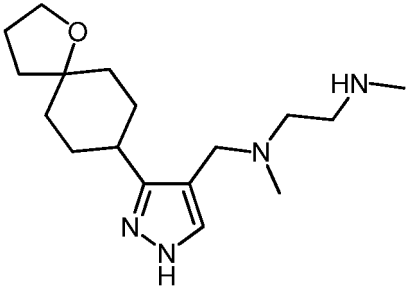
Table 1B. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
47		319.15
48		305.15
49		319.15
50		293.1
51		307.10

Table 1B. Exemplary Compounds

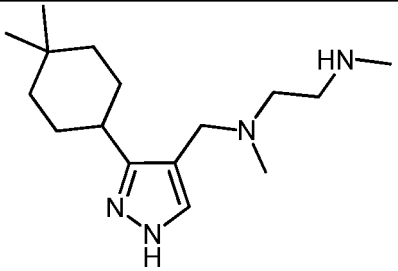
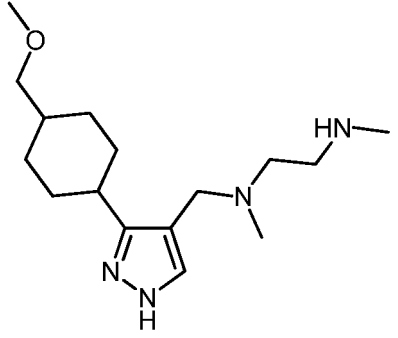
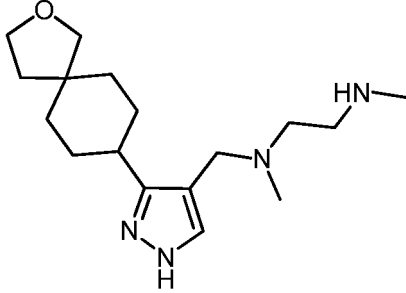
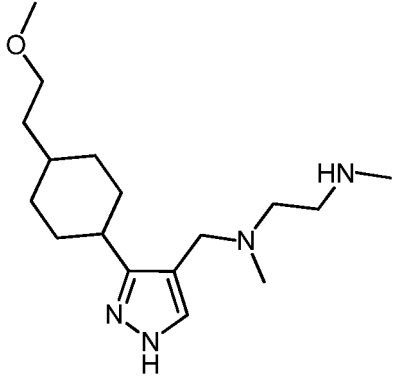
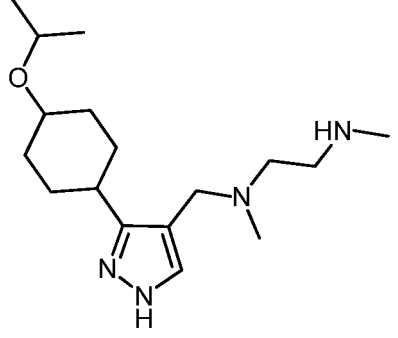
Cmpd No	Structure	LC-MS m/z (M+H)
52		279.10
53		295.1
54		307.1
55		309.1
56		309.15

Table 1B. Exemplary Compounds

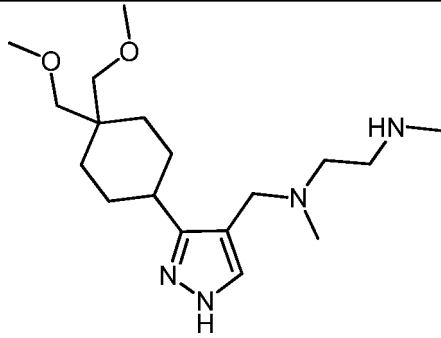
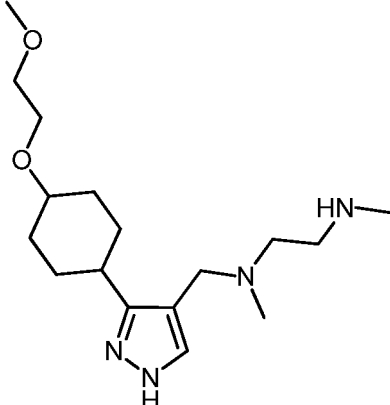
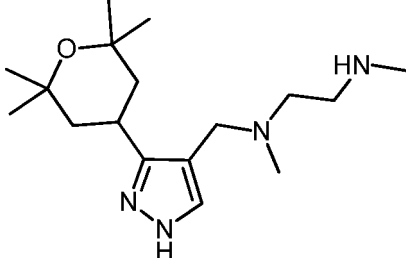
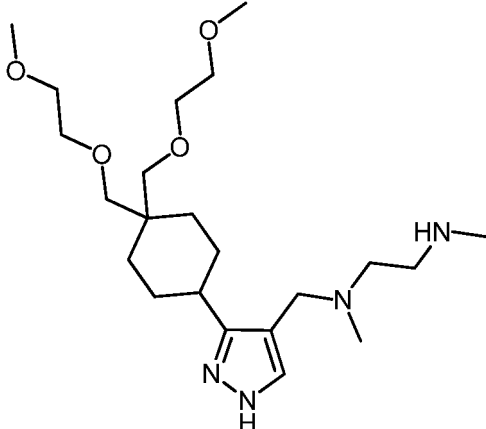
Cmpd No	Structure	LC-MS m/z (M+H)
57		339.10
58		325.15
59		309.25
60		427.25

Table 1B. Exemplary Compounds

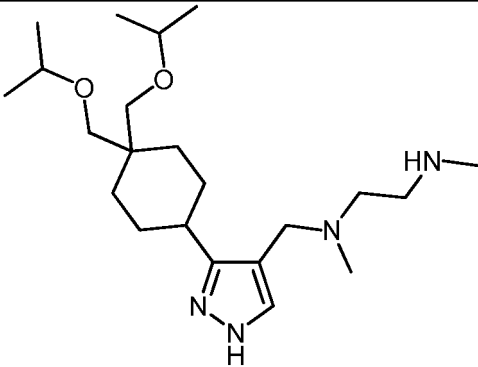
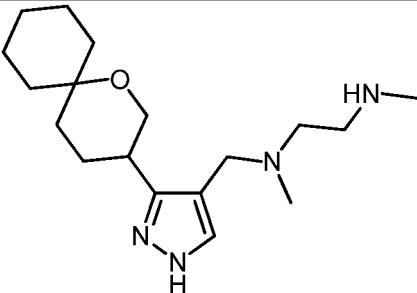
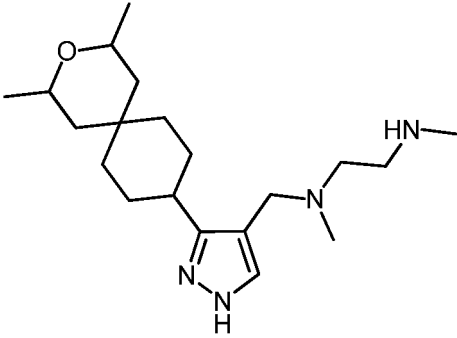
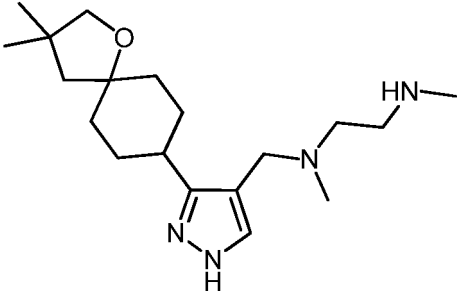
Cmpd No	Structure	LC-MS m/z (M+H)
61		395.3
62		-
63		349.25
64		-

Table 1B. Exemplary Compounds

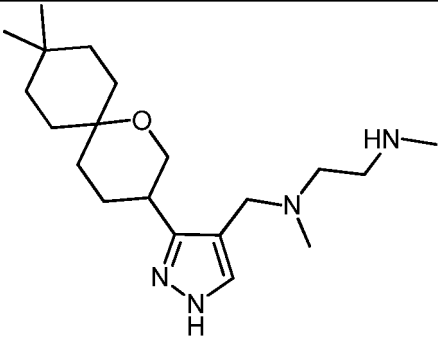
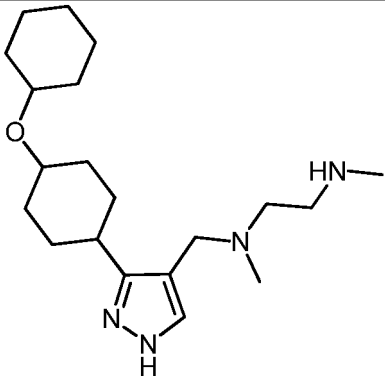
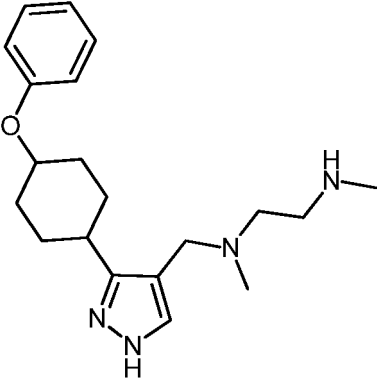
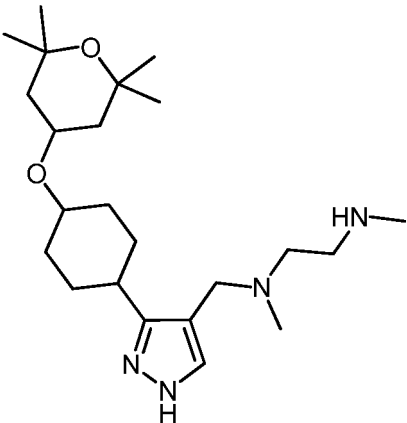
Cmpd No	Structure	LC-MS m/z (M+H)
65		-
66		-
67		343.15
68		-

Table 1B. Exemplary Compounds

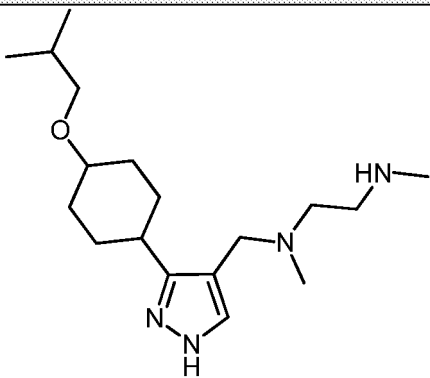
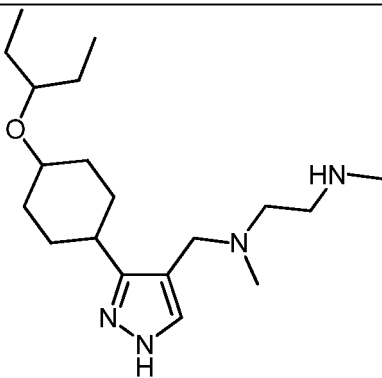
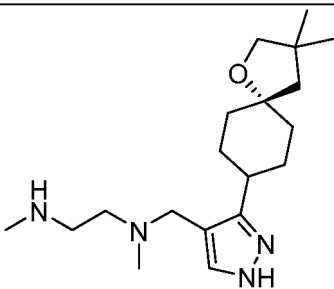
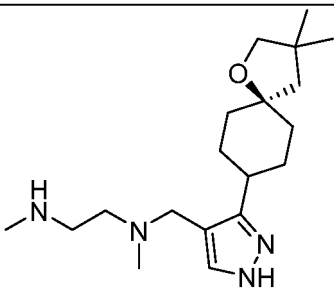
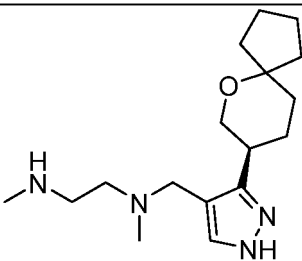
Cmpd No	Structure	LC-MS m/z (M+H)
69		-
70		337.2
71		-
72		-
73		-

Table 1B. Exemplary Compounds

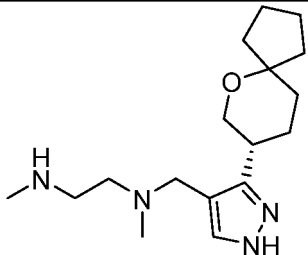
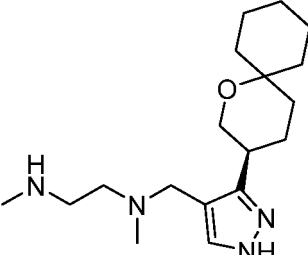
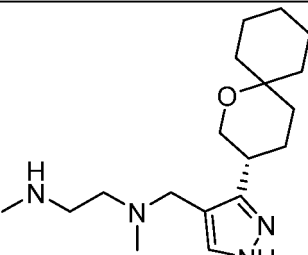
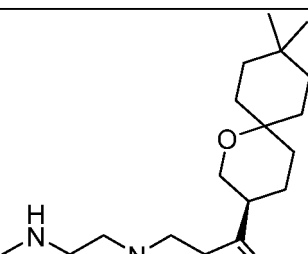
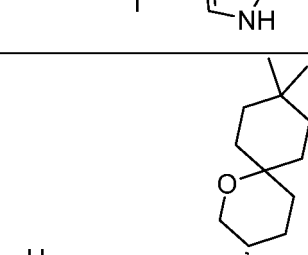
Cmpd No	Structure	LC-MS m/z (M+H)
74		-
75		-
76		-
77		-
78		-

Table 1B. Exemplary Compounds

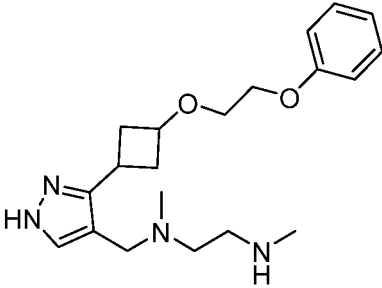
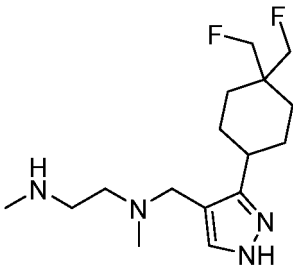
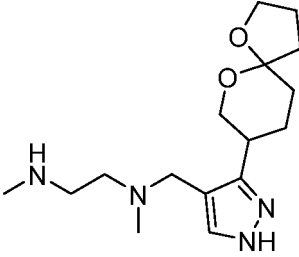
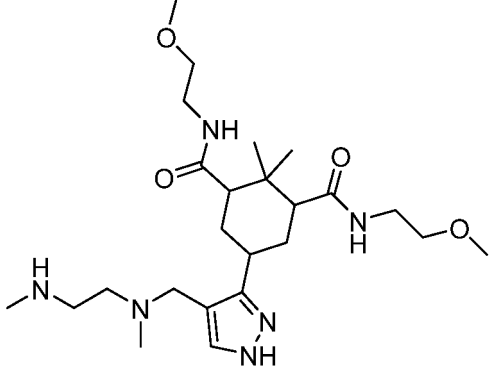
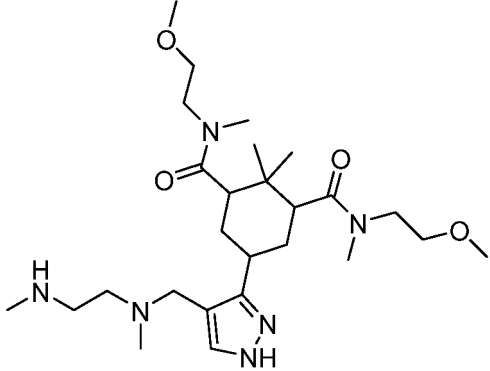
Cmpd No	Structure	LC-MS m/z (M+H)
79		-
80		-
81		-
82		-
83		-

Table 1B. Exemplary Compounds

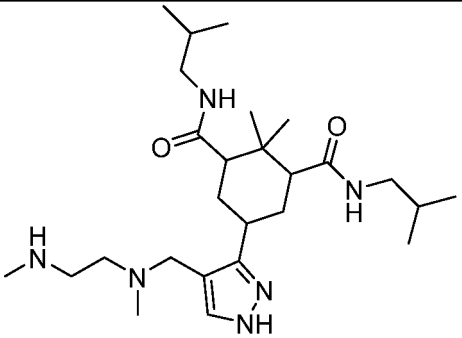
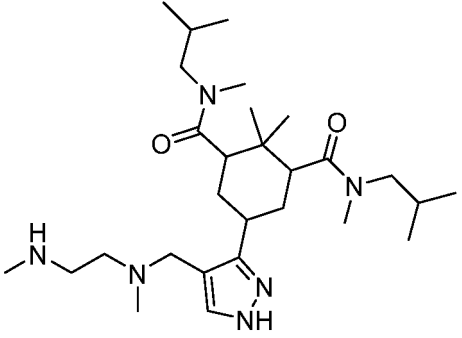
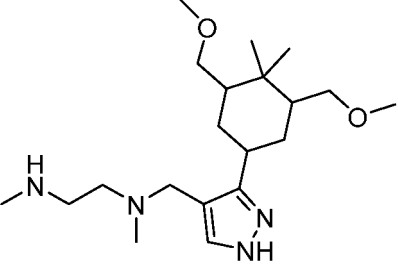
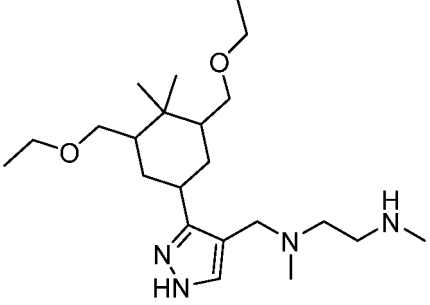
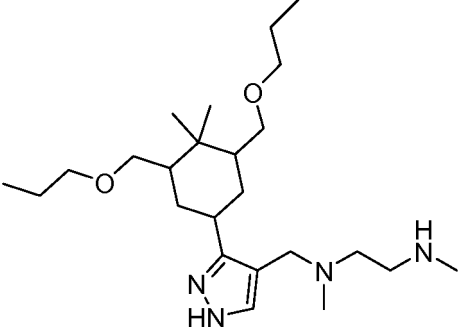
Cmpd No	Structure	LC-MS m/z (M+H)
84		-
85		-
86		-
87		-
88		-

Table 1B. Exemplary Compounds

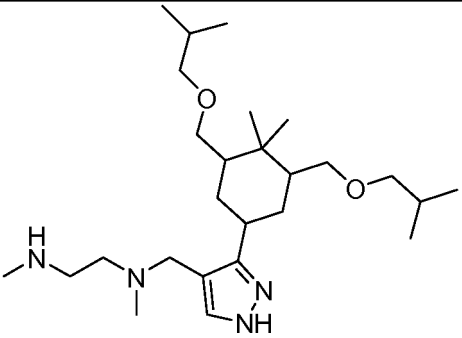
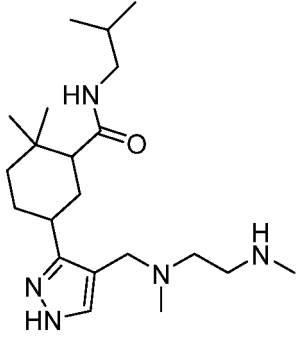
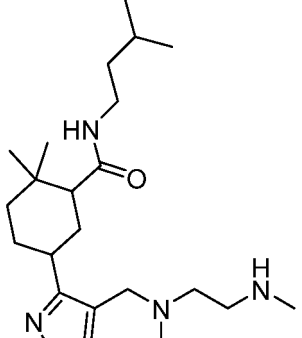
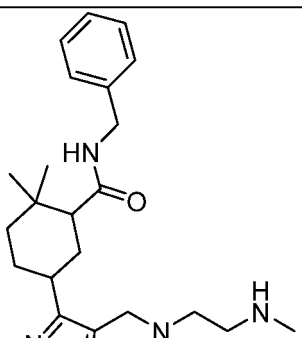
Cmpd No	Structure	LC-MS m/z (M+H)
89		-
90		-
91		-
92		-

Table 1B. Exemplary Compounds

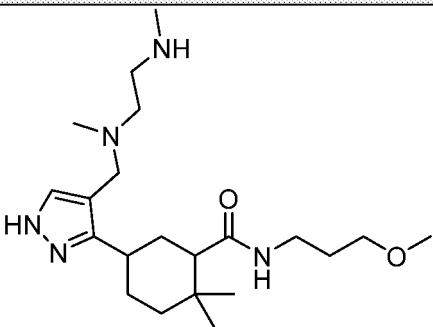
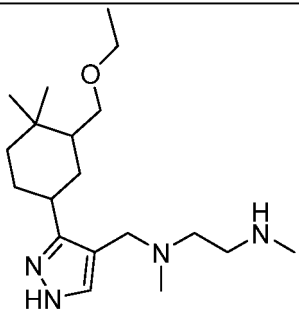
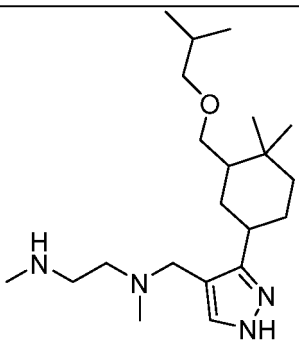
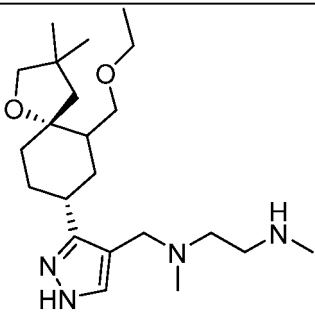
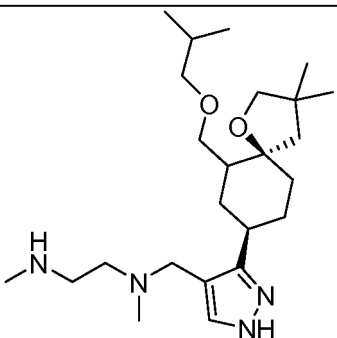
Cmpd No	Structure	LC-MS m/z (M+H)
93		-
94		-
95		-
96		-
97		-

Table 1B. Exemplary Compounds

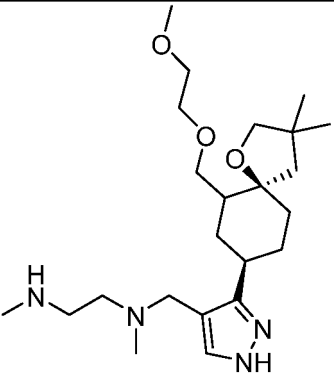
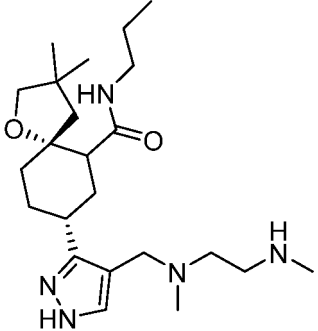
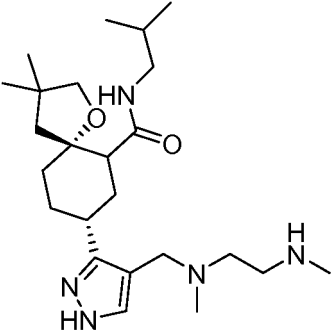
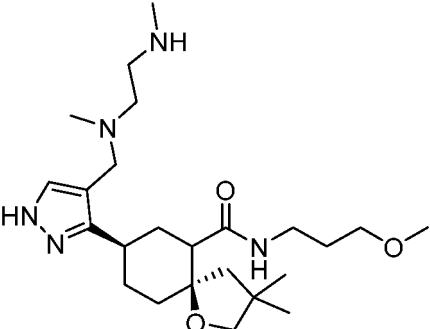
Cmpd No	Structure	LC-MS m/z (M+H)
98		-
99		-
100		-
101		-

Table 1B. Exemplary Compounds

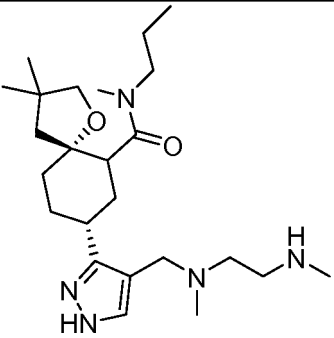
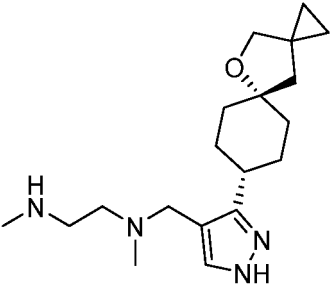
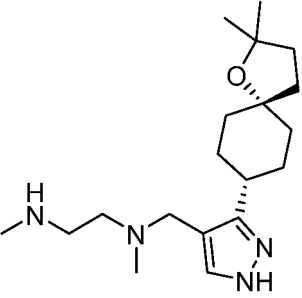
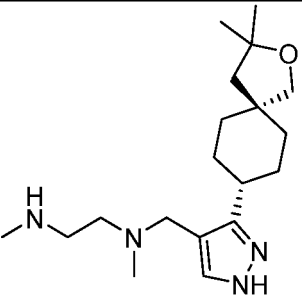
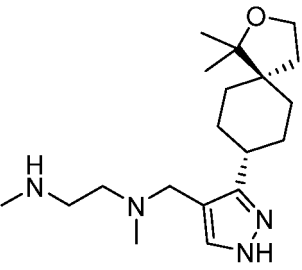
Cmpd No	Structure	LC-MS m/z (M+H)
102		-
103		-
104		-
105		-
106		-

Table 1B. Exemplary Compounds

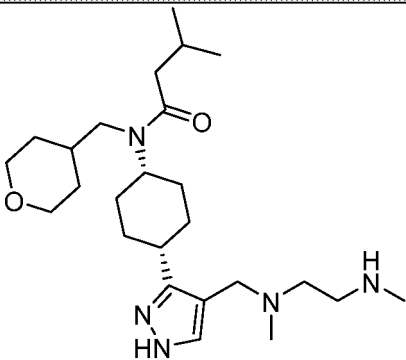
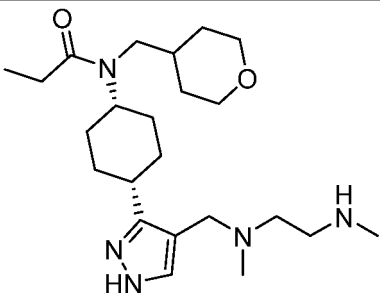
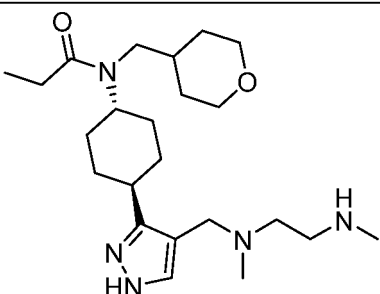
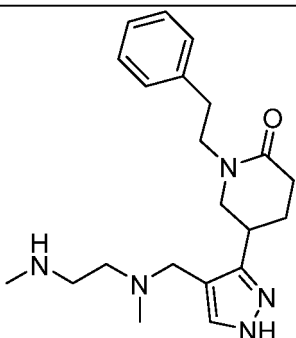
Cmpd No	Structure	LC-MS m/z (M+H)
107		448.4
108		420.2
109		420.2
110		370.1

Table 1B. Exemplary Compounds

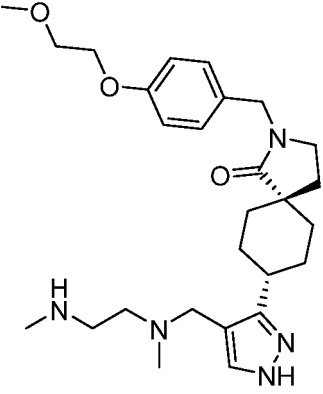
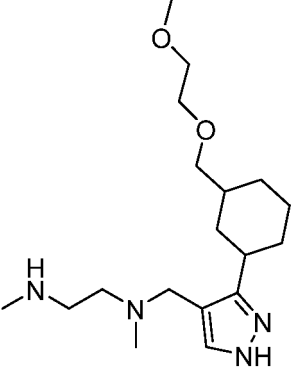
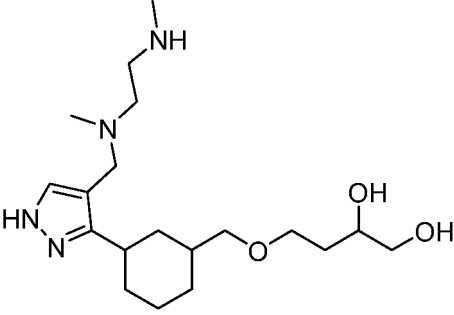
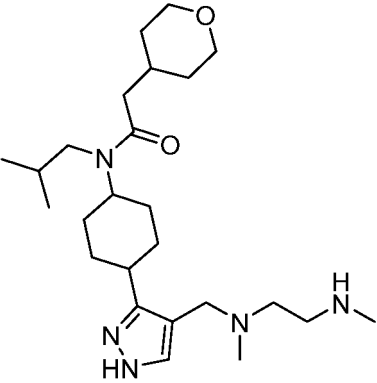
Cmpd No	Structure	LC-MS m/z (M+H)
111		484.2
112		339.15
113		369.25
114		448.3

Table 1B. Exemplary Compounds

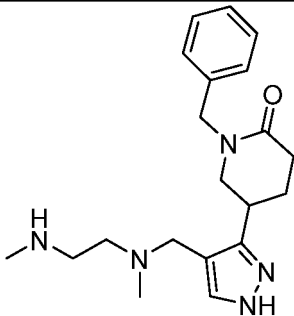
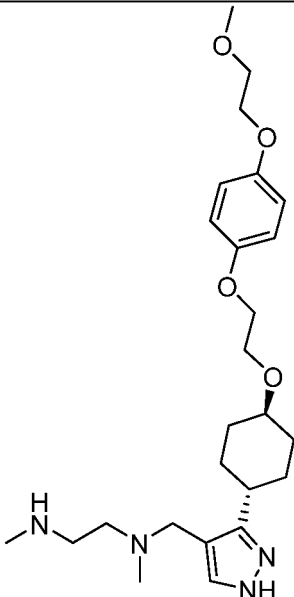
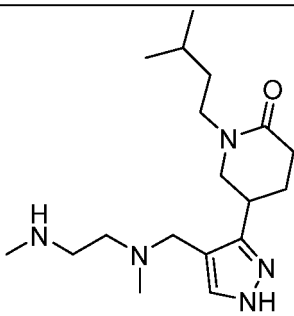
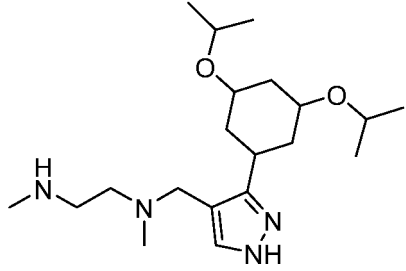
Cmpd No	Structure	LC-MS m/z (M+H)
115		356.15
116		461.4
117		336.2
118		367.3

Table 1B. Exemplary Compounds

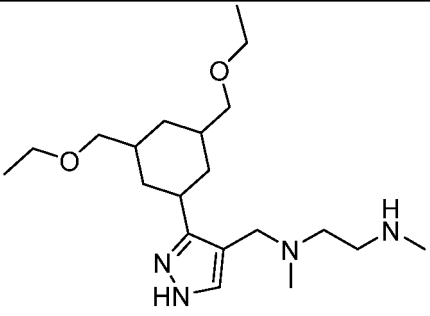
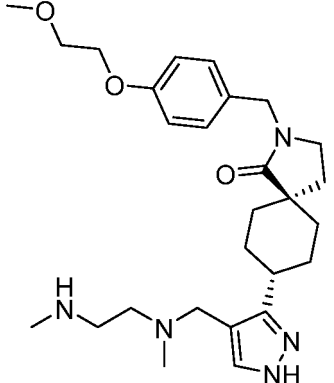
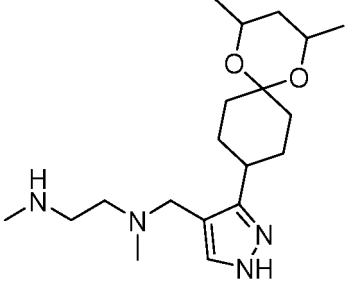
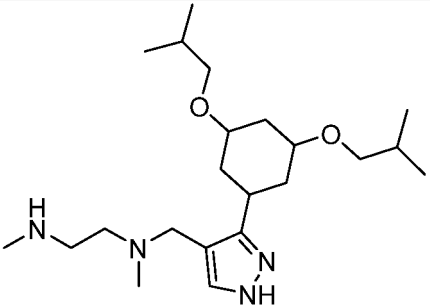
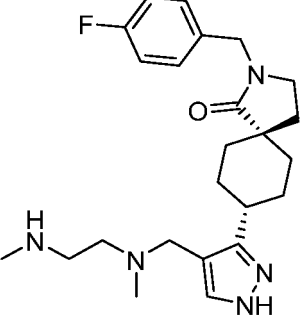
Cmpd No	Structure	LC-MS m/z (M+H)
119		367.3
120		484.35
121		351.25
122		395.25
123		428.3

Table 1B. Exemplary Compounds

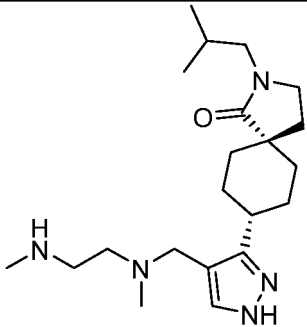
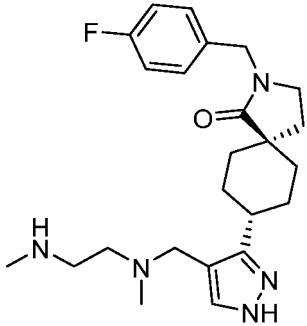
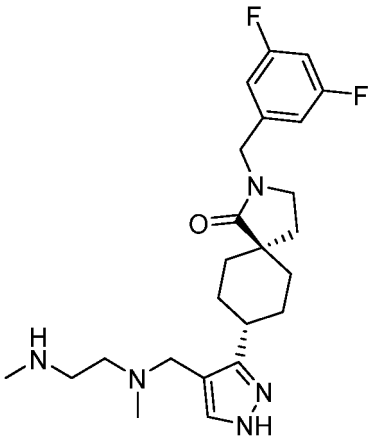
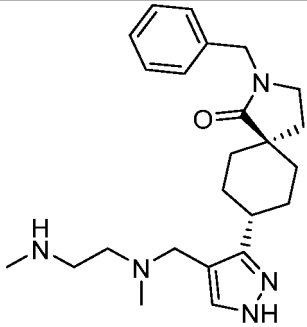
Cmpd No	Structure	LC-MS m/z (M+H)
124		376.3
125		428.3
126		446.3
127		410.25

Table 1B. Exemplary Compounds

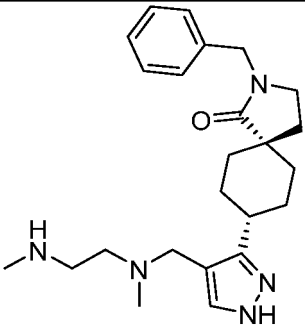
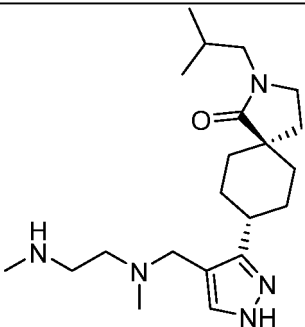
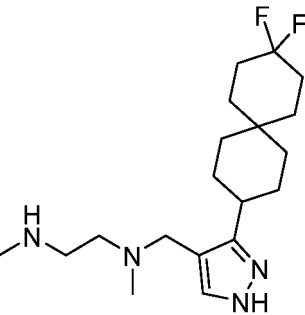
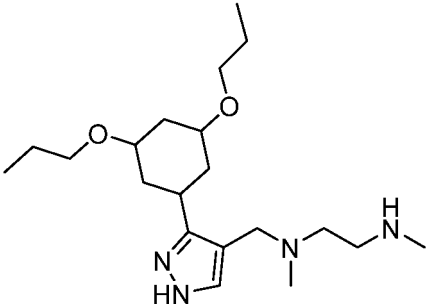
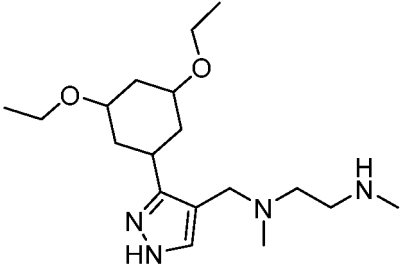
Cmpd No	Structure	LC-MS m/z (M+H)
128		410.3
129		376.3
130		355.25
131		367.3
132		339.2

Table 1B. Exemplary Compounds

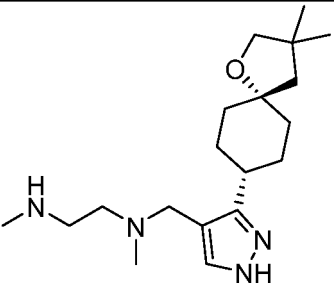
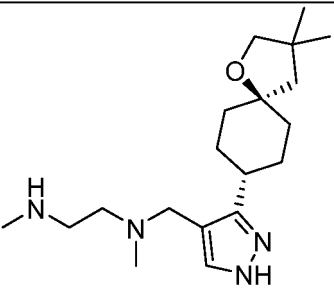
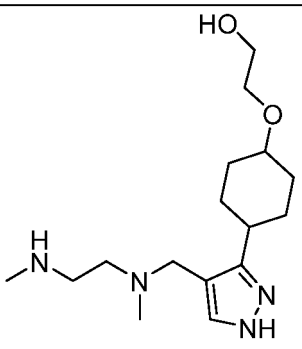
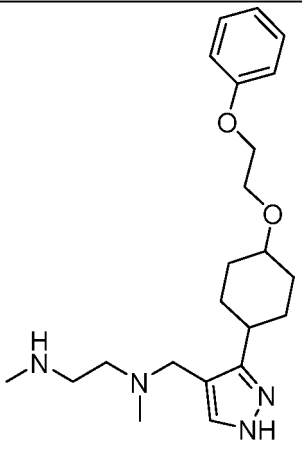
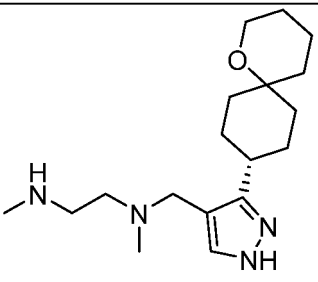
Cmpd No	Structure	LC-MS m/z (M+H)
133		335.2
134		335.2
135		311.25
136		387.3
137		321.1

Table 1B. Exemplary Compounds

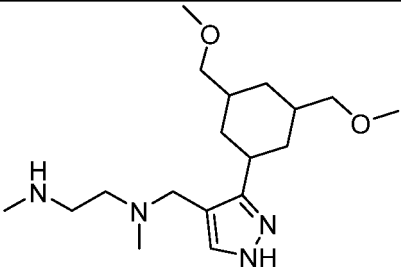
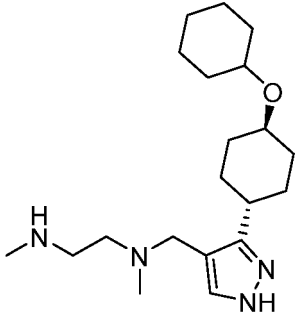
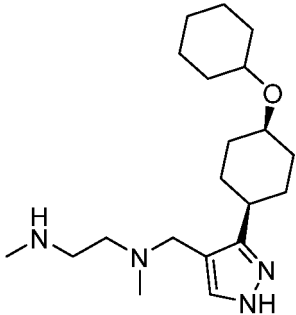
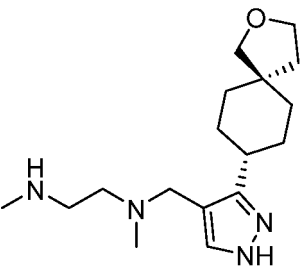
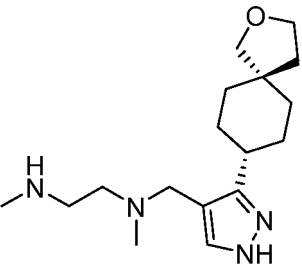
Cmpd No	Structure	LC-MS m/z (M+H)
138		339.1
139		349.25
140		349.25
141		307.15
142		307.15

Table 1B. Exemplary Compounds

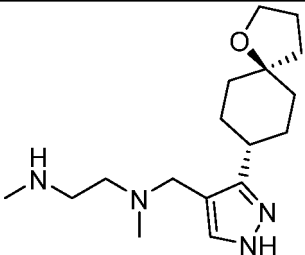
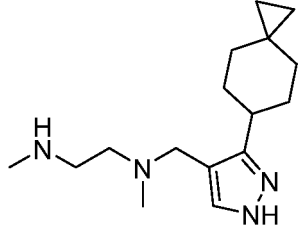
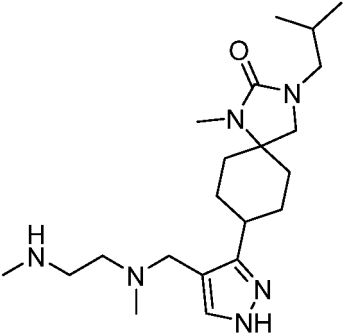
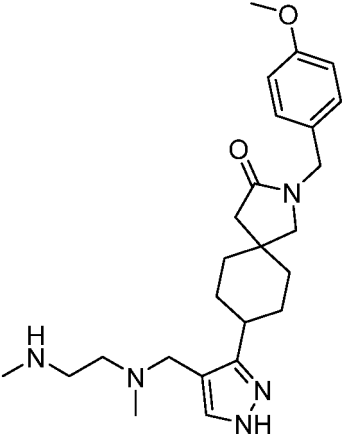
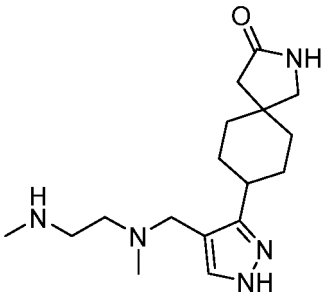
Cmpd No	Structure	LC-MS m/z (M+H)
143		307.25
144		277.15
145		391.15
146		440.15
147		320.1

Table 1B. Exemplary Compounds

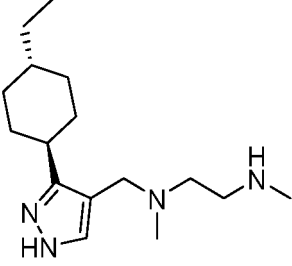
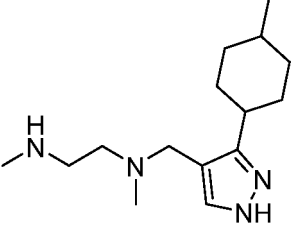
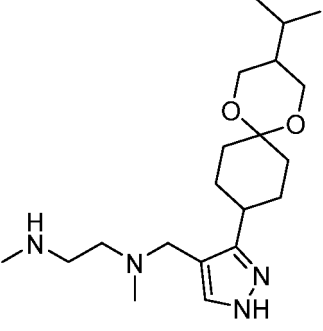
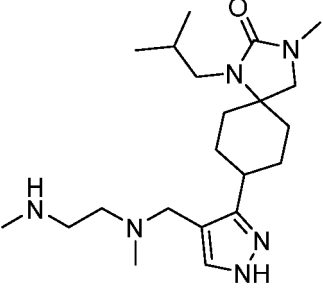
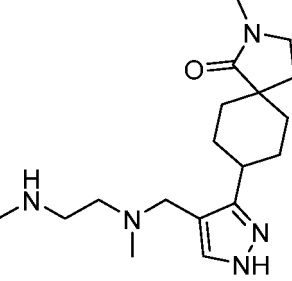
Cmpd No	Structure	LC-MS m/z (M+H)
148		279.25
149		265.1
150		365.25
151		391.3
152		334.15

Table 1B. Exemplary Compounds

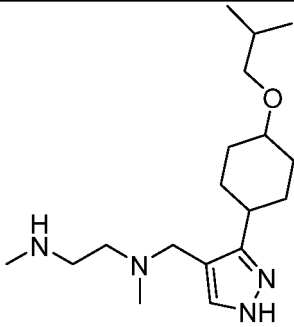
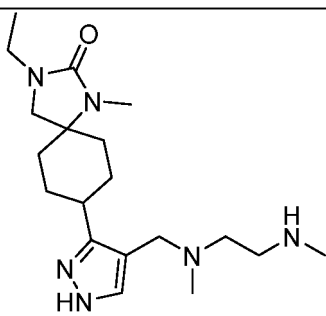
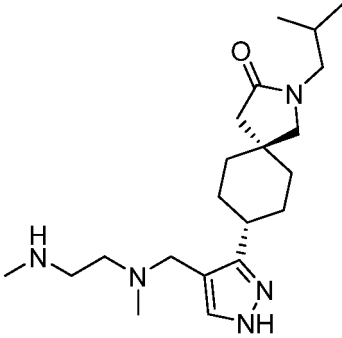
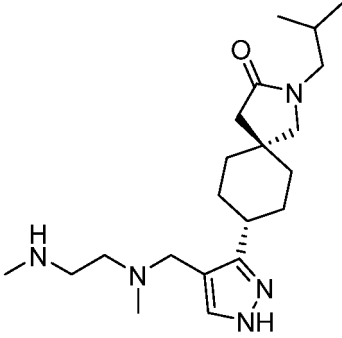
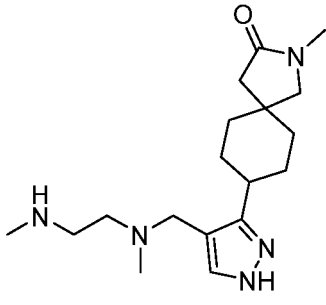
Cmpd No	Structure	LC-MS m/z (M+H)
153		323.15
154		363.15
155		376.25
156		376.25
157		334.15

Table 1B. Exemplary Compounds

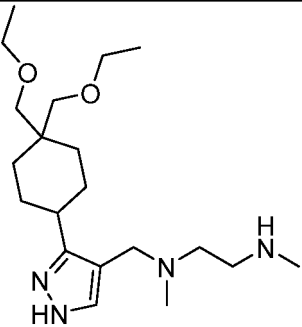
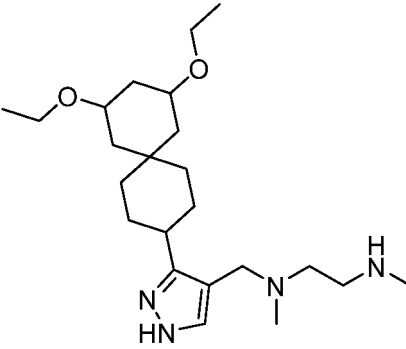
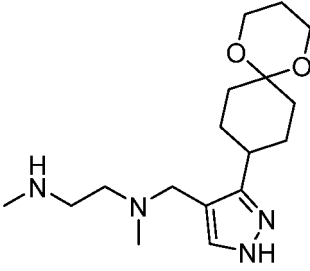
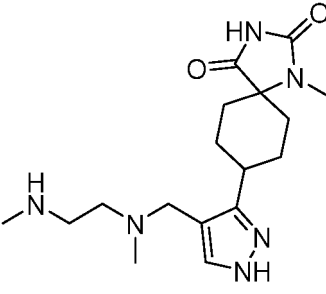
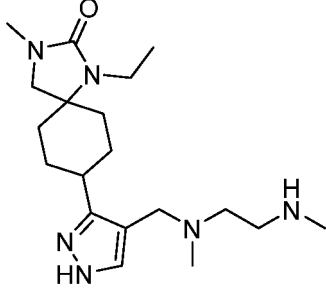
Cmpd No	Structure	LC-MS m/z (M+H)
158		367.2
159		407.35
160		323.2
161		349
162		363.05

Table 1B. Exemplary Compounds

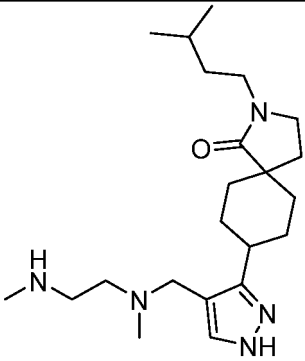
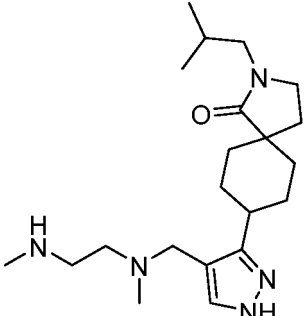
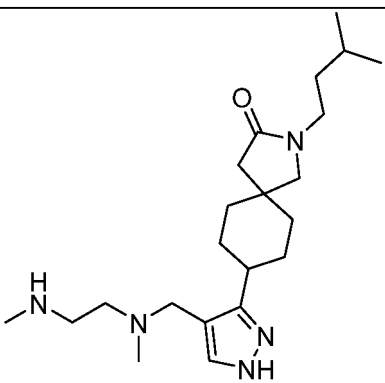
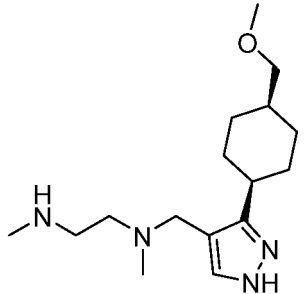
Cmpd No	Structure	LC-MS m/z (M+H)
163		390.3
164		376.25
165		390.3
166		295.1

Table 1B. Exemplary Compounds

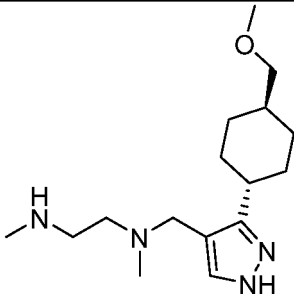
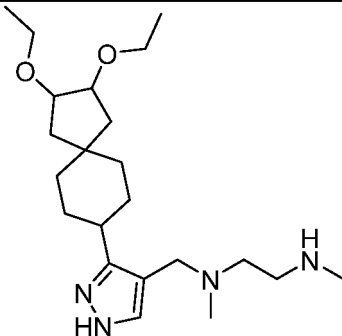
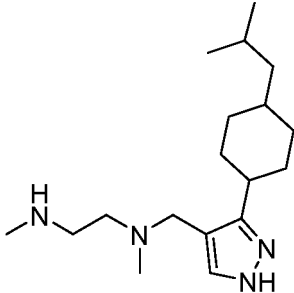
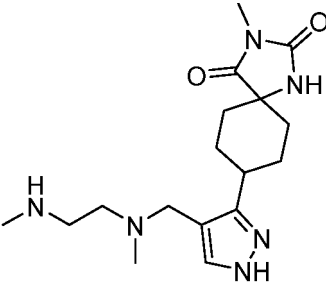
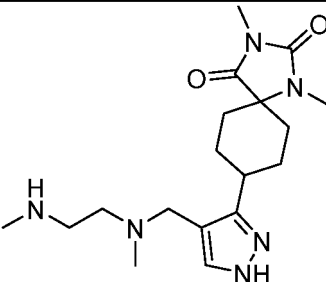
Cmpd No	Structure	LC-MS m/z (M+H)
167		295.1
168		393.3
169		307.15
170		349.15
171		363.2

Table 1B. Exemplary Compounds

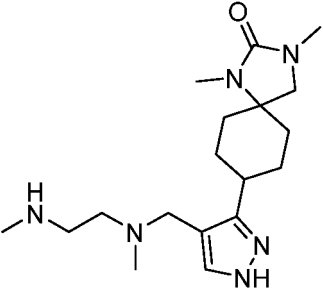
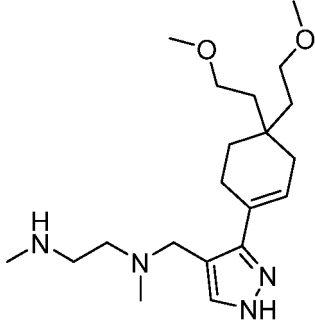
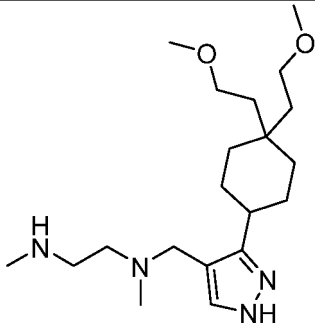
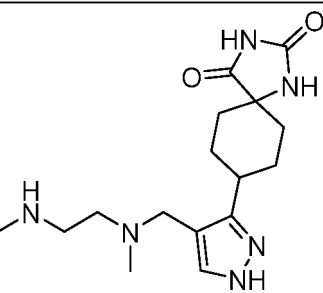
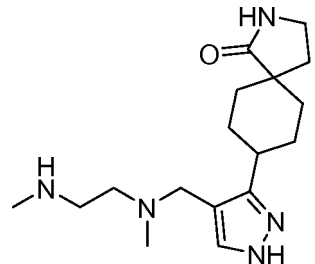
Cmpd No	Structure	LC-MS m/z (M+H)
172		349.2
173		365.2
174		367.35
175		335.1
176		320.1

Table 1B. Exemplary Compounds

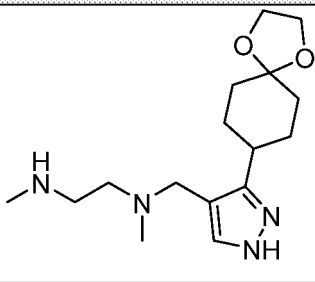
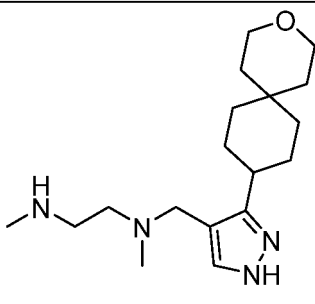
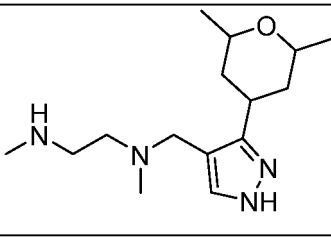
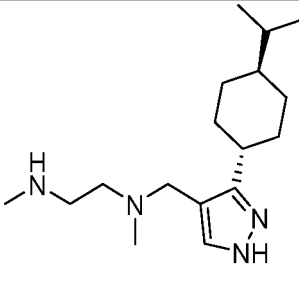
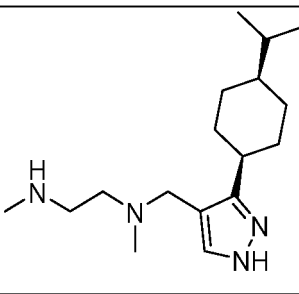
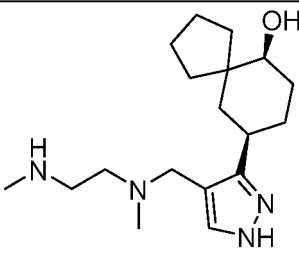
Cmpd No	Structure	LC-MS m/z (M+H)
177		309.1
178		321.05
179		281.1
180		293.15
181		293.15
182		321.3

Table 1B. Exemplary Compounds

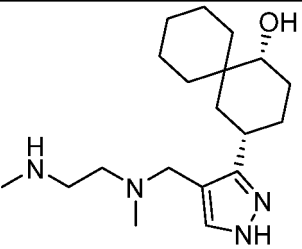
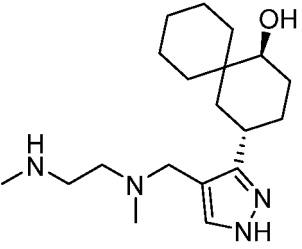
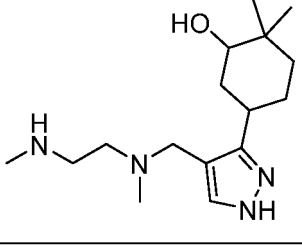
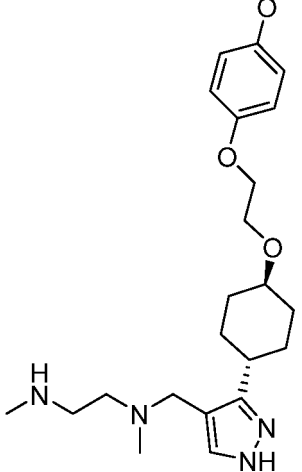
Cmpd No	Structure	LC-MS m/z (M+H)
183		-
184		-
185		295.05
186		417.10

Table 1B. Exemplary Compounds

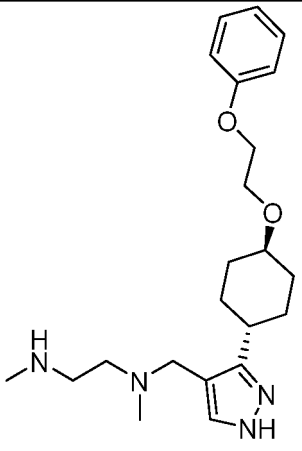
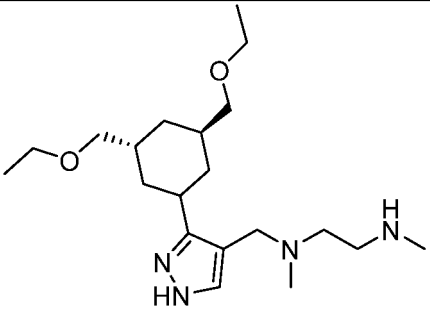
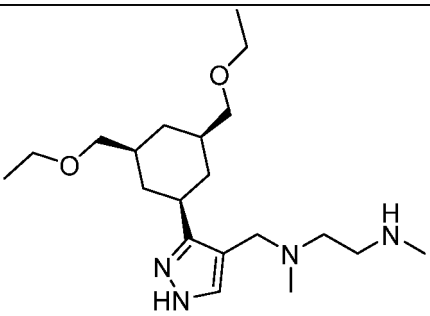
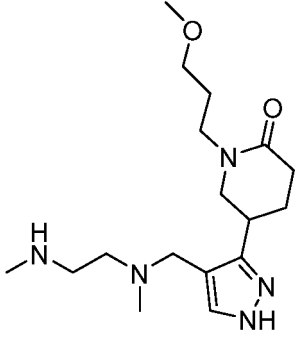
Cmpd No	Structure	LC-MS m/z (M+H)
187		387.10
188		367.2
189		367.2
190		338.1

Table 1B. Exemplary Compounds

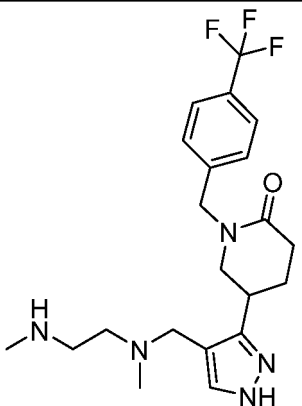
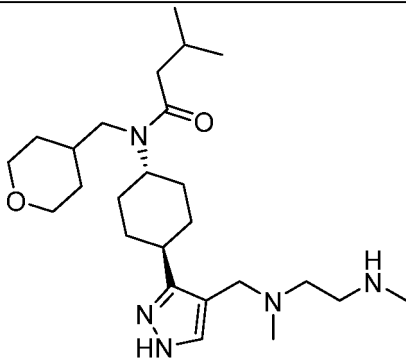
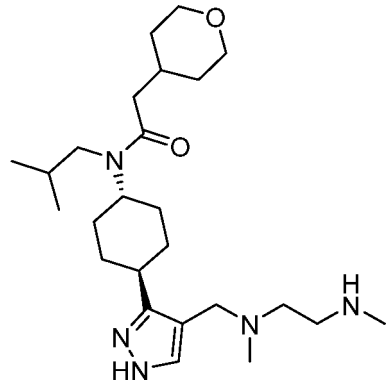
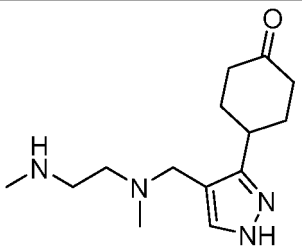
Cmpd No	Structure	LC-MS m/z (M+H)
191		424.2
192		448.2
193		448.4
194		265.1

Table 1B. Exemplary Compounds

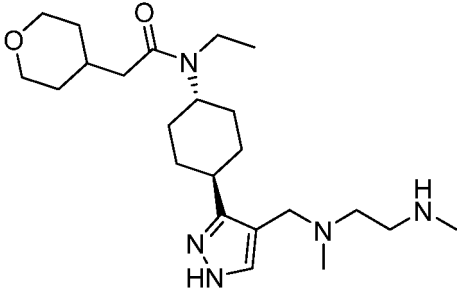
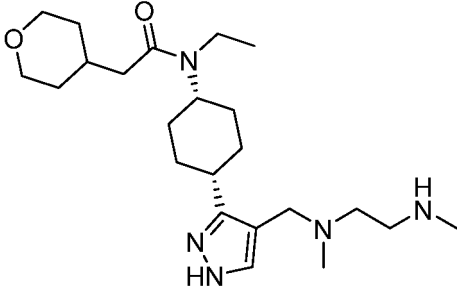
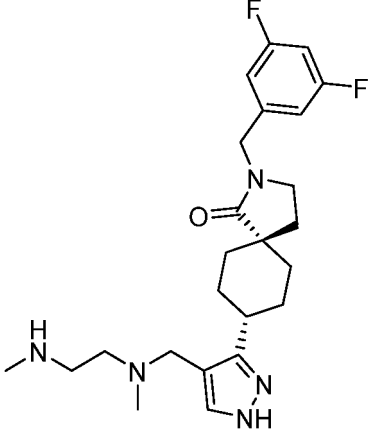
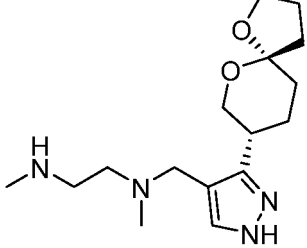
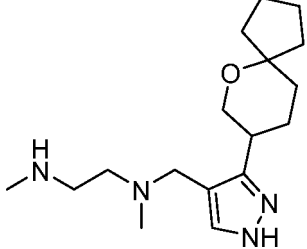
Cmpd No	Structure	LC-MS m/z (M+H)
195		420.4
196		420.5
197		446.2
198		309.2
199		307.15

Table 1B. Exemplary Compounds

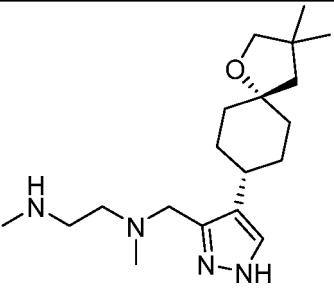
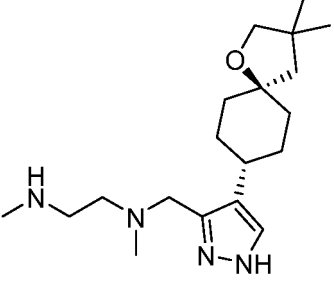
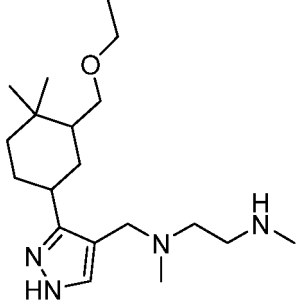
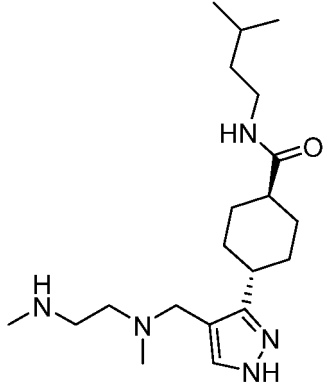
Cmpd No	Structure	LC-MS m/z (M+H)
200		335.1
201		335.2
202		337.1
203		364.2

Table 1B. Exemplary Compounds

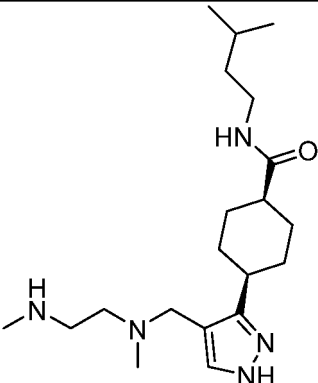
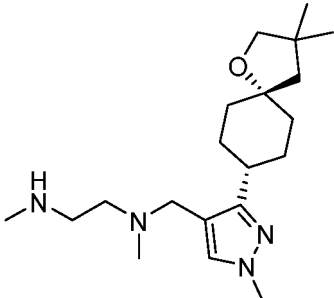
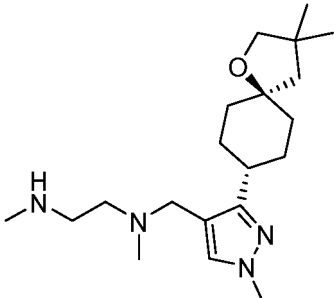
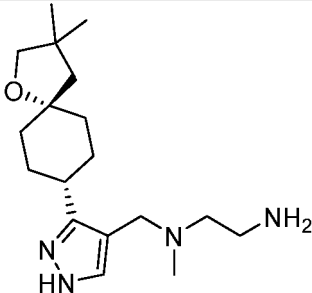
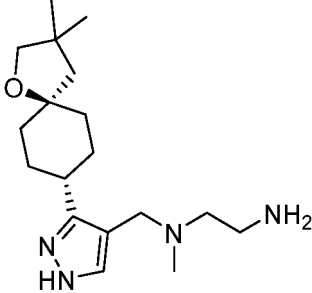
Cmpd No	Structure	LC-MS m/z (M+H)
204		364.2
205		349.2
206		349.15
207		321.15
208		321.1

Table 1B. Exemplary Compounds

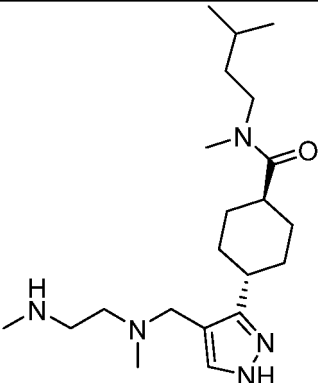
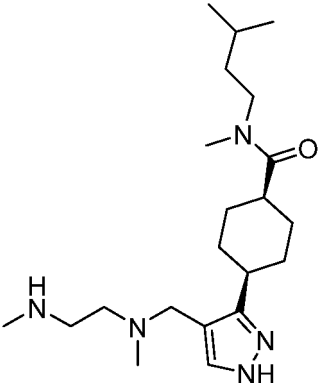
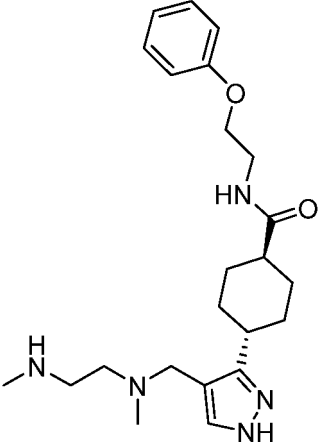
Cmpd No	Structure	LC-MS m/z (M+H)
209		378.2
210		378.2
211		414.1

Table 1B. Exemplary Compounds

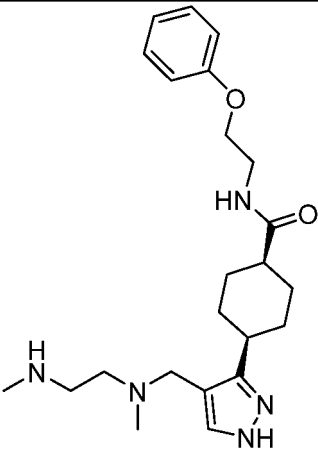
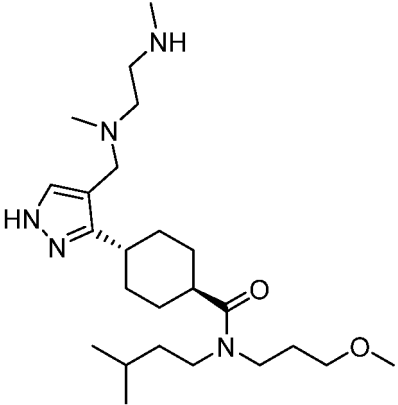
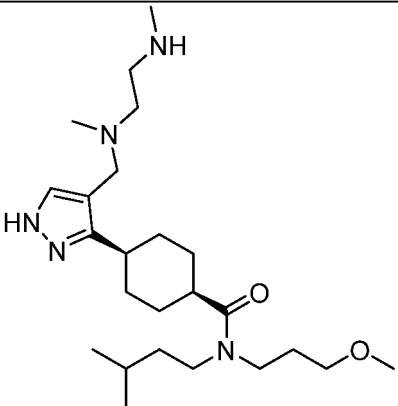
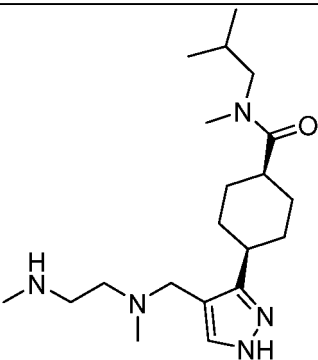
Cmpd No	Structure	LC-MS m/z (M+H)
212		414.1
213		436.2
214		436.2
215		364.2

Table 1B. Exemplary Compounds

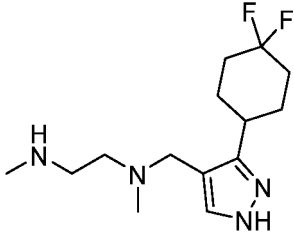
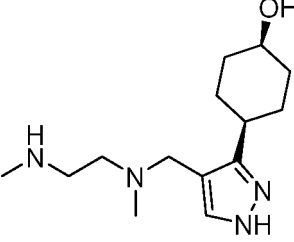
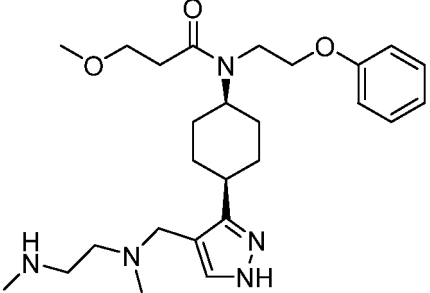
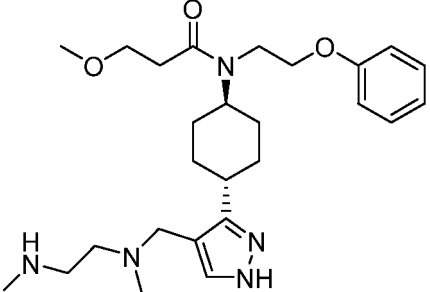
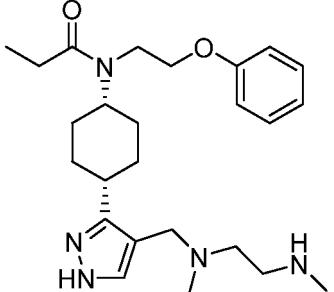
Cmpd No	Structure	LC-MS m/z (M+H)
216		287.05
217		267.05
218		472.4
219		472.4
220		442.2

Table 1B. Exemplary Compounds

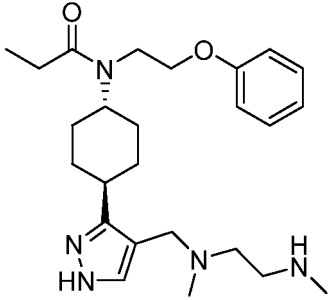
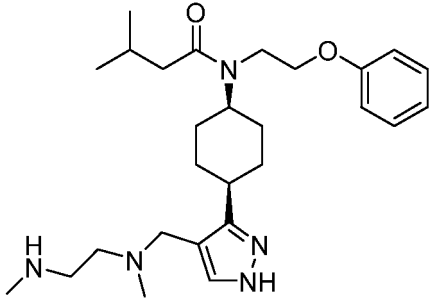
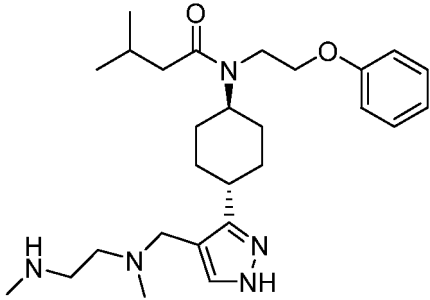
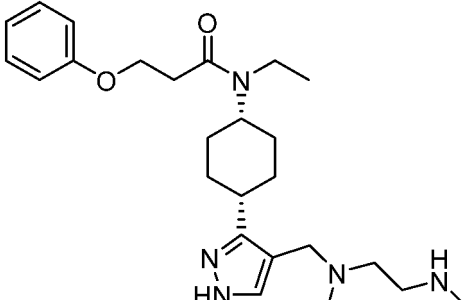
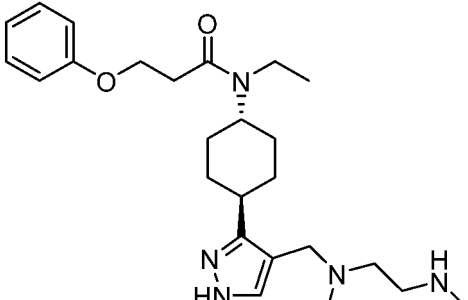
Cmpd No	Structure	LC-MS m/z (M+H)
221		442.2
222		470.2
223		470.4
224		442.3
225		442.3

Table 1B. Exemplary Compounds

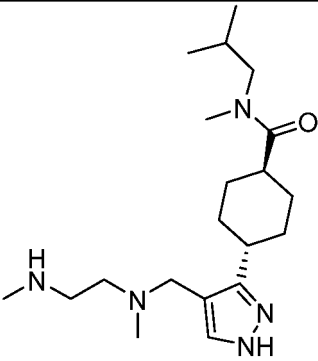
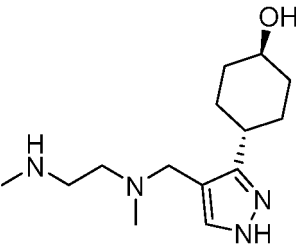
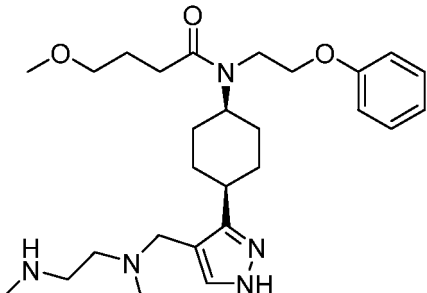
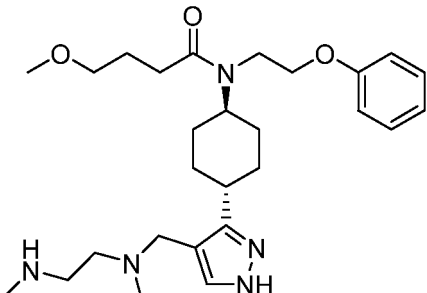
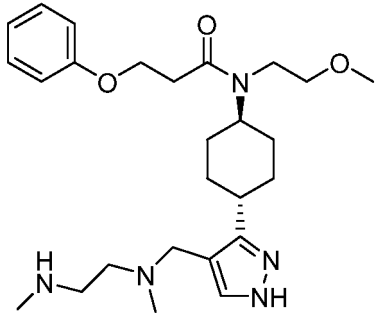
Cmpd No	Structure	LC-MS m/z (M+H)
226		364.2
227		267.05
228		486.4
229		486.4
230		472.4

Table 1B. Exemplary Compounds

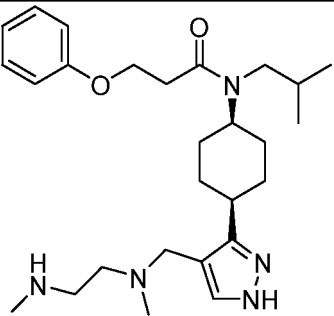
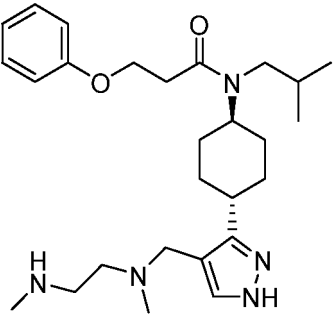
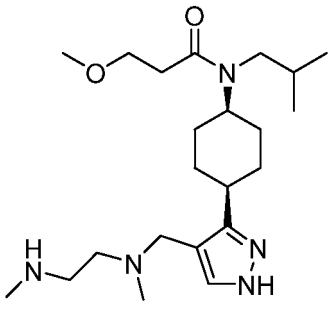
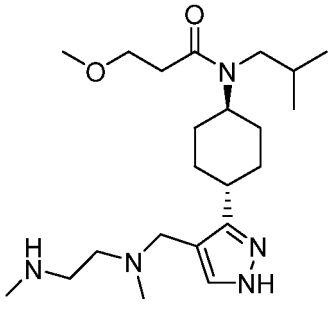
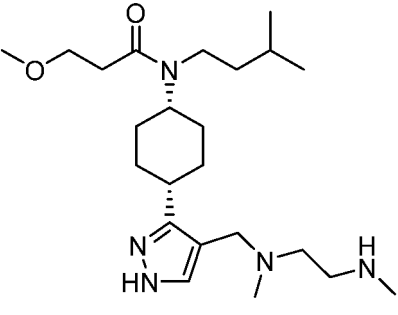
Cmpd No	Structure	LC-MS m/z (M+H)
231		470.2
232		470.2
233		408.2
234		408.2
235		422.4

Table 1B. Exemplary Compounds

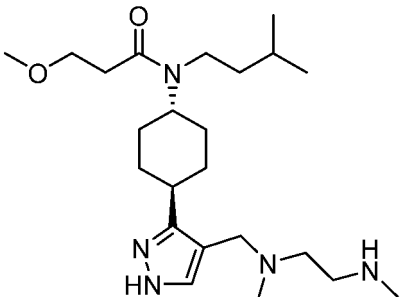
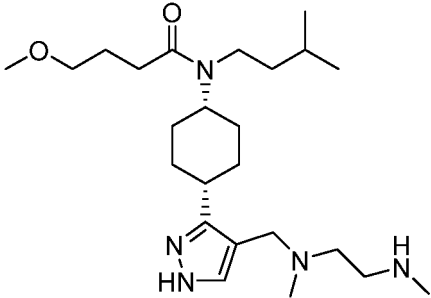
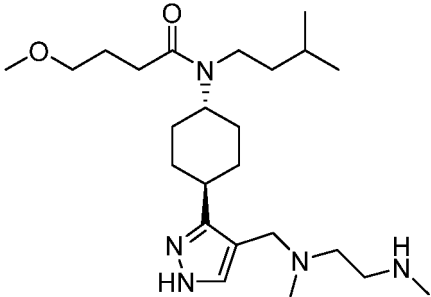
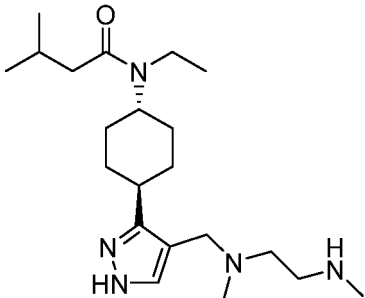
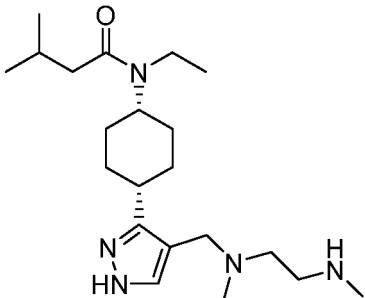
Cmpd No	Structure	LC-MS m/z (M+H)
236		422.4
237		436.4
238		436.4
239		378.3
240		378.3

Table 1B. Exemplary Compounds

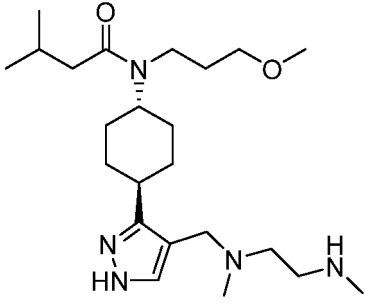
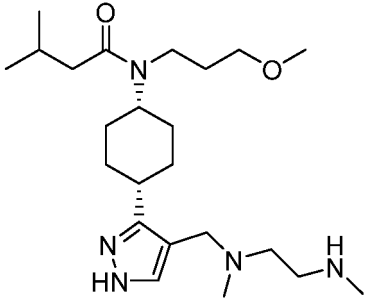
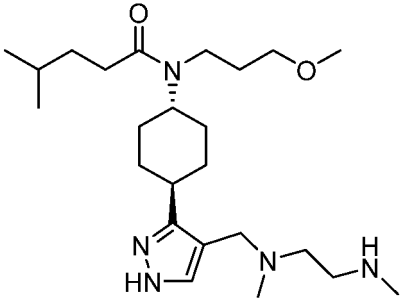
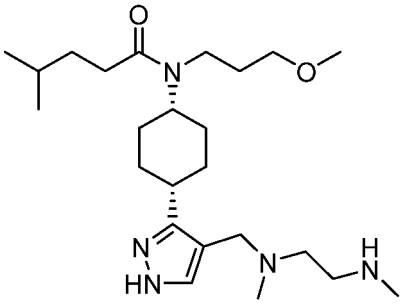
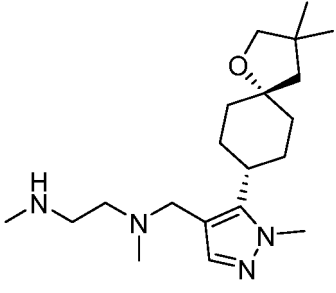
Cmpd No	Structure	LC-MS m/z (M+H)
241		422.2
242		422.2
243		436.2
244		436.2
245		349.1

Table 1B. Exemplary Compounds

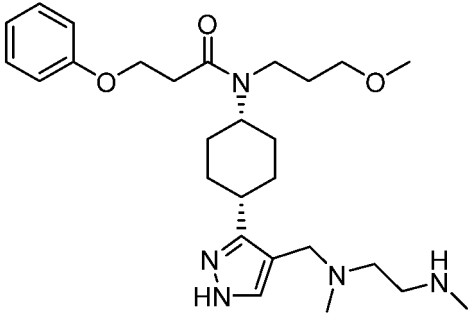
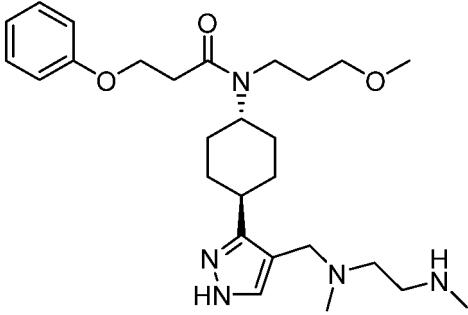
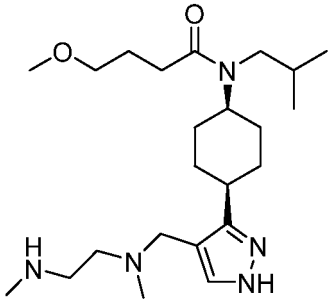
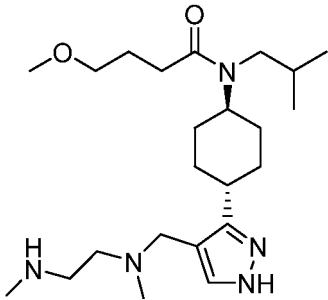
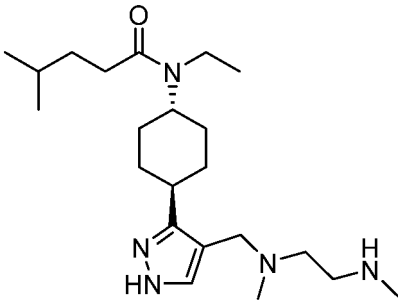
Cmpd No	Structure	LC-MS m/z (M+H)
246		486.3
247		486.3
248		422.3
249		422.3
250		392.2

Table 1B. Exemplary Compounds

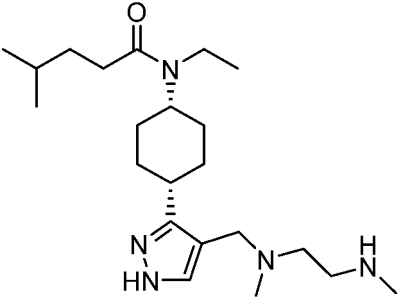
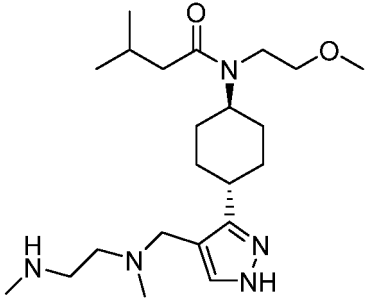
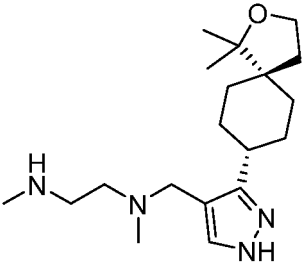
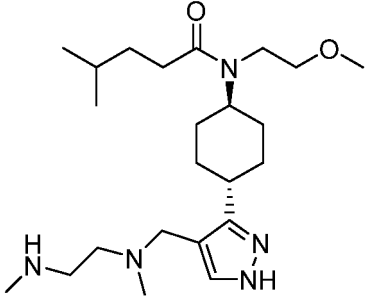
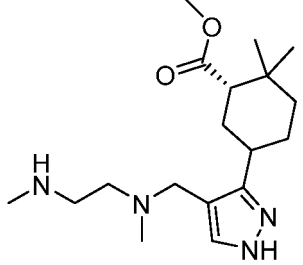
Cmpd No	Structure	LC-MS m/z (M+H)
251		392.3
252		408.2
253		335.2
254		422.3
255		-

Table 1B. Exemplary Compounds

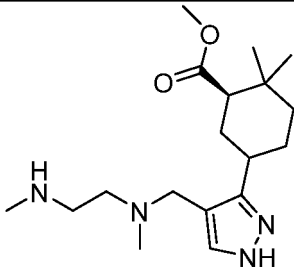
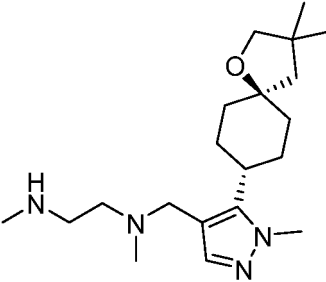
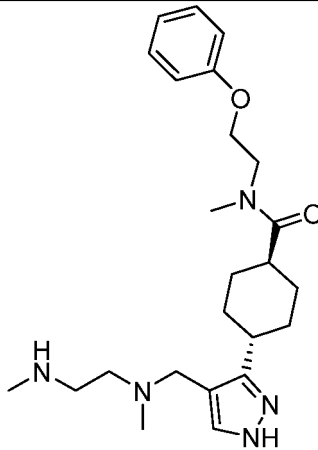
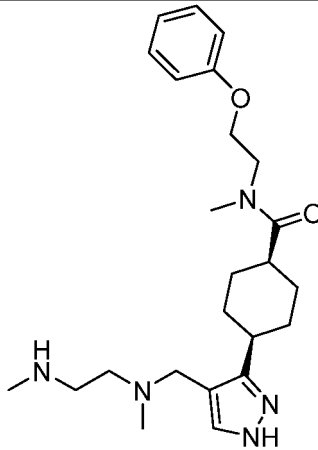
Cmpd No	Structure	LC-MS m/z (M+H)
256		337.5
257		349.2
258		428.1
259		428.1

Table 1B. Exemplary Compounds

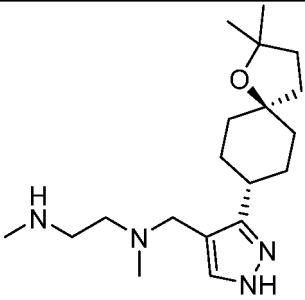
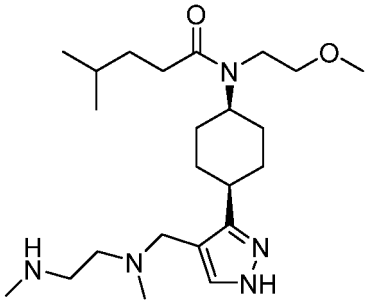
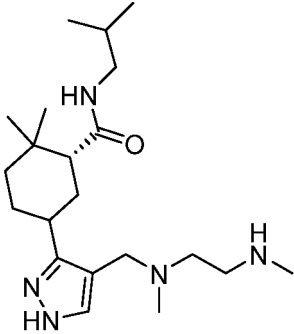
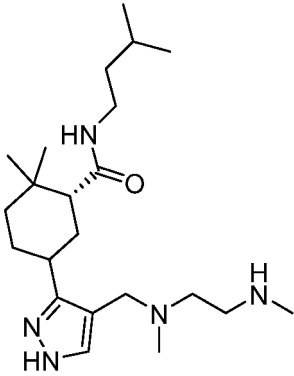
Cmpd No	Structure	LC-MS m/z (M+H)
260		335.1
261		422.3
262		378.2
263		392.2

Table 1B. Exemplary Compounds

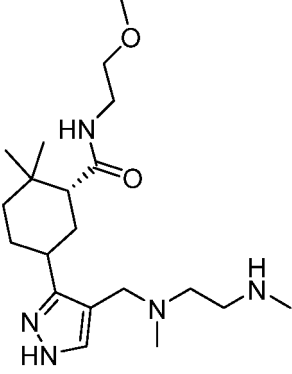
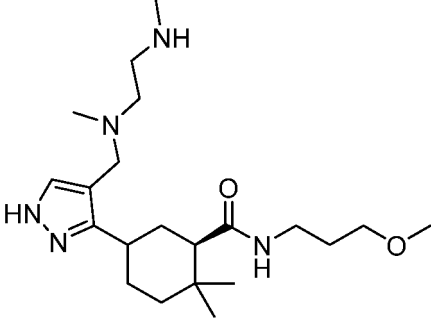
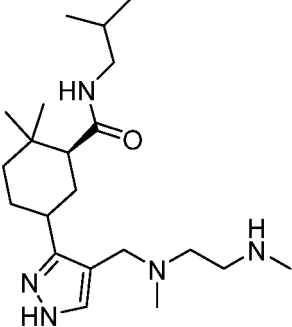
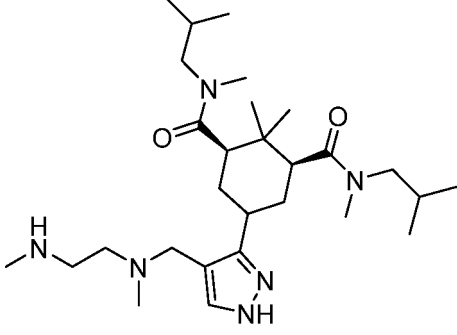
Cmpd No	Structure	LC-MS m/z (M+H)
264		380.2
265		394.2
266		378.15
267		505.2

Table 1B. Exemplary Compounds

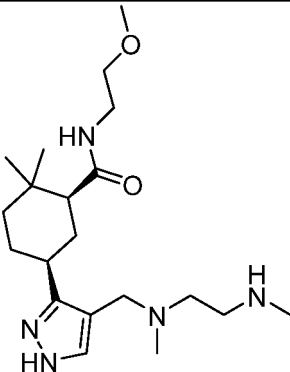
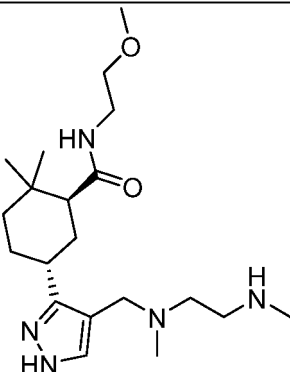
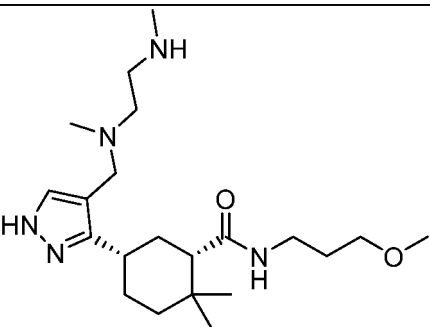
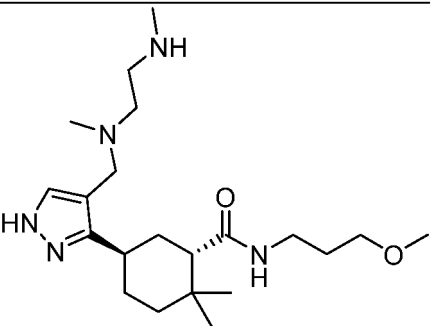
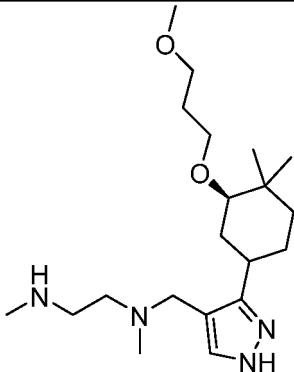
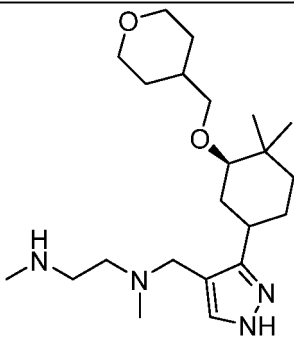
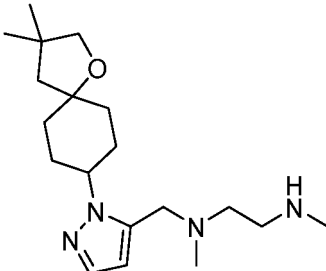
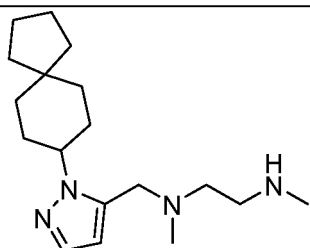
Cmpd No	Structure	LC-MS m/z (M+H)
268		380.3
269		380.3
270		394.3
271		394.5

Table 1B. Exemplary Compounds		
Cmpd No	Structure	LC-MS m/z (M+H)
272		367.15
273		393.21
274		335.1
275		305.4

[00194] In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8). In certain embodiments, a provided compound inhibits wild-type PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8. In certain embodiments, a provided compound inhibits a mutant RMT. In certain embodiments, a provided compound inhibits PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8, *e.g.*, as measured in an assay described herein. In certain embodiments, the RMT is from a human.

In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) at an IC_{50} less than or equal to 10 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) at an IC_{50} less than or equal to 1 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) at an IC_{50} less than or equal to 0.1 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) at an IC_{50} less than or equal to 0.01 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) in a cell at an EC_{30} less than or equal to 10 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) in a cell at an EC_{30} less than or equal to 12 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) in a cell at an EC_{30} less than or equal to 3 μ M. In certain embodiments, a provided compound inhibits PRMT1 in a cell at an EC_{30} less than or equal to 12 μ M. In certain embodiments, a provided compound inhibits PRMT1 in a cell at an EC_{30} less than or equal to 3 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) in a cell at an EC_{30} less than or equal to 1 μ M. In certain embodiments, a provided compound inhibits an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) in a cell at an EC_{30} less than or equal to 0.1 μ M. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 10 μ M. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 1 μ M. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 0.1 μ M.

[00195] It will be understood by one of ordinary skill in the art that the RMT can be wild-type, or any mutant or variant.

[00196] The present disclosure provides pharmaceutical compositions comprising a compound described herein, *e.g.*, a compound of 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 amorphous, 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 an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8). In certain embodiments, the effective amount is an amount effective for treating an RMT-mediated disorder (*e.g.*, a PRMT1-, PRMT3-, CARM1-, PRMT6-, and/or PRMT8-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 an RMT-mediated disorder.

[00197] 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).

[00198] 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.

[00199] 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.

[00200] 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.

[00201] In some embodiments, a pharmaceutical composition described herein is sterilized.

[00202] 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.

[00203] 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.

[00204] 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.

[00205] 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.

[00206] 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.

[00207] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (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.

[00213] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, 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.

[00214] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] 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 as 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] 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).

[00228] 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.

[00229] 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.

[00230] 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.

[00231] 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 ophthalmically-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.

[00232] 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.

[00233] 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.

[00234] 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).

[00235] 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).

[00236] 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.

[00237] 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.

[00238] 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.

[00239] 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.

[00240] 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.

[00241] 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 (I). In certain embodiments, the additional therapeutically active agent is not a compound of Formula (I). In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It 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.

[00242] 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. In certain embodiments, an additional therapeutically active agent is prednisolone, dexamethasone, doxorubicin, vincristine, mafosfamide, cisplatin, carboplatin, Ara-C, rituximab, azacitadine, panobinostat, vorinostat, everolimus, rapamycin, ATRA (all-trans retinoic acid), daunorubicin, decitabine, Vidaza, mitoxantrone, or IBET-151.

[00243] Also encompassed by the present disclosure 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.

[00244] Compounds and compositions described herein are generally useful for the inhibition of RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8). In some embodiments, methods of treating an RMT-mediated disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of 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 RMT-mediated disorder. In certain embodiments, the subject is susceptible to a RMT-mediated disorder.

[00245] As used herein, the term “RMT-mediated disorder” means any disease, disorder, or other pathological condition in which an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) 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 an RMT is known to play a role.

[00246] In some embodiments, the present disclosure provides a method of inhibiting an RMT comprising contacting the RMT with an effective amount of a compound described herein (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof. The RMT 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* RMT 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 an RMT does not necessarily require that all of the RMT be occupied by an inhibitor at once. Exemplary levels of inhibition of an RMT (*e.g.*, PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8) 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.

[00247] In some embodiments, provided is a method of inhibiting RMT activity in a subject in need thereof (*e.g.*, a subject diagnosed as having an RMT-mediated disorder) comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00248] In certain embodiments, provided is a method of modulating gene expression in a cell which comprises contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell is 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.

[00249] In certain embodiments, provided is a method of modulating transcription in a cell which comprises contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell is 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.

[00250] In certain embodiments, a method is provided of selecting a therapy for a subject having a disease associated with an RMT-mediated disorder or mutation comprising the steps

of determining the presence of an RMT-mediated disorder or gene mutation in an RMT gene (e.g., a PRMT1, PRMT3, CARM1, PRMT6, and/or PRMT8 gene) or and selecting, based on the presence of an RMT-mediated disorder a gene mutation in the RMT gene a therapy that includes the administration of a provided compound. In certain embodiments, the disease is cancer.

[00251] In certain embodiments, a method of treatment is provided for a subject in need thereof comprising the steps of determining the presence of an RMT-mediated disorder or a gene mutation in the RMT gene and treating the subject in need thereof, based on the presence of a RMT-mediated disorder or gene mutation in the RMT gene with a therapy that includes the administration of a provided compound. In certain embodiments, the subject is a cancer patient.

[00252] In some embodiments, a compound provided herein is useful in treating a proliferative disorder, such as cancer. For example, while not being bound to any particular mechanism, protein arginine methylation by PRMTs is a modification that has been implicated in signal transduction, gene transcription, DNA repair and mRNA splicing, among others; and overexpression of PRMTs within these pathways is often associated with various cancers. Thus, compounds which inhibit the action of PRMTs, as provided herein, are effective in the treatment of cancer.

[00253] In some embodiments, compounds provided herein are effective in treating cancer through the inhibition of PRMT1. For example, PRMT1 overexpression has been observed in various human cancers, including, but not limited to, breast cancer, prostate cancer, lung cancer, colon cancer, bladder cancer, and leukemia. In one example, PRMT1 specifically deposits an asymmetric dimethylarginine (aDMA) mark on histone H4 at arginine 3 (H4R3me2a), and this mark is associated with transcription activation. In prostate cancer, the methylation status of H4R3 positively correlates with increasing tumor grade and can be used to predict the risk of prostate cancer recurrence (Seligson *et al.*, *Nature* 2005 435, 1262–1266). Thus, in some embodiments, inhibitors of PRMT1, as described herein, are useful in treating cancers associated with the methylation status of H4R3, e.g., prostate cancer. Additionally, the methylarginine effector molecule TDRD3 interacts with the H4R3me2a mark, and overexpression of TDRD3 is linked to poor prognosis for the survival of patients with breast cancer (Nagahata *et al.*, *Cancer Sci.* 2004 95, 218–225). Thus, in some embodiments, inhibitors of PRMT1, as described herein, are useful in treating cancers associated with overexpression of TDRD3, e.g., breast cancer, as inhibition of PRMT1 leads to a decrease in methylation of H4R3, thereby preventing the association of overexpressed

TDRD3 with H4R3me2a. In other examples, PRMT1 is known to have non-histone substrates. For example, PRMT1, when localized to the cytoplasm, methylates proteins that are involved in signal transduction pathways, e.g., the estrogen receptor (ER). The expression status of ER in breast cancer is critical for prognosis of the disease, and both genomic and non-genomic ER pathways have been implicated in the pathogenesis of breast cancer. For example, it has been shown that PRMT1 methylates ER α , and that ER α methylation is required for the assembly of ER α with SRC (a proto-oncogene tyrosine-protein kinase) and focal adhesion kinase (FAK). Further, the silencing of endogenous PRMT1 resulted in the inability of estrogen to activate AKT. These results suggested that PRMT1-mediated ER α methylation is required for the activation of the SRC–PI3K–FAK cascade and AKT, coordinating cell proliferation and survival. Thus, hypermethylation of ER α in breast cancer is thought to cause hyperactivation of this signaling pathway, providing a selective survival advantage to tumor cells (Le Romancer *et al.*, *Mol. Cell* 2008 31, 212–221; Le Romancer *et al.*, *Steroids* 2010 75, 560–564). Accordingly, in some embodiments, inhibitors of PRMT1, as described herein, are useful in treating cancers associated with ER α methylation, e.g., breast cancer. In yet another example, PRMT1 has been shown to be involved in the regulation of leukemia development. For example, SRC-associated in mitosis 68 kDa protein (SAM68; also known as KHDRBS1) is a well-characterized PRMT1 substrate, and when either SAM68 or PRMT1 is fused directly to the myeloid/lymphoid leukemia (MLL) gene, these fusion proteins can activate MLL oncogenic properties, implying that the methylation of SAM68 by PRMT1 is a critical signal for the development of leukemia (Cheung *et al.*, *Nature Cell Biol.* 2007 9, 1208–1215). Accordingly, in some embodiments, inhibitors of PRMT1, as described herein, are useful in treating cancers associated with SAM68 methylation, e.g., leukemia. In still another example, PRMT1 is implicated in leukemia development through its interaction with AE9a, a splice isoform of AML1-ETO (Shia *et al.*, *Blood* 2012 119:4953–62). Knockdown of PRMT1 affects expression of certain AE9a-activated genes and suppresses AE9a's self-renewal capability. It has also been shown that AE9a recruits PRMT1 to AE9a activated gene promoters, which leads to increased H4 Arg3 methylation, H3 Lys9/14 acetylation, and transcription activated. Accordingly, in some embodiments, inhibitors of PRMT1, as described herein, are useful in treating cancers associated with AML1-ETO, e.g., leukemia. Thus, without being bound by any particular mechanism, the inhibition of PRMT1, e.g., by compounds described herein, is beneficial in the treatment of cancer.

[00254] In some embodiments, compounds provided herein are effective in treating cancer through the inhibition of PRMT3. In one example, the DAL1 tumor suppressor protein has been shown to interact with PRMT3 and inhibits its methyltransferase activity (Singh *et al.*, *Oncogene* 2004 23, 7761–7771). Epigenetic downregulation of DAL1 has been reported in several cancers (e.g., meningiomas and breast cancer), thus PRMT3 is expected to display increased activity, and cancers that display DAL1 silencing may, in some aspects, be good targets for PRMT3 inhibitors, e.g., those described herein. Thus, without being bound by any particular mechanism, the inhibition of PRMT3, e.g., by compounds described herein, is beneficial in the treatment of cancer.

[00255] In some embodiments, compounds provided herein are effective in treating cancer through the inhibition of PRMT4, also known as CARM1. For example, PRMT4 levels have been shown to be elevated in castration-resistant prostate cancer (CRPC), as well as in aggressive breast tumors (Hong *et al.*, *Cancer* 2004 101, 83–89; Majumder *et al.*, *Prostate* 2006 66, 1292–1301). Thus, in some embodiments, inhibitors of PRMT4, as described herein, are useful in treating cancers associated with PRMT4 overexpression. PRMT4 has also been shown to affect ER α -dependent breast cancer cell differentiation and proliferation (Al-Dhaheri *et al.*, *Cancer Res.* 2011 71, 2118–2128), thus in some aspects PRMT4 inhibitors, as described herein, are useful in treating ER α -dependent breast cancer by inhibiting cell differentiation and proliferation. In another example, PRMT4 has been shown to be recruited to the promoter of E2F1 (which encodes a cell cycle regulator) as a transcriptional co-activator (Fietze *et al.*, *Cancer Res.* 2008 68, 301–306). Thus, PRMT4-mediated upregulation of E2F1 expression may contribute to cancer progression and chemoresistance as increased abundance of E2F1 triggers invasion and metastasis by activating growth receptor signaling pathways, which in turn promote an antiapoptotic tumor environment (Engelmann and Pützer, *Cancer Res* 2012 72; 571). Accordingly, in some embodiments, the inhibition of PRMT4, e.g., by compounds provided herein, is useful in treating cancers associated with E2F1 upregulation. Thus, without being bound by any particular mechanism, the inhibition of PRMT4, e.g., by compounds described herein, is beneficial in the treatment of cancer.

[00256] In some embodiments, compounds provided herein are effective in treating cancer through the inhibition of PRMT6. For example, PRMT6 has been reported to be overexpressed in a number of cancers, e.g., bladder and lung cancer (Yoshimatsu *et al.*, *Int. J. Cancer* 2011 128, 562–573). Thus, in some embodiments, the inhibition of PRMT6, by

compounds provided herein, is useful in treating cancers associated with PRMT6 overexpression. In some aspects, PRMT6 is primarily thought to function as a transcriptional repressor, although it has also been reported that PRMT6 functions as a co-activator of nuclear receptors. For example, as a transcriptional repressor, PRMT6 suppresses the expression of thrombospondin 1 (TSP1; also known as THBS1; a potent natural inhibitor of angiogenesis and endothelial cell migration) and p21 (a natural inhibitor of cyclin dependent kinase), thereby contributing to cancer development and progression (Michaud-Levesque and Richard, *J. Biol. Chem.* 2009 284, 21338–21346; Kleinschmidt et al., *PLoS ONE* 2012 7, e41446). Accordingly, in some embodiments, the inhibition of PRMT6, by compounds provided herein, is useful in treating cancer by preventing the repression of THBS1 and/or p21. Thus, without being bound by any particular mechanism, the inhibition of PRMT6, e.g., by compounds described herein, is beneficial in the treatment of cancer.

[00257] In some embodiments, compounds provided herein are effective in treating cancer through the inhibition of PRMT8. For example, deep-sequencing efforts of cancer genomes (e.g., COSMIC) have revealed that of all the PRMTs, PRMT8 is reported to be the most mutated. Of 106 sequenced genomes, 15 carry mutations in the PRMT8 coding region, and nine of these result in an amino acid change (Forbes *et al.*, *Nucleic Acids Res.* 2011 39, D945–D950). Because of its high rate of mutation in cancer, PRMT8 is thought to contribute to the initiation or progression of cancer. Thus, without being bound by any particular mechanism, the inhibition of PRMT8, e.g., by compounds described herein, is beneficial in the treatment of cancer.

[00258] 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 adenocarcinoma), Ewing sarcoma, eye cancer

(*e.g.*, intraocular melanoma, retinoblastoma), familial 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 (*e.g.*, “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 fungoides, 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 neuroendocrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, 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).

[00259] In some embodiments, a compound provided herein is useful in treating diseases associated with increased levels of circulating asymmetric dimethylarginine (aDMA), *e.g.*, cardiovascular disease, diabetes, kidney failure, renal disease, pulmonary disease, etc. Circulating aDMA is produced by the proteolysis of asymmetrically dimethylated proteins. PRMTs which mediate aDMA methylation include, *e.g.*, PRMT1, PRMT3, PRMT4, PRMT6, and PRMT8. aDMA levels are directly involved in various diseases as aDMA is an endogenous competitive inhibitor of nitric oxide synthase (NOS), thereby reducing the production of nitric oxide (NO) (Vallance *et al.*, *J. Cardiovasc. Pharmacol.* 1992 20(Suppl. 12):S60–2). NO functions as a potent vasodilator in endothelial vessels, and as such inhibiting its production has major consequences on the cardiovascular system. For example, since PRMT1 is a major enzyme that generates aDMA, the dysregulation of its activity is likely to regulate cardiovascular diseases (Boger *et al.*, *Ann. Med.* 2006 38:126–36), and other pathophysiological conditions such as diabetes mellitus (Sydow *et al.*, *Vasc. Med.* 2005 10(Suppl. 1):S35–43), kidney failure (Vallance *et al.*, *Lancet* 1992 339:572–5), and chronic pulmonary diseases (Zakrzewicz *et al.*, *BMC Pulm. Med.* 2009 9:5). Additionally, it has been demonstrated that the expression of PRMT1 and PRMT3 are increased in coronary heart disease (Chen *et al.*, *Basic Res. Cardiol.* 2006 101:346–53). In another example, aDMA elevation is seen in patients with renal failure, due to impaired clearance of this metabolite from the circulation (Jacobi *et al.*, *Am. J. Nephrol.* 2008 28:224–37). Thus, circulating

aDMA levels is observed in many pathophysiological situations. Accordingly, without being bound by any particular mechanism, the inhibition of PRMTs, *e.g.*, by compounds described herein, results in the decrease of circulating aDMA, which is beneficial in the treatment of diseases associated with increased levels of circulating aDMA, *e.g.*, cardiovascular disease, diabetes, kidney failure, renal disease, pulmonary disease, etc. In certain embodiments, a compound described herein is useful for treating or preventing vascular diseases.

[00260] In some embodiments, a compound provided herein is useful in treating metabolic disorders. For example, PRMT1 has been shown to enhance mRNA levels of FoxO1 target genes in gluconeogenesis, which results in increased hepatic glucose production, and knockdown of PRMT promotes inhibition of FoxO1 activity and thus inhibition of hepatic gluconeogenesis (Choi *et al.*, *Hepatology* 2012 56:1546-56). Additionally, genetic haploinsufficiency of *Prmt1* has been shown to reduce blood glucose levels in mouse models. Thus, without being bound by any particular mechanism, the inhibition of PRMT1, *e.g.*, by compounds described herein, is beneficial in the treating of metabolic disorders, such as diabetes. In some embodiments, a provided compound is useful in treating type I diabetes. In some embodiments, a provided compound is useful in treating type II diabetes.

[00261] In some embodiments, a compound provided herein is useful in treating muscular dystrophies. For example, PRMT1, as well as PRMT3 and PRMT6, methylate the nuclear poly(A)-binding protein (PABPN1) in a region located near its C-terminus (Perreault *et al.*, *J. Biol. Chem.* 2007 282:7552–62). This domain is involved in the aggregation of the PABPN1 protein, and abnormal aggregation of this protein is involved in the disease oculopharyngeal muscular dystrophy (Davies *et al.*, *Int. J. Biochem. Cell. Biol.* 2006 38:1457–62). Thus, without being bound by any particular mechanism, the inhibition of PRMTs, *e.g.*, by compounds described herein, is beneficial in the treatment of muscular dystrophies, *e.g.*, oculopharyngeal muscular dystrophy, by decreasing the amount of methylation of PABPN1, thereby decreasing the amount of PABPN1 aggregation.

[00262] CARM1 is also the most abundant PRMT expressed in skeletal muscle cells, and has been found to selectively control the pathways modulating glycogen metabolism, and associated AMPK (AMP-activated protein kinase) and p38 MAPK (mitogen-activated protein kinase) expression. See, *e.g.*, Wang *et al.*, *Biochem* (2012) 444:323-331. Thus, in some embodiments, inhibitors of CARM1, as described herein, are useful in treating metabolic disorders, *e.g.*, for example skeletal muscle metabolic disorders, *e.g.*, glycogen and glucose metabolic disorders. Exemplary skeletal muscle metabolic disorders include, but are not limited to, Acid Maltase Deficiency (Glycogenosis type 2; Pompe disease), Debrancher

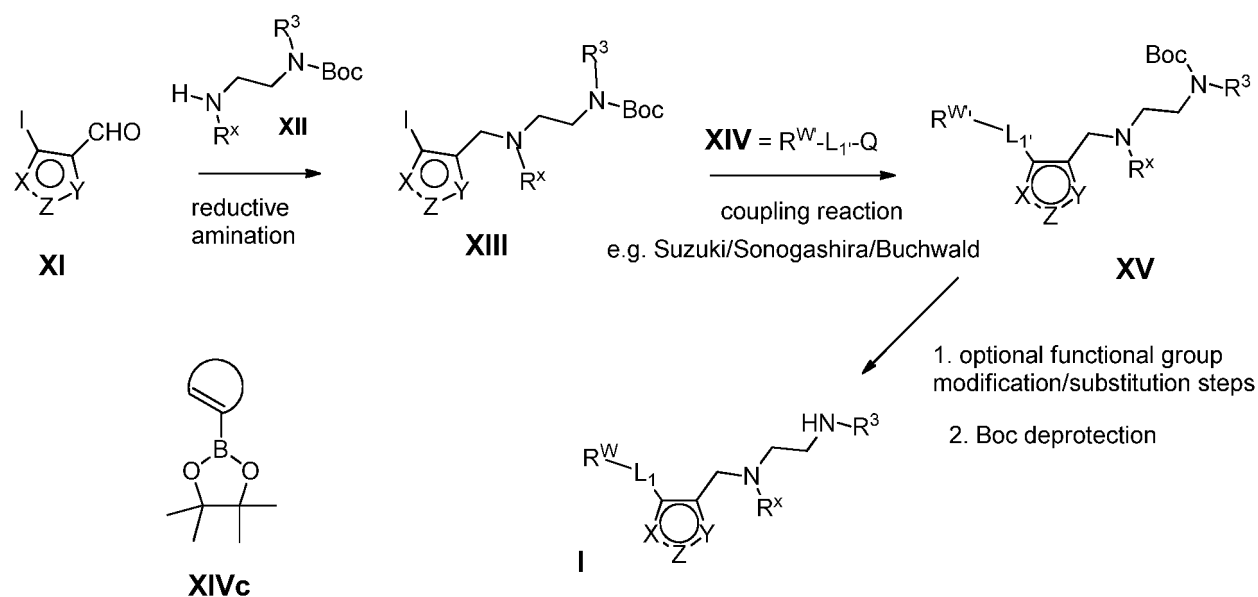
deficiency (Glycogenosis type 3), Phosphorylase deficiency (McArdle's; GSD 5), X-linked syndrome (GSD9D), Autosomal recessive syndrome (GSD9B), Tarui's disease (Glycogen storage disease VII; GSD 7), Phosphoglycerate Mutase deficiency (Glycogen storage disease X; GSDX; GSD 10), Lactate dehydrogenase A deficiency (GSD 11), Branching enzyme deficiency (GSD 4), Aldolase A (muscle) deficiency, β -Enolase deficiency, Triosephosphate isomerase (TIM) deficiency, Lafora's disease (Progressive myoclonic epilepsy 2), Glycogen storage disease (Muscle, Type 0, Phosphoglucomutase 1 Deficiency (GSD 14)), and Glycogenin Deficiency (GSD 15).

[00263] In some embodiments, a compound provided herein is useful in treating autoimmune disease. For example, several lines of evidence strongly suggest that PRMT inhibitors may be valuable for the treatment of autoimmune diseases, *e.g.*, rheumatoid arthritis. PRMTs are known to modify and regulate several critical immunomodulatory proteins. For example, post-translational modifications (*e.g.*, arginine methylation), within T cell receptor signaling cascades allow T lymphocytes to initiate a rapid and appropriate immune response to pathogens. Co-engagement of the CD28 costimulatory receptor with the T cell receptor elevates PRMT activity and cellular protein arginine methylation, including methylation of the guanine nucleotide exchange factor Vav1 (Blanchet *et al.*, *J. Exp. Med.* 2005 202:371–377). PRMT inhibitors are thus expected to diminish methylation of the guanine exchange factor Vav1, resulting in diminished IL-2 production. In agreement, siRNA directed against PRMT5 was shown to both inhibit NFAT-driven promoter activity and IL-2 secretion (Richard *et al.*, *Biochem J.* 2005 388:379–386). In another example, PRMT1 is known to cooperate with PRMT4 to enhance NF κ B p65-driven transcription and facilitate the transcription of p65 target genes like TNF α (Covic *et al.*, *Embo. J.* 2005 24:85–96). Thus, in some embodiments, PRMT1 and/or PRMT4 inhibitors, *e.g.*, those described herein, are useful in treating autoimmune disease by decreasing the transcription of p65 target genes like TNF α . These examples demonstrate an important role for arginine methylation in inflammation. Thus, without being bound by any particular mechanism, the inhibition of PRMTs, *e.g.*, by compounds described herein, is beneficial in the treatment of autoimmune diseases.

[00264] In some embodiments, a compound provided herein is useful in treating neurological disorders, such as amyotrophic lateral sclerosis (ALS). For example, a gene involved in ALS, TLS/FUS, often contains mutated arginines in certain familial forms of this disease (Kwiatkowski *et al.*, *Science* 2009 323:1205–8). These mutants are retained in the cytoplasm, which is similar to reports documenting the role arginine methylation plays in

nuclear-cytoplasmic shuffling (Shen *et al.*, *Genes Dev.* 1998 12:679–91). This implicates PRMT, e.g., PRMT1, function in this disease, as it was demonstrated that TLS/FUS is methylated on at least 20 arginine residues (Rappsilber *et al.*, *Anal. Chem.* 2003 75:3107–14). Thus, in some embodiments, the inhibition of PRMTs, e.g., by compounds provided herein, are useful in treating ALS by decreasing the amount of TLS/FUS arginine methylation.

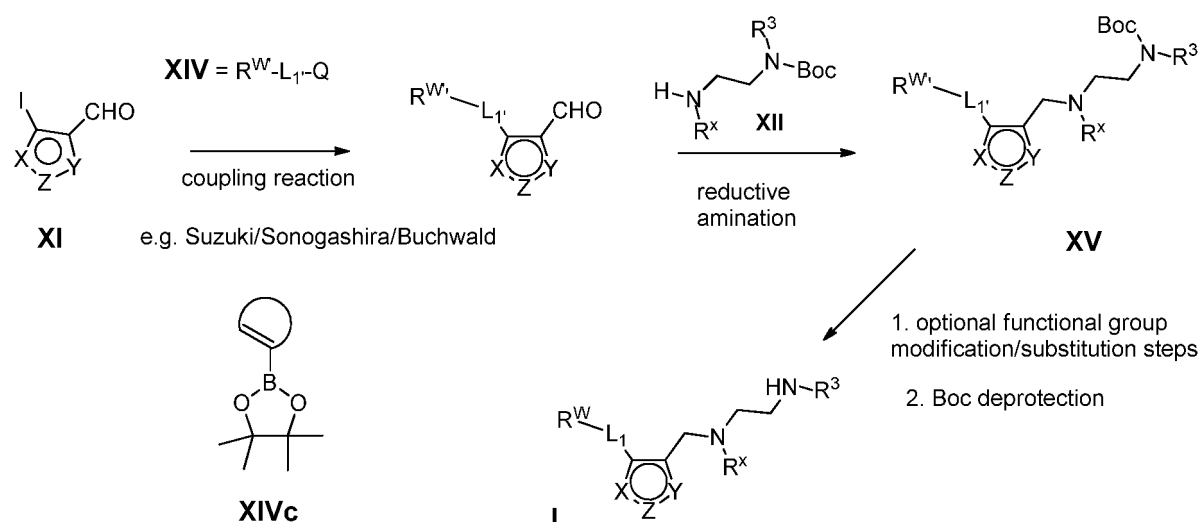
Scheme 1



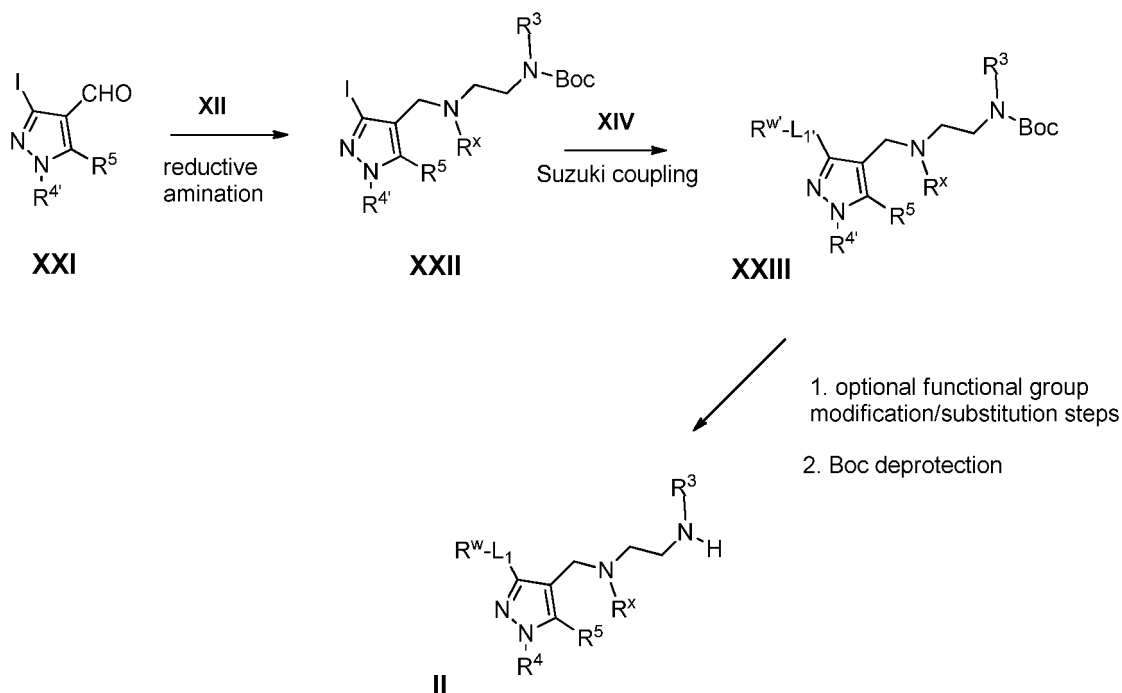
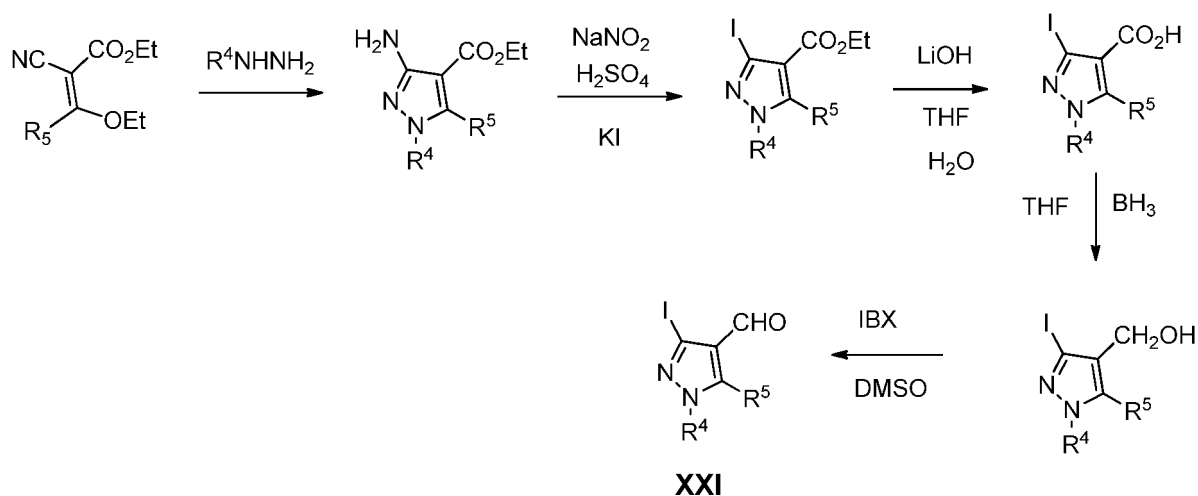
[00265] Scheme 1 shows an exemplary general synthesis route to pyrazole compounds of formula I, wherein R^W is either the same as R^W or is precursor of R^W and L₁' is either the same as L₁ or is a precursor of L₁ and R^W, L₁, R^x, R³, X, Y and Z are as defined above. In the first step iodopyrazole carboxaldehydes of general formula XI are allowed to react with mono-Boc protected ethylenediamines XII under reductive amination conditions (e.g. sodium cyanoborohydride and catalytic acid such as acetic acid) in an appropriate solvent such as methanol to give intermediates of general formula XIII. In certain embodiments, Sonagashira reaction of intermediates of general formula XIII with boronic acids or boronic esters of general formula XIV in which L₁' is an acetylene linker and Q is a boronic acid or boronic ester group in the presence of a palladium catalyst (e.g. PdCl₂(dppf)) and a base (e.g. potassium carbonate) in an organic solvent (e.g. toluene) at elevated temperature yields intermediates of general formula XV-a in which L₁' is an acetylene linker. Boc deprotection of intermediates of general formula XV-a gives acetylene compounds of formula VI-a. In certain embodiments, Suzuki reaction of intermediates of general formula XIII with boronic

acids or boronic esters of general formula XIV in which L_1 is a *trans*-olefin linker and Q is a boronic acid or boronic ester group in the presence of a palladium catalyst (e.g. $PdCl_2(dppf)$) and a base (e.g. potassium carbonate) in an organic solvent (e.g. toluene) at elevated temperature yields intermediates of general formula XV-b in which L_1 is an olefin linker. Boc deprotection of intermediates of general formula XV-b gives olefin compounds of formula VI-b. In certain embodiments, Suzuki reaction of intermediates of general formula XIII with pinacol boranes of general formula XIVc in which L_1 is bond, R^W is a heterocycloalkenyl or cycloalkenyl group and Q is a pinacol borane group yields intermediates of general formula XV-c in which L_1 is bond and R^W is a heterocycloalkenyl or cycloalkenyl group. In certain embodiments, compounds of formula I wherein L_1 is bond and R^W is a heterocyclyl or carbocyclyl group can be prepared by hydrogenation of intermediates of formula XV-c followed by Boc deprotection. In certain embodiments, compounds of formula I where L_1 is -O- can be synthesized from intermediates of general formula XIII by Goldberg reaction with alcohols of formula $R^W OH$ followed by Boc deprotection. In certain embodiments, compounds of formula I where L_1 is -N(R^B)- can be synthesized from intermediates of general formula XIII by palladium catalyzed Buchwald coupling reaction conditions with amines of formula $R^W N(R^B)H$ followed by Boc deprotection. In certain embodiments, compounds of formula I where L_1 is -C(=O)NR^B- can be synthesized from intermediates of general formula XIII under known copper catalyzed coupling reaction conditions of amides with aryl iodides using copper iodide an amine ligand and a base with amides of formula $R^W C(=O)NHR^B$ followed by Boc deprotection.

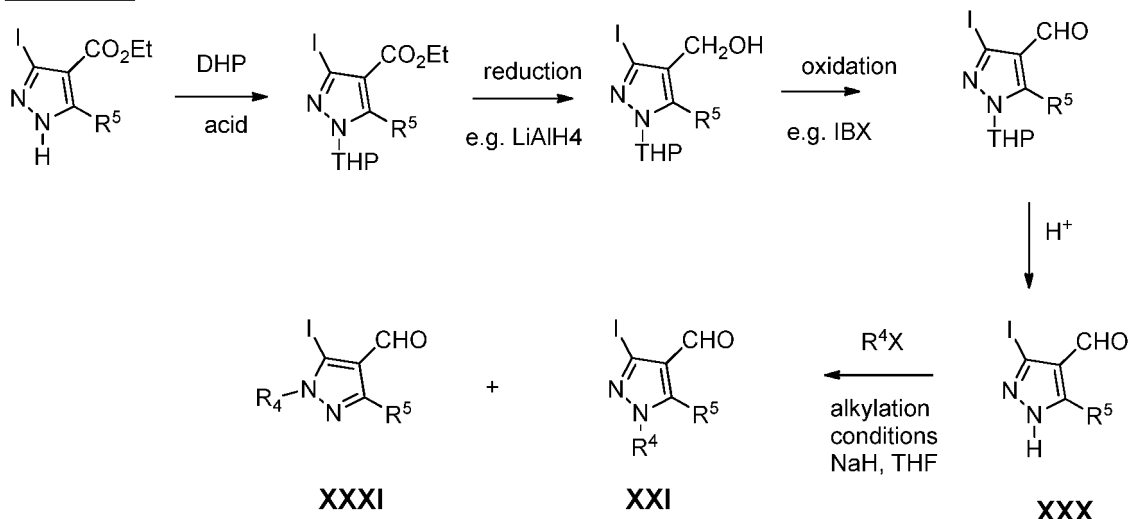
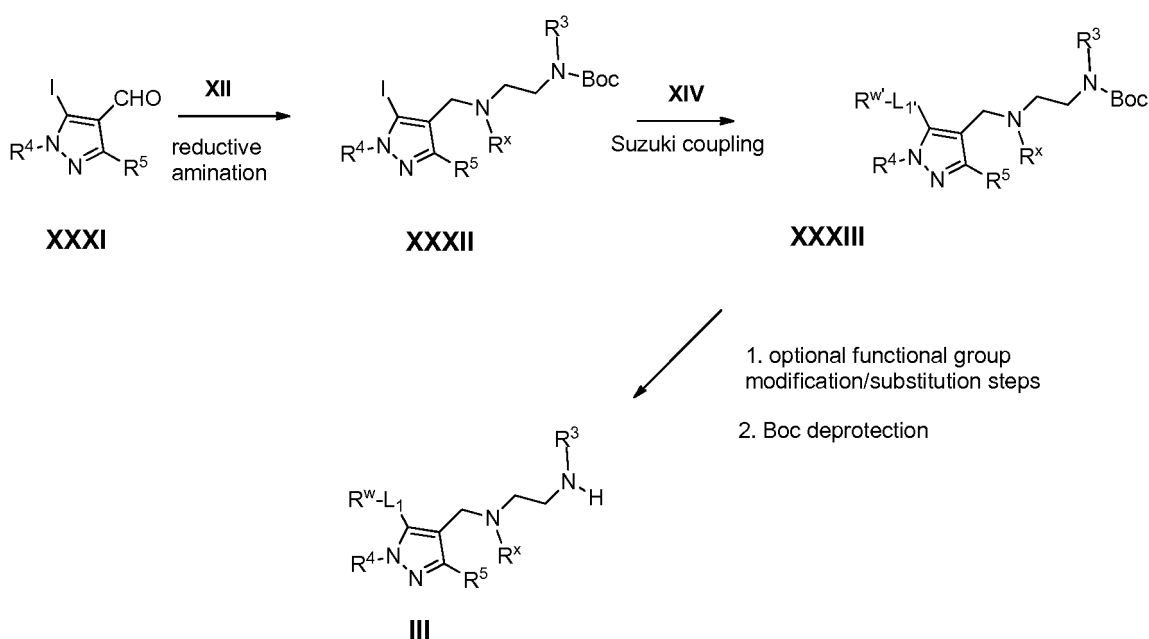
[00266] Scheme 1.1 shows an alternative general synthesis route to pyrazole compounds of Formula (I), that involves reversal in the order of the first two steps of the reaction sequence detailed for Scheme 1.0. Thus, in the first step iodopyrazole carboxaldehydes of general formula XI are coupled with compounds or reagents of general formula XIV (e.g. via Suzuki reaction with pinacol boranes of general formula XIVc in which L_1 is bond, R^W is a heterocycloalkenyl or cycloalkenyl group and Q is a pinacol borane group) and in a second step the corresponding reductive amination reaction to yield common intermediates of general formula XV is a carried out.

Scheme 1.1

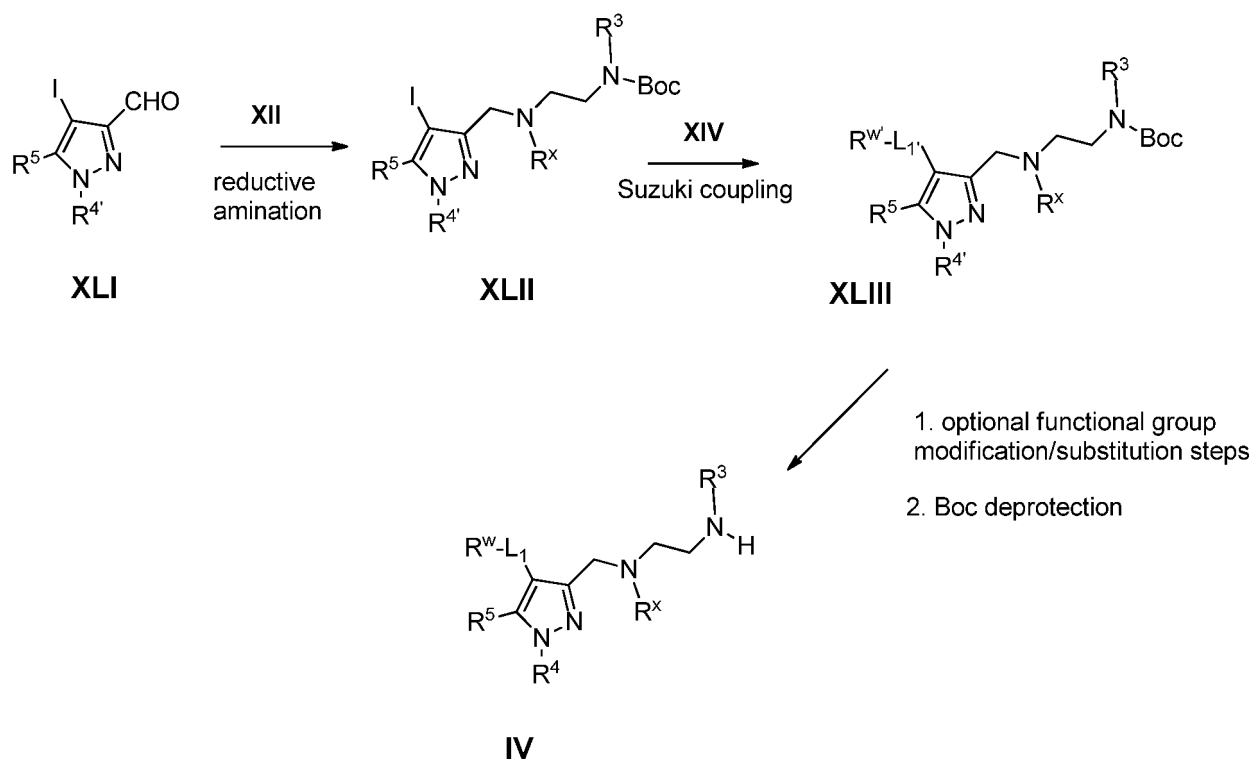
[00267] In certain embodiments, iodopyrazole carboxaldehydes of general formula XI may be prepared from suitable known pyrazole compound intermediates by established synthetic chemistry methods. Standard methods include direct iodination of a pyrazole 3-carboxylate and Sandmeyer reaction of a 3-amino pyrazole 4-carboxylate. In certain embodiments, iodopyrazole carboxaldehydes can be derived from iodopyrazole carboxylates by reduction to a hydroxymethyl group followed by oxidation to carboxaldehyde. In certain embodiments, mono-Boc protected ethylenediamines XII can be synthesized by standard methods known in the literature for derivatizing or preparing ethylenediamines. For example intermediates of formula XII may be prepared by treatment of the corresponding unprotected diamine precursors with Boc_2O and purifying the mixture of mono and dibocylated products. In certain embodiments, pyrazole compounds of general formula II can be prepared from iodopyrazole carboxaldehydes of general formula XXI as depicted in Scheme 2. In certain embodiments where R^4 is hydrogen compounds of general formula II are equivalent to compounds of general formula III which are tautomers. In certain embodiments, R^4 is a protecting group such as tetrahydropyranyl (THP) which maybe cleaved to hydrogen under acidic conditions in the final Boc-deprotection step. In certain embodiments, iodopyrazole carboxaldehydes of general formula XXI can be prepared as depicted in Scheme 3.

Scheme 2**Scheme 3**

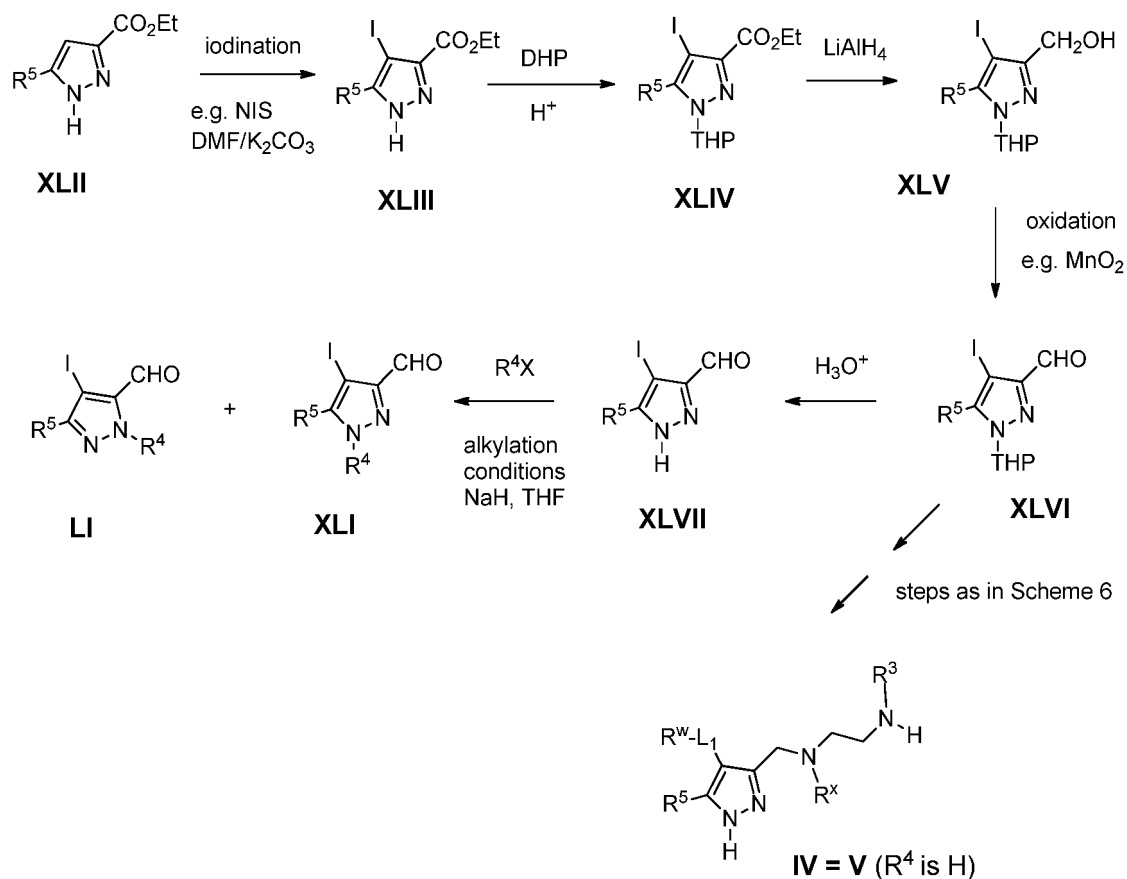
[00268] In certain embodiments, iodopyrazole carboxaldehydes of general formula XXI can be prepared as depicted in Scheme 4 which also provides iodopyrazole carboxyaldehydes of general formula XXXI. In certain embodiments, alkylation of intermediates of general formula XXX gives a mixture of pyrazole nitrogen alkylated isomers which are separated by chromatography to give pure isomers XXI and XXXI. In certain embodiments, pyrazole compounds of general formula III can be prepared from iodopyrazole carboxaldehydes of general formula XXXI as depicted in Scheme 5.

Scheme 4**Scheme 5**

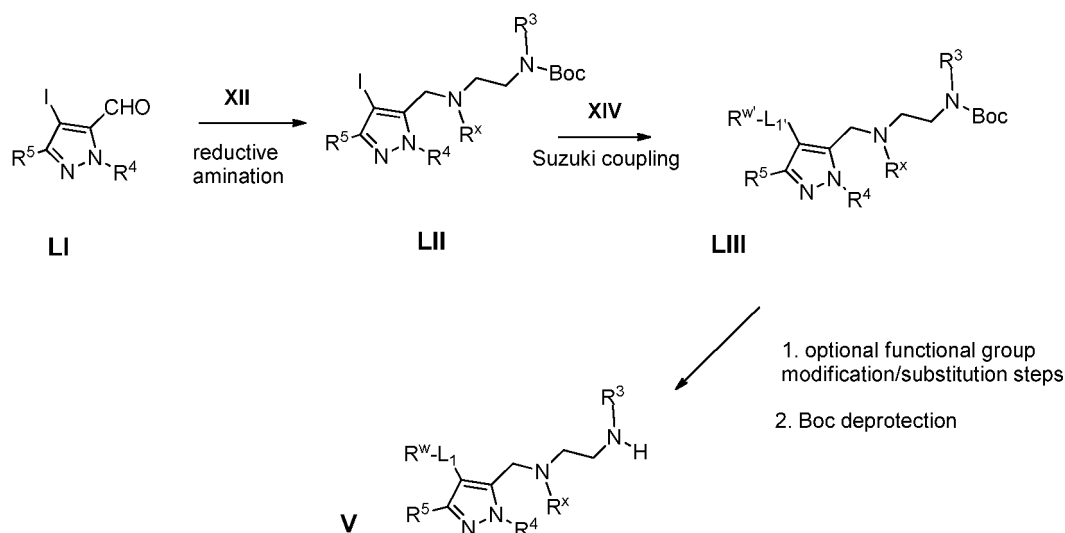
[00269] In certain embodiments, pyrazole compounds of general formula IV can be prepared from iodopyrazole carboxaldehydes of general formula XLI as depicted in Scheme 6. In certain embodiments where R^4 is hydrogen compounds of general formula IV are equivalent to compounds of general formula V which are tautomers. In certain embodiments where R^4 in compounds of formula IV is hydrogen, $R^{4'}$ in intermediate XLI may be a selected protecting group such as tetrahydropyranyl (THP) which can be cleaved to hydrogen under acidic conditions in the final Boc-deprotection step.

Scheme 6

[00270] In certain embodiments, iodopyrazole carboxaldehydes of general formula XLI and LI can be prepared as depicted in Scheme 7. In certain embodiments, an R^4 group of iodopyrazole carboxaldehydes may be introduced by alkylation of intermediates of formula XLVII. This reaction can give a mixture of intermediate compounds of formulas XLI and LI which may be separated by chromatography. In certain embodiments, THP protected intermediates of formula XLVI can be used to prepare compounds of formula IV where $R^4 = H$ as also depicted in Scheme 7.

Scheme 7

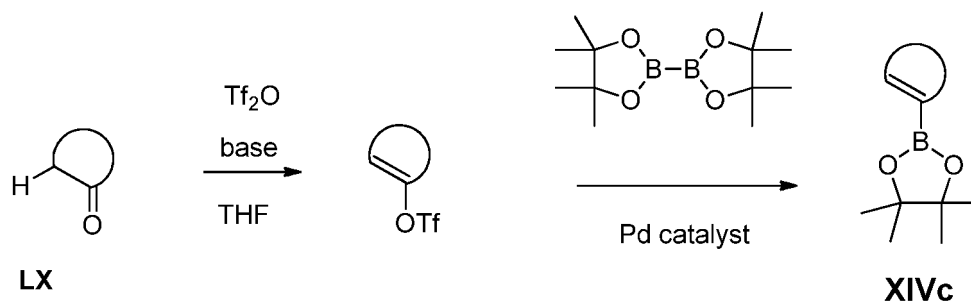
[00271] In certain embodiments, pyrazole compounds of general formula V can be prepared from iodopyrazole carboxaldehydes of general formula LI as depicted in Scheme 8.

Scheme 8

[00272] In certain embodiments, boronic acids or esters of general formula XIVa, XIVb and XIVc are commercially available. In certain embodiments, compounds of general formula XIVa, and XIVb can also be prepared from alkenyl bromides and terminal alkynes

using standard methods such as treatment with n-BuLi followed by trapping the intermediate lithium species with trimethylborate. In certain embodiments, compounds of general formula XIVc can be prepared from the corresponding cyclic ketones LX via intermediate enol triflates as depicted in Scheme 9.

Scheme 9



Examples

[00273] 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

[00274] General methods and experimental procedures for preparing and characterizing compounds of the present invention are set forth below. Wherever needed, reactions were heated using conventional hotplate apparatus or heating mantle or microwave irradiation equipment. Reactions were conducted with or without stirring, under atmospheric or elevated pressure in either open or closed vessels. Reaction progress was monitored using conventional techniques such as TLC, HPLC, UPLC, or LCMS using instrumentation and methods described below. Reactions were quenched and crude compounds isolated using conventional methods as described in the specific examples provided. Solvent removal was carried out with or without heating, under atmospheric or reduced pressure, using either a rotary or centrifugal evaporator.

Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates. Compound purity and mass confirmations were conducted using standard HPLC and / or UPLC and / or MS spectrometers and / or LCMS and / or GC equipment (*e.g.*, including, but not limited to the following instrumentation: Waters Alliance 2695 with 2996 PDA detector connected with ZQ detector and ESI source; Shimadzu LDMS-2020; Waters

Acquity H Class with PDA detector connected with SQ detector and ESI source; Agilent 1100 Series with PDA detector; Waters Alliance 2695 with 2998 PDA detector; AB SCIEX API 2000 with ESI source; Agilent 7890 GC). Exemplified compounds were dissolved in either MeOH or MeCN to a concentration of approximately 1 mg/mL and analyzed by injection of 0.5-10 μ L into an appropriate LCMS system using the methods provided in the following table:

Method	Column	Mobile Phase A	Mobile Phase B	Flow Rate (mL/min)	Gradient Profile	MS Heat Block Temp (°C)	MS Detector Voltage (kV)
A	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.2 minutes, then stop	250	1.5
B	Gemini-NX 3 μ m C18 110A	Water / 0.04% Ammonia	ACN	1	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	200	0.75
C	Shim-pack XR-ODS 1.6 μ m 2.0x50mm	Water/0.05% FA	ACN/0.05% FA	1	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.85
D	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.95
E	Waters Xselect C18 3.5 μ m 3.0x50mm	Water/0.05% FA	ACN/0.05% FA	0.9	5% to 100% B in 2.0 minutes, 100% B for 1.2 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.5
F	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 80% B in 3.25 minutes, 80% B for 1.35 minutes, 80% to 5% B in 0.3 minutes, then stop	200	0.95
G	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 70% B in 2.50 minutes, 70% B for 0.70 minutes, 70% to 5% B in 0.1 minutes, then stop	200	0.95
H	Shim-pack XR-ODS 2.2 μ m 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 2.20 minutes, 100% B for 1.00 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.95

Method	Column	Mobile Phase A	Mobile Phase B	Flow Rate (mL/min)	Gradient Profile	MS Heat Block Temp (°C)	MS Detector Voltage (kV)
I	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 1.20 minutes, 100% B for 1.00 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.95
J	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 70% B in 3.20 minutes, 70% B for 0.75 minutes, 70% to 5% B in 0.35 minutes, then stop	250	0.95
K	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 80% B in 3.00 minutes, 80% B for 0.8 minutes, 80% to 5% B in 0.1 minutes, then stop	250	1.5
L	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 3.00 minutes, 100% B for 0.8 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.5
M	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 2.20 minutes, 100% B for 1.00 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.5
N	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 80% B in 2.20 minutes, 80% B for 1.0 minutes, 80% to 5% B in 0.1 minutes, then stop	250	1.5
O	Zorbax Eclipse Plus C18 4.6x100mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 70% B in 8.00 minutes, 70% B for 2.0 minutes, then stop	250	1.5
P	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 65% B in 3.00 minutes, 65% B for 0.80 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.5
Q	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 60% B in 2.50 minutes, 60% B for 0.7 minutes, 60% to 5% B in 0.1 minutes, then stop	250	0.95
R	Shim-pack XR-ODS 2.2μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 50% B in 2.50 minutes, 50% B for 0.7 minutes, 50% to 5% B in 0.1 minutes, then stop	250	0.95
S	XBridge C18 3.5μm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 95% B in 2.20 minutes, 95% B for 1.00 minutes, 95% to 5% B in 0.1 minutes, then stop	250	0.9

Method	Column	Mobile Phase A	Mobile Phase B	Flow Rate (mL/min)	Gradient Profile	MS Heat Block Temp (°C)	MS Detector Voltage (kV)
T	Shim-pack XR-ODS 1.6µm 2.0x50mm	Water/0.05% FA	ACN/0.05% FA	0.7	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.85
U	Shim-pack XR-ODS 2.2µm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 40% B in 2.50 minutes, 40% B for 0.7 minutes, 40% to 5% B in 0.1 minutes, then stop	250	0.95
V	Shim-pack XR-ODS 2.2µm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 60% B in 4.20 minutes, 60% B for 1.0 minutes, 60% to 5% B in 0.1 minutes, then stop	200	1.05
W	Shim-pack XR-ODS 2.2µm 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 2.20 minutes, 100% B for 1.00 minutes, 100% to 5% B in 0.1 minutes, then stop	200	0.95
X	Shim-pack XR-ODS 1.6µm 2.0x50mm	Water/0.05% FA	ACN/0.05% FA	0.7	5% to 100% B in 2.0 minutes, 100% B for 1.1 minutes, 100% to 5% B in 0.1 minutes, then stop	200	0.85
Y	Ecliplis Plus C18 3.5µm 4.6x50mm	Water/0.05% TFA	ACN	1	5% to 100% B in 2.0 minutes, 100% B for 1.0 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1
Z	Ecliplis Plus C18 3.5µm 4.6x50mm	Water/10 mM ammonium carbonate	ACN / 5% water	1	5% to 100% B in 2.0 minutes, 100% B for 1.0 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.1
A1	Shim-pack XR-ODS 2.2µm 3.0x50mm	Water/0.05% TFA	ACN	1	5% to 100% B in 2.0 minutes, 100% B for 1.0 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1
A2	Ecliplis Plus C18 3.5µm 4.6x50mm	Water/10 mM ammonium acetate	ACN	1	5% to 100% B in 2.0 minutes, 100% B for 1.4 minutes, 100% to 5% B in 0.1 minutes, then stop	250	0.95
A3	Acquity BEH C18 1.7 µm 2.1 X 50 mm	Water / 5 mM ammonium acetate / 0.1% FA	ACN / 0.1% FA	0.55	5% B at 0.01 min up to 0.4 min, 35% B at 0.8 min, 55% B at 1.2 min, 100% B in 1.3 minutes, at 2.5 min up to 3.30 min, 5% B at 3.31 min up to 4.0 min, then stop		

Method	Column	Mobile Phase A	Mobile Phase B	Flow Rate (mL/min)	Gradient Profile	MS Heat Block Temp (°C)	MS Detector Voltage (kV)
A4	Shim-pack XR-ODS 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 30% B in 8.0 minutes, 30% B for 2.0 minutes, then stop	250	1.5
A5	Shim-pack XR-ODS 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 100% B in 2.2 minutes, 100% B for 1.0 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.5
A6	Atlantis HILIC 3.0x100mm	Water/0.05% TFA	ACN/0.05% TFA	0.8	95% to 60% B in 4.0 minutes, 60% B for 4.0 minutes, then stop	250	1.5
A7	Shim-pack XR-ODS 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% B for 0.5 minutes, 5% to 75% B at 2.2 minutes, 100% B for 1.0 minutes, 100% to 5% B in 0.1 minutes, then stop	250	1.5
A8	Zorbax SB-C18 5μm 4.6x150mm	Water/0.05% TFA	ACN/0.05% TFA	1.2	5% to 70% B in 10.0 minutes, 70% B for 5.0 minutes, then stop	250	1.05
A9	Shim-pack XR-ODS 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 40% B in 4.4 minutes, 40% B for 0.9 minutes, then stop	250	0.95
A10	Atlantis T3 3μm 4.6x100mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% to 50% B in 8.0 minutes, 50% B for 2.0 minutes, then stop	200	1.05
A11	Shim-pack XR-ODS 3.0x50mm	Water/0.05% TFA	ACN/0.05% TFA	1	5% B for 0.5 minutes, 5% to 100% B in 1.7 minutes, 100% B for 1.0 minute, 100% to 5% B in 0.1 minute, then stop	250	1.50

[00275] Compound structure confirmations were carried out using standard 300 or 400 MHz NMR spectrometers with NOe's conducted whenever necessary.

The following abbreviations are used herein:

Abbreviation

ACN
atm.

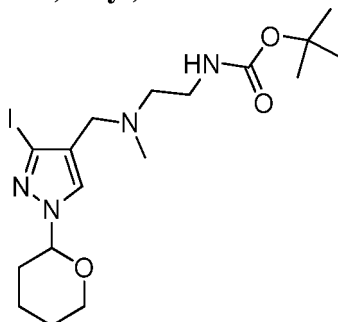
Meaning

acetonitrile
atmosphere

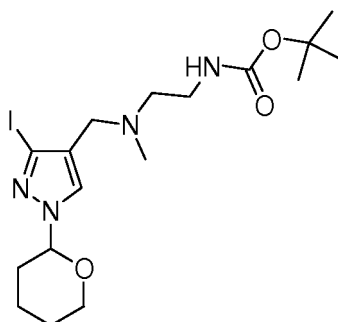
DCM	dichloromethane
DHP	dihydropyran
DIBAL	diisobutyl aluminum hydride
DIEA	diisopropyl ethylamine
DMF	dimethyl formamide
DMF-DMA	dimethyl formamide dimethyl acetal
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EA	ethyl acetate
ESI	electrospray ionization
EtOH	ethanol
FA	formic acid
GC	gas chromatography
h	hour
Hex	hexanes
HMDS	hexamethyl disilazide
HPLC	high performance liquid chromatography
IPA	isopropanol
LCMS	liquid chromatography / mass spectrometry
MeOH	methanol
min	minutes
NBS	<i>N</i> -bromo succinimide
NCS	<i>N</i> -chloro succinimide
NIS	<i>N</i> -iodo succinimide
NMR	nuclear magnetic resonance
NOe	nuclear Overhauser effect
Prep.	preparative
PTSA	<i>para</i> -toluene sulfonic acid
R _f	retardation factor
rt	room temperature
RT	retention time
sat.	saturated
SGC	silica gel chromatography
TBAF	tetrabutyl ammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography
LiHMDS	lithium hexamethyldisilazide
TMAD	tetramethyl azocarboxamide

Intermediate Synthesis

Synthesis of intermediate *tert*-butyl (2-(((3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)carbamate

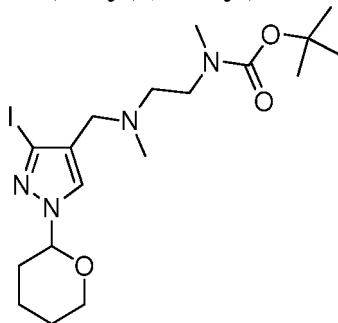


Step 1: *tert*-butyl (2-(((3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)carbamate

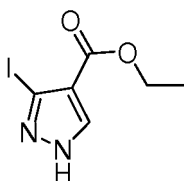


[00276] A mixture of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde (3.2 g, 10.45 mmol, 1.00 equiv), *tert*-butyl *N*-[2-(methylamino)ethyl]carbamate (2.2 g, 12.63 mmol, 1.21 equiv) and NaBH(OAc)₃ (6.65 g, 31.38 mmol, 3.00 equiv) in dichloroethane (30 mL) was stirred for 2 h at room temperature. The reaction was quenched with 50 mL of saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with 3x200 mL of dichloromethane. The combined organic layers was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with 30-100% ethyl acetate in petroleum ether to give 4.05 g (83%) of *tert*-butyl (2-(((3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)carbamate as a light yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.48 (s, 1H), 5.35-5.30 (m, 1H), 4.13-4.03 (m, 1H), 3.71-3.63 (m, 1H), 3.36 (s, 2H), 3.26-3.25 (m, 2H), 2.52-2.49 (m, 2H), 2.21 (s, 3H), 2.09-2.01 (m, 3H), 1.68-1.58 (m, 3H), 1.44 (s, 9H) ppm. LCMS (method C, ESI): RT = 0.58 min, m/z = 465.0 [M+H]⁺.

Synthesis of intermediate *tert*-butyl (2-(((3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate

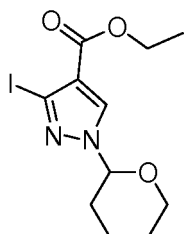


Step 1: Ethyl 3-iodo-1*H*-pyrazole-4-carboxylate



[00277] To a stirred solution of ethyl 3-amino-1*H*-pyrazole-4-carboxylate (10 g, 64.45 mmol, 1.00 equiv) in 50% sulfuric acid (90 mL) at 5°C was added dropwise a solution of NaNO₂ (7.4 g, 107.25 mmol, 1.66 equiv) in water (15 mL). The reaction was stirred at 5°C for another 30 min. A solution of KI (32.1 g, 193.37 mmol, 3.00 equiv) in water (15 mL) was added dropwise at 5°C. The reaction was allowed to stir at 5°C for 1 h and then quenched by the addition of 50 mL of water. The precipitate was collected by filtration and then dissolved in 150 mL of ethyl acetate. The resulting solution was washed sequentially with 1x100 mL of saturated Na₂SO₃ solution, 1x100 mL of saturated sodium bicarbonate solution and 1x100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give 10.8 g (63%) of ethyl 3-iodo-1*H*-pyrazole-4-carboxylate as a yellow solid. ¹H-NMR (300 MHz, CDCl₃): δ 8.18 (s, 1H), 4.38-4.29 (m, 2H), 1.41-1.33 (m, 3H) ppm. LCMS (method B, ESI): RT = 1.36 min, m/z = 267.0 [M+H]⁺.

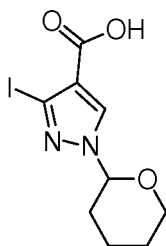
Step 2: Ethyl 3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-4-carboxylate



[00278] A solution of ethyl 3-iodo-1*H*-pyrazole-4-carboxylate (10.8 g, 40.60 mmol, 1.00 equiv), 3,4-dihydro-2*H*-pyran (10 g, 118.88 mmol, 2.93 equiv) and TsOH (780 mg, 4.53 mmol, 0.11 equiv) in THF (100 mL) was stirred for 2 h at 60°C. The reaction mixture was cooled to room temperature and quenched by the addition of 100 mL of saturated sodium

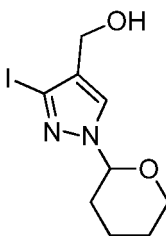
bicarbonate solution. The resulting solution was extracted with 2x80 mL of dichloromethane. The combined organic layers was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:20) to give 13 g (91%) of ethyl 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carboxylate as a yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ 8.04 (s, 1H), 5.40-5.38 (m, 1H), 4.34-4.29 (m, 2H), 4.08-4.05 (m, 1H), 3.73-3.70 (m, 1H), 2.07-1.98 (m, 3H), 1.69-1.62 (m, 3H), 1.39-1.32 (m, 3H) ppm. LCMS (method C, ESI): RT = 1.53 min, m/z = 351.0 [M+H]⁺.

Step 3: 3-Iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-4-carboxylic acid



[00279] To a solution of ethyl 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carboxylate (85 g, 242.75 mmol, 1.00 equiv) in THF (300 mL) and methanol (300 mL) was added a solution of LiOH (17.5 g, 730.69 mmol, 3.01 equiv) in water (400 mL). The resulting solution was stirred at room temperature overnight and then concentrated under vacuum to remove the organic solvent. The resulting solution was diluted with 400 mL of H₂O and then acidified to pH 6.0 with 1M hydrochloric acid. The mixture was extracted with 3x800 mL of dichloromethane. The combined organic layers was washed with 3x1000 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum to give 75 g (96%) of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carboxylic acid as an off-white solid. LCMS (method D, ESI): RT = 1.23 min, m/z = 323.0 [M+H]⁺.

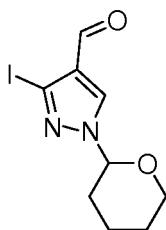
Step 4: (3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methanol



[00280] To a solution of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carboxylic acid (28 g, 86.93 mmol, 1.00 equiv) in anhydrous THF (300 mL) maintained under nitrogen at 5°C was added a 1M solution of BH₃ in THF (300 mL) dropwise with stirring. The reaction was stirred overnight at room temperature and then quenched by the addition of 300 mL of saturated

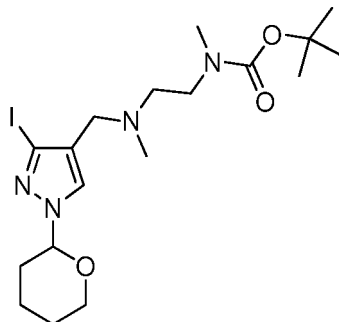
NH₄Cl solution. The resulting mixture was extracted with 3x1000 mL of dichloromethane. The combined organic layers was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:1) to give 12.67 g (47%) of (3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methanol as a white solid. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.73 (s, 1H), 5.37-5.34 (m, 1H), 4.92 (s, 1H), 4.20 (d, *J* = 3.6 Hz, 2H), 3.89-3.88 (m, 1H), 3.65-3.57 (m, 1H), 2.09-2.00 (m, 1H), 1.99-1.90 (m, 2H), 1.69-1.61 (m, 1H), 1.49-1.46 (m, 2H) ppm. LCMS (method A, ESI): RT = 1.16 min, *m/z* = 309.0 [M+H]⁺.

Step 5: 3-Iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-4-carbaldehyde



[00281] Into a 250-mL 3-necked round-bottom flask purged and. To a stirred solution of oxalyl chloride (18.576 g, 146.35 mmol, 3.01 equiv) in anhydrous dichloromethane (300 mL) maintained under nitrogen at -78°C was added DMSO (15.138 g, 193.75 mmol, 3.98 equiv) dropwise. The reaction mixture was stirred at -65°C for 30 min. A solution of (3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methanol (15.0 g, 48.68 mmol, 1.00 equiv) in dichloromethane (100 mL) was then added dropwise at -65°C and the reaction was stirred for another 60 min at -65°C. Triethylamine (40.6 mL) was added dropwise at -65°C and the reaction was stirred for 30 min at -65°C. The reaction was warmed to 0°C then quenched by the addition of 100 mL of saturated NH₄Cl solution. The resulting mixture was extracted with 3x400 mL of dichloromethane. The combined organic layers was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:20) to give 13.48 g (90%) of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde as a golden oil. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 9.69 (s, 1H), 8.57 (s, 1H), 5.49 (dd, *J* = 2.7 Hz, 9.9 Hz, 1H), 3.95-3.91 (m, 1H), 3.68-3.62 (m, 1H), 2.11-2.01 (m, 3H), 1.69-1.62 (m, 3H) ppm. LCMS (method A, ESI): RT = 1.35 min, *m/z* = 307.0 [M+H]⁺.

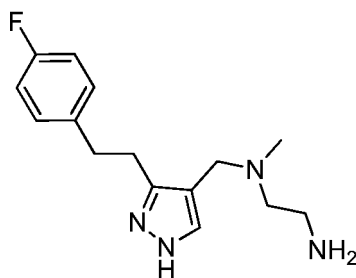
Step 6: *tert*-Butyl (2-(((3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate



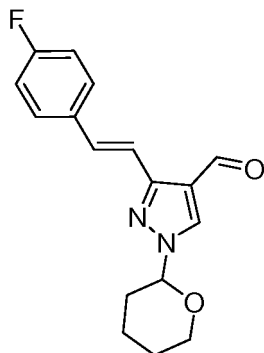
[00282] A mixture of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde (21.5 g, 70.24 mmol, 1.00 equiv), *tert*-butyl *N*-methyl-*N*-(2-(methylamino)ethyl)carbamate (20 g, 106.23 mmol, 1.51 equiv) and NaBH(OAc)₃ (29.8 g, 137.98 mmol, 1.96 equiv) in dichloroethane (300 mL) was stirred for 1 h at room temperature. The reaction was diluted with 300 mL of dichloromethane and then washed with 3x300 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with 0-7% methanol in dichloromethane to give 31 g (92%) of *tert*-butyl (2-(((3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)(methyl)carbamate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.62 (s, 1H), 5.34-5.30 (m, 1H), 4.06-4.02 (m, 1H), 3.68-3.62 (m, 1H), 3.42-3.38 (m, 4H), 2.85 (s, 4H), 2.62-2.53 (m, 2H), 2.47-2.46 (m, 2H), 2.13-1.97 (m, 3H), 1.74-1.69 (m, 3H), 1.46 (s, 9H) ppm. LCMS (method A, ESI): RT = 1.17 min, m/z = 479.0 [M+H]⁺.

Compound 23

***N*¹-((3-(4-fluorophenethyl)-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine**

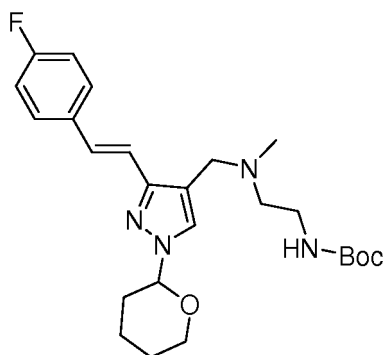


Step 1: (*R/S*) (*E*)-3-(4-fluorostyryl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-4-carbaldehyde



[00283] A mixture of (*R/S*) 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde (800 mg, 2.61 mmol, 1.00 equiv), 1-ethenyl-4-fluorobenzene (957 mg, 7.84 mmol, 3.00 equiv), Pd(PPh₃)₄ (302 mg, 0.26 mmol, 0.10 equiv) and potassium carbonate (1082 mg, 7.83 mmol, 3.00 equiv) in *N,N*-dimethylformamide (10 mL) was stirred under nitrogen at 100°C overnight. The reaction was cooled to room temperature then quenched by the addition of 100 mL of water. The resulting mixture was extracted with 3x100 mL of ethyl acetate. The combined organic layers was washed with 3x100 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with 1-15% ethyl acetate in petroleum ether to give 220 mg (28%) of (*E*)-3-(4-fluorostyryl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-4-carbaldehyde as a yellow oil. LCMS (method D, ESI): RT = 1.49 min, *m/z* = 301.0 [M+H]⁺.

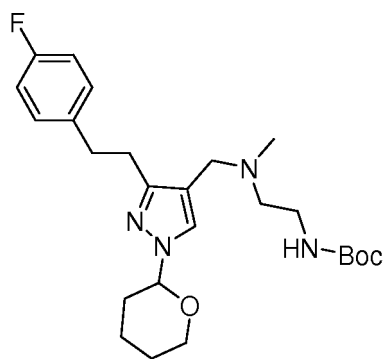
Step 2: (*R/S*) (*E*)-*tert*-butyl 2-(((3-(4-fluorostyryl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl]carbamate



[00284] To a solution of (*R/S*) (*E*)-3-(4-fluorostyryl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-4-carbaldehyde (220 mg, 0.73 mmol, 1.00 equiv) and *tert*-butyl *N*-[2-(methylamino)ethyl]carbamate (153 mg, 0.88 mmol, 1.20 equiv) in 1,2-dichloroethane (10 mL) was added NaBH(OAc)₃ (311 mg, 1.44 mmol, 1.97 equiv). The reaction was stirred at room temperature for 2 h and then diluted with 100 mL of ethyl acetate. The resulting

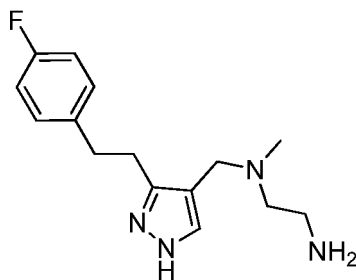
mixture was washed with 3x100 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with 20-60% ethyl acetate in petroleum ether to give 220 mg (65%) of (*R/S*) (*E*)-*tert*-butyl 2-(((3-(4-fluorostyryl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 8.20 (br s, 1H), 7.51-7.36 (m, 3H), 7.05 (t, *J* = 8.7Hz, 2H), 6.90 (d, *J* = 15.9Hz, 1H), 5.38 (t, *J* = 2.7Hz, 1H), 4.12 (s, 2H), 3.75-3.68 (m, 1H), 3.51 (br s, 2H), 2.98 (br s, 1H), 2.60 (br s, 2H), 2.19-2.08 (m, 6H), 1.72-1.62 (m, 3H) ppm. LCMS (method D, ESI): RT = 1.31min, *m/z* = 459.2 [M+H]⁺.

Step 3: (*R/S*) *tert*-butyl 2-(((3-(4-fluorophenethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate



[00285] A mixture of (*R/S*) (*E*)-*tert*-butyl 2-(((3-(4-fluorostyryl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate (220 mg, 0.48 mmol, 1.00 equiv) and Raney Ni (20 mg) in methanol (50 mL) was stirred under hydrogen at room temperature for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified on a silica gel column eluted with 1-7% of ethyl acetate in petroleum ether to yield 150 mg (68%) of (*R/S*) *tert*-butyl 2-(((3-(4-fluorophenethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.11 (t, *J* = 7.8Hz, 2H), 6.94 (t, *J* = 8.7Hz, 2H), 5.31 (d, *J* = 6.6Hz, 1H), 4.08 (d, *J* = 11.4Hz, 1H), 3.69 (t, *J* = 11.4Hz, 1H), 3.44 (br s, 4H), 3.00-2.85 (m, 4H), 2.12-2.09 (m, 3H), 1.76-1.52 (m, 6H), 1.45 (s, 9H) ppm. LCMS (method D, ESI): RT = 1.29min, *m/z* = 461.2 [M+H]⁺.

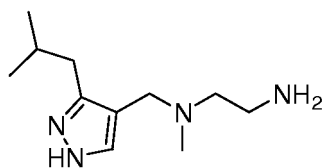
Step 4: *N*¹-((3-(4-fluorophenethyl)-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine (Compound 23)



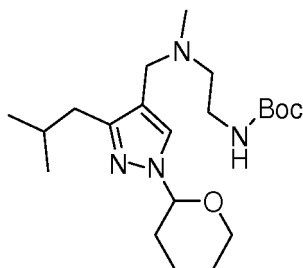
[00286] A solution of (*R/S*) *tert*-butyl 2-(((3-(4-fluorophenethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate (150 mg, 0.33 mmol, 1.00 equiv) in 3*N* hydrochloric acid (20 mL) was stirred overnight at 60°C. The resulting mixture was cooled to room temperature and washed with 3x20 mL of dichloromethane. The aqueous layer was concentrated under vacuum and the crude product was purified by Prep-HPLC with the following conditions (Prep-HPLC-025): Column, XBridge Prep Phenyl OBD Column, 5μm, 19x150mm; mobile phase, water with 10mmol NH₄HCO₃ and MeCN (20.0% MeCN up to 30.0% in 10 min, up to 95.0% in 1 min, hold 95.0% in 1 min, down to 20.0% in 2 min); Detector, UV 254/220nm to give 42.9 mg (26%) of *N*¹-((3-(4-fluorophenethyl)-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine trifluoroacetate as a yellow oil. ¹H-NMR (300 MHz, D₂O) δ: 7.70 (s, 1H), 6.98-6.86 (m, 4H), 3.86 (s, 2H), 3.30 (s, 4H), 2.97-2.80 (m, 4H), 2.58 (s, 3H) ppm. LCMS (method G, ESI): RT = 1.22 min, *m/z* = 277.1 [M+H]⁺.

Compound 28

***N*¹-((3-*iso*-butyl-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine**

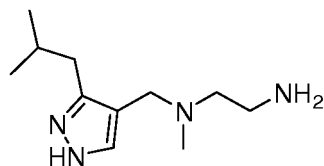


Step 1: *tert*-butyl 2-(((3-*iso*-butyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate

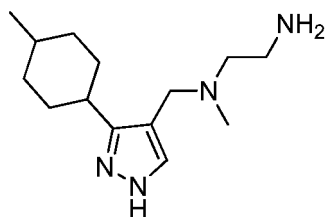
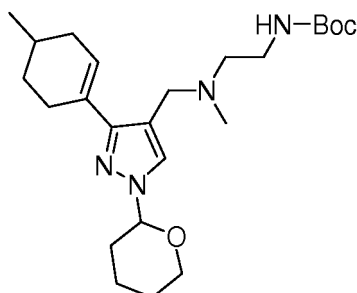


[00287] A mixture of (*R/S*) *tert*-butyl *N*-[2-([3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl]carbamate (400 mg, 0.86 mmol, 1.00 equiv), (2-methylpropyl)boronic acid (168 mg, 1.65 mmol, 1.50 equiv), K₃PO₄·3H₂O (877 mg, 3.00 equiv) and A-Phos-PdCl₂ (77.8 mg, 0.10 equiv) in ethylene glycol dimethyl ether (20 mL) and H₂O (2 mL) was stirred under nitrogen at 100°C overnight. The resulting mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-005 (Waters)): Column, XBridge Shield RP18 OBD Column, 5μm, 19x150mm; mobile phase, water with 10 mmol NH₄HCO₃ and CH₃CN (18% CH₃CN up to 58% in 10 min, up to 95% in 1 min, down to 18% in 2 min); Detector, UV 254/220 nm to give 50 mg (15%) of *tert*-butyl 2-(((3-*iso*-butyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate as a colorless oil. LCMS (method A, ESI): RT = 1.27 min, *m/z* = 395.0 [M+H]⁺.

Step 2: *N*¹-((3-*iso*-butyl-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine (Compound 28)

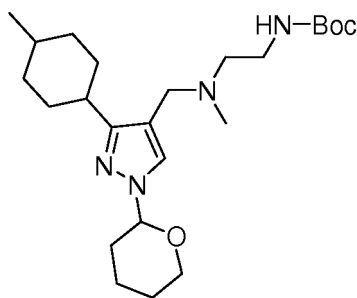


[00288] A solution of *tert*-butyl 2-(((3-*iso*-butyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate (50 mg, 0.13 mmol, 1.00 equiv) in THF (10 mL) and 12N hydrochloric acid (2 mL) was stirred overnight at 25°C. The resulting mixture was concentrated under vacuum. The residue was diluted with 5 mL of tetrahydrofuran and the pH value of the solution was adjusted to 9 with 10% sodium carbonate solution. The resulting mixture was concentrated under vacuum and the residue was dissolved in 5 mL of methanol then purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-005 (Waters)): Column, XBridge Shield RP18 OBD Column, 5μm, 19x150mm; mobile phase, water with 10 mmol NH₄HCO₃ and CH₃CN (18% CH₃CN up to 58% in 10 min, up to 95% in 1 min, down to 18% in 2 min); Detector, UV 254/220 nm to yield 6 mg (23%) of *N*¹-((3-*iso*-butyl-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine as a light yellow oil. ¹H-NMR (300MHz, CD₃OD) 7.49 (s, 1H), 3.44 (s, 2H), 2.84-2.80 (m, 2H), 2.56-2.50 (m, 4H), 2.21 (s, 3H), 2.03-1.93 (m, 1H), 0.95-0.92 (m, 6H) ppm. LCMS (method AA1 ESI): RT = 1.02 min, *m/z* = 211.0 [M+H]⁺.

Compound 37***N*¹-methyl-*N*¹-((3-(4-methylcyclohexyl)-1*H*-pyrazol-4-yl)methyl)ethane-1,2-diamine****Step 1: (*R/S*) *tert*-butyl 2-(methyl((3-(4-methylcyclohex-1-en-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate**

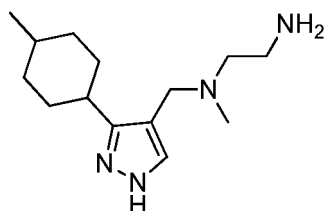
[00289] A mixture of (*R/S*) *tert*-butyl *N*-[2-([3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl)](methyl)amino)ethyl]carbamate (50 mg, 0.11 mmol, 1.00 equiv), potassium carbonate (45 mg, 0.33 mmol, 3.02 equiv), 4,4,5,5-tetramethyl-2-(4-methylcyclohex-1-en-1-yl)-1,3,2-dioxaborolane (36 mg, 0.16 mmol, 1.51 equiv), Pd(dppf)Cl₂ (8 mg, 0.01 mmol, 0.10 equiv) in water (1 mL) and 1,4-dioxane (10 mL) was stirred under nitrogen at 100°C overnight. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified on a silica gel column eluted with 0-50% of ethyl acetate in petroleum ether to give 30 mg (64%) of (*R/S*) *tert*-butyl 2-(methyl((3-(4-methylcyclohex-1-en-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate as a brown oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.29 (s, 1H), 6.14-6.13 (m, 1H), 5.36-5.32 (m, 1H), 4.16-4.07 (m, 2H), 3.70-3.27 (m, 2H), 2.54-2.29 (m, 6H), 2.54-2.29 (m, 4H), 2.22 (s, 3H), 2.13-2.07 (m, 3H), 1.86-1.56 (m, 4H), 1.47 (s, 9H), 1.46-1.38 (m, 3H) ppm. LCMS (method A, ESI): RT = 1.31 min, *m/z* = 433.0 [M+H]⁺.

Step 2: (*R/S*) *tert*-butyl 2-(methyl((3-(4-methylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate



[00290] A mixture of (*R/S*) *tert*-butyl 2-(methyl((3-(4-methylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate (200 mg, 0.46 mmol, 1.00 equiv) and 10% palladium on carbon (30 mg) catalyst in methanol (20 mL) was stirred under 20 atm of hydrogen in a 50-mL high pressure reactor at 25°C for 2 days. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to give 200 mg of crude (*R/S*) *tert*-butyl 2-(methyl((3-(4-methylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate as a yellow oil. The crude product was used in the next step without further purification. LCMS (method C, ESI): RT = 0.77 min, m/z = 435.0 [M+H]⁺.

Step 3: *N*¹-methyl-*N*¹-((3-(4-methylcyclohexyl)-1*H*-pyrazol-4-yl)methyl)ethane-1,2-diamine (Compound 37)

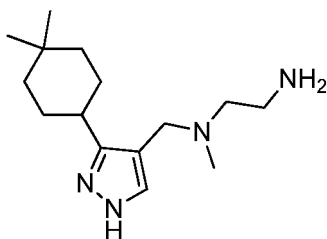


[00291] A solution of (*R/S*) *tert*-butyl 2-(methyl((3-(4-methylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate (200 mg, 0.46 mmol, 1.00 equiv) in 4N hydrochloric acid (10 mL) was stirred at 60°C for 2 h. The resulting mixture was cooled to room temperature and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-Waters 2767-2(HPLC-08)): Column, XBridge Shield RP 18, 5μm, 19x150mm; mobile phase, water with 50 mmol CF₃COOH and CH₃CN (10.0% CH₃CN up to 28.0% in 2 min, up to 46.0% in 10 min, up to 100.0% in 1 min, down to 10.0% in 1 min); Detector, UV 254 nm to yield 62.3 mg (28%) of *N*¹-methyl-*N*¹-((3-(4-methylcyclohexyl)-1*H*-pyrazol-4-yl)methyl)ethane-1,2-diamine trifluoroacetate as a colorless semi-solid. ¹H-NMR (300 MHz, D₂O): δ 7.78 (s, 1H), 4.28 (s, 2H), 3.47-3.31 (m,

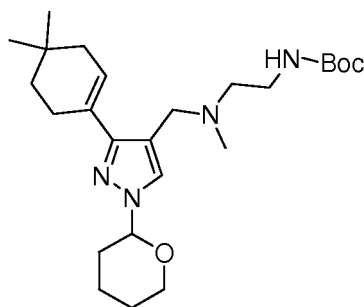
4H), 2.79-2.60 (s, 4H), 2.74-2.70 (m, 1H), 1.90-1.25 (m, 8H), 0.89 (d, $J = 7.2$ Hz, 3H) ppm. LCMS (method V, ESI): RT= 1.51 min, 9.12 min, $m/z = 251.1$ $[M+H]^+$.

Compound 38

***N*¹-((3-(4,4-dimethylcyclohexyl)-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine**

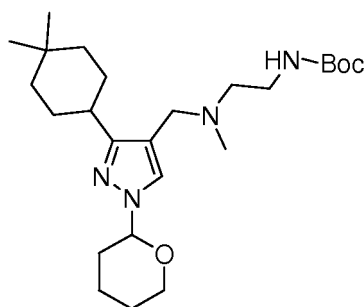


Step 1: (*R/S*) *tert*-butyl 2-(((3-(4,4-dimethylcyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate



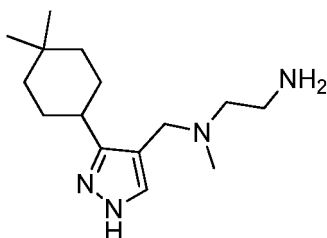
[00292] A mixture of (*R/S*) *tert*-butyl *N*-[2-([3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl]carbamate (300 mg, 0.65 mmol, 1.00 equiv), Pd(dppf)Cl₂ (52 mg, 0.07 mmol, 0.11 equiv), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (229 mg, 0.97 mmol, 1.50 equiv) and potassium carbonate (268 mg, 1.94 mmol, 3.00 equiv) in 1,4-dioxane (20 mL) and water (4 mL) was stirred under nitrogen at 100°C overnight. The resulting mixture was cooled to room temperature and concentrated under vacuum. The residue was purified on a silica gel column eluted with 1-41% of ethyl acetate in petroleum ether to give 250 mg (87%) of (*R/S*) *tert*-butyl 2-(((3-(4,4-dimethylcyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)carbamate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.50 (s, 1H), 6.14-6.13 (m, 1H), 5.36-5.32 (m, 1H), 4.18-4.07 (m, 2H), 3.74-3.67 (m, 1H), 3.41-3.25 (m, 4H), 2.51-2.50 (m, 3H), 2.20-2.02 (m, 6H), 1.73-1.71 (m, 3H), 1.70-1.66 (m, 6H), 1.47 (s, 9H), 1.28-1.26 (m, 4H) ppm. LCMS (method D, ESI): RT = 1.33 min, $m/z = 447.0$ $[M+H]^+$.

Step 2: (*R/S*) *tert*-butyl 2-(((3-(4,4-dimethylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-

1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)carbamate

[00293] A mixture of (*R/S*) *tert*-butyl 2-(((3-(4,4-dimethylcyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethylcarbamate (250 mg, 0.56 mmol, 1.00 equiv) and 10% palladium on carbon (30 mg) catalyst in methanol (20 mL) was stirred under 20 atm. of hydrogen in a 50-mL high pressure reactor at 25°C for 2 days. The catalyst was removed by filtration. The filtrate was concentrated under vacuum to give 250 mg of crude (*R/S*) *tert*-butyl 2-(((3-(4,4-dimethylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)carbamate as a yellow oil. The crude product was used in the next step without further purification. LCMS (method C, ESI): RT = 0.80 min, *m/z* = 449.0 [M+H]⁺.

Step 3: *N*¹-((3-(4,4-dimethylcyclohexyl)-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine (Compound 38)

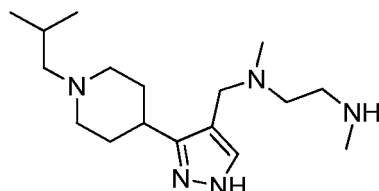


[00294] A solution of (*R/S*) *tert*-butyl 2-(((3-(4,4-dimethylcyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)carbamate (250 mg, 0.56 mmol, 1.00 equiv) in 4*N* hydrochloric acid (10 mL) was stirred at 60°C for 2 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-Waters 2767-2 (HPLC-08)): Column, XBridge Shield RP 18, 5μm, 19x150mm; mobile phase, water with 50 mmol CF₃COOH and CH₃CN (10.0% CH₃CN up to 28.0% in 2 min, up to 46.0% in 10 min, up to 100.0% in 1 min, down to 10.0% in 1 min); Detector, UV 254 nm to yield 171.2 mg (62%) of *N*¹-((3-(4,4-dimethylcyclohexyl)-1*H*-pyrazol-4-yl)methyl)-*N*¹-methylethane-1,2-diamine trifluoroacetate as a light yellow oil. ¹H-NMR (300 MHz, D₂O): δ 7.75 (s, 1H), 4.30 (s, 2H), 3.47-3.35 (m, 4H), 2.77 (s, 3H), 2.68-2.58 (m, 1H), 1.71-1.53 (m, 4H), 1.49-1.37 (m, 2H),

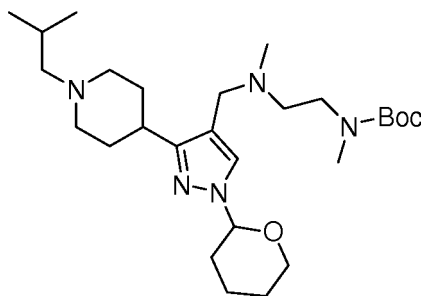
1.31-1.17 (m, 2H), 1.89 (s, 3H), 1.87 (s, 3H) ppm. LCMS (method M, ESI): RT = 1.15, m/z = 265.1 [M+H]⁺.

Compound 39

***N*¹-((3-(1-isobutylpiperidin-4-yl)-1*H*-pyrazol-4-yl)methyl)-*N*¹,*N*²-dimethylethane-1,2-diamine**

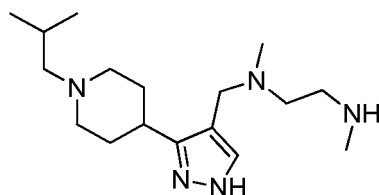


Step 1: (*R/S*) *tert*-butyl 2-(((3-(1-isobutylpiperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)(methyl)carbamate



[00295] To a solution of (*R/S*) *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-(oxan-2-yl)-3-(piperidin-4-yl)-1*H*-pyrazol-4-yl)methyl])amino]ethyl]carbamate (250 mg, 0.57 mmol, 1.00 equiv) and 2-methylpropanal (62 mg, 0.86 mmol, 1.50 equiv) in 1,2-dichloroethane (15 mL) was added NaBH(OAc)₃ (364 mg, 3.00 equiv). The resulting solution was stirred at room temperature overnight and then concentrated under vacuum to give 160 mg of crude (*R/S*) *tert*-butyl 2-(((3-(1-isobutylpiperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)(methyl)carbamate as a light yellow oil. LCMS (method A, ESI): RT = 1.52 min, m/z = 492.2 [M+H]⁺.

Step 2: *N*¹-((3-(1-isobutylpiperidin-4-yl)-1*H*-pyrazol-4-yl)methyl)-*N*¹,*N*²-dimethylethane-1,2-diamine (Compound 39)

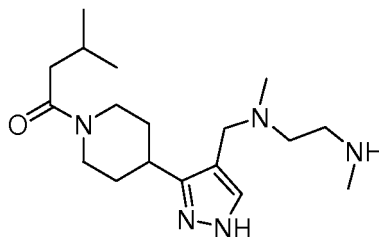


[00296] A solution of *tert*-butyl 2-(((3-(1-isobutylpiperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl)(methyl)carbamate (130 mg, 0.26 mmol,

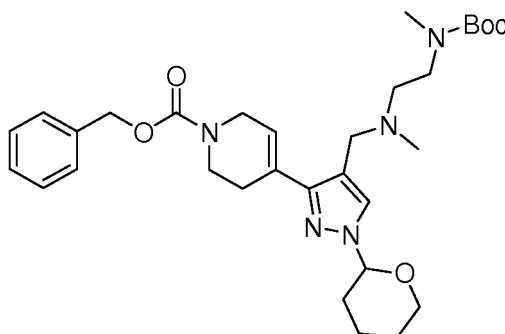
1.00 equiv) in ethanol (2 mL), 1,4-dioxane (4 mL) and 3N hydrochloric acid (2 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was purified by Pre-HPLC with the following conditions (1#-Pre-HPLC-005(Waters)): Column, SunFire Prep C18 OBD Column, 5 μ m, 19x150mm; mobile phase, phase A: water with 0.05% TFA; phase B: MeCN (5% CH₃CN up to 17% in 10 min, down to 0% in 0 min); Detector, UV 254/220 nm to give 39.5 mg (28%) of *N*¹-((3-(1-isobutylpiperidin-4-yl)-1*H*-pyrazol-4-yl)methyl)-*N*¹,*N*²-dimethylethane-1,2-diamine trifluoroacetate as a colorless solid. ¹H-NMR (300 MHz, D₂O): δ 7.81 (s, 1H), 4.32 (s, 2H), 3.71-3.35 (m, 7H), 3.15-2.89 (m, 4H), 2.82-2.68 (m, 6H), 2.22-1.92 (m, 5H), 0.93 (d, *J* = 6.8 Hz, 6H) ppm. LCMS (method U, ESI): *m/z* = 308.2 [M+H]⁺.

Compound 40

3-methyl-1-(4-(4-((methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)piperidin-1-yl)butan-1-one



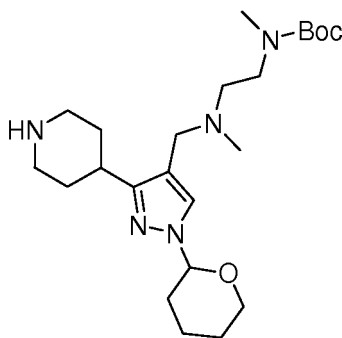
Step 1: (*R/S*) benzyl 4-(4-(((2-(*tert*-butoxycarbonyl(methyl)amino)ethyl)(methyl)amino)methyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate



[00297] A mixture of (*R/S*) *tert*-butyl *N*-[2-([4-iodo-1-(oxan-2-yl)-1*H*-pyrrol-3-yl]methyl)(methyl)amino)ethyl]-*N*-methylcarbamate (3.15 g, 6.60 mmol, 1.00 equiv), benzyl 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (2.5 g, 7.28 mmol, 1.10 equiv), Pd(dppf)Cl₂ (1.39 g, 1.90 mmol, 0.29 equiv) and potassium carbonate (2.72 g, 19.68 mmol, 2.98 equiv) in 1,4-dioxane (30 mL) and water (3 mL) was stirred under

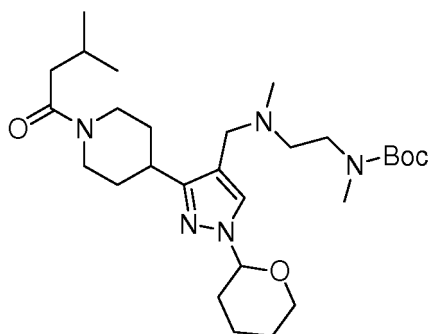
nitrogen at 100°C overnight. The reaction was cooled to room temperature and then quenched by the addition of 30 mL of water. The resulting mixture was extracted with 3x250 mL of ethyl acetate. The combined organic layers was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with 0-15% of ethyl acetate in petroleum ether to give 2.1 g (56%) of (*R/S*) benzyl 4-(4-(((2-(*tert*-butoxycarbonyl(methyl)amino)ethyl)(methyl)amino)methyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.58-7.49 (m, 1H), 7.49-7.35 (m, 4H), 7.35-7.30 (m, 1H), 5.33-5.30 (m, 1H), 5.20 (s, 2H), 4.25-4.00 (m, 3H), 3.70-3.69 (m, 3H), 3.39-3.31 (m, 3H), 2.84 (m, 3H), 2.66 (m, 2H), 2.50 (m, 2H), 2.25 (m, 2H), 2.08-2.07 (m, 3H), 1.73-1.62 (m, 4H), 1.46 (s, 9H), 1.31-1.27 (m, 1H) ppm. LCMS (method A, ESI): RT = 0.74 min, m/z = 568.0 [M+H]⁺.

Step 2: (*R/S*) *tert*-butyl methyl(2-(methyl((3-(piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate



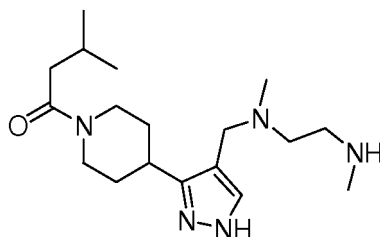
[00298] A mixture of benzyl 4-(4-(((2-(*tert*-butoxycarbonyl(methyl)amino)ethyl)(methyl)amino)methyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (2 g, 3.52 mmol, 1.00 equiv) and 10% palladium on carbon (2 g) catalyst in methanol (100 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 6 h. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to yield 1.1 g (72%) of (*R/S*) *tert*-butyl methyl(2-(methyl((3-(piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate as a brown oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.46 (s, 1H), 5.33-5.32 (m, 1H), 4.24-4.06 (m, 1H), 3.75-3.66 (m, 1H), 3.51 (s, 1H), 3.41-3.15 (m, 6H), 2.95-2.70 (m, 6H), 2.62-2.40 (m, 2H), 2.22 (s, 3H), 1.55-1.41 (m, 10H), 1.35-1.21 (m, 1H) ppm. LCMS (method A, ESI): RT = 1.49 min, m/z = 436.2 [M+H]⁺.

Step 3: (*R/S*) *tert*-butyl methyl(2-(methyl((3-(1-(3-methylbutanoyl)piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate



[00299] To a solution of (*R/S*) *tert*-butyl methyl(2-(methyl((3-(piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate (200 mg, 0.46 mmol, 1.00 equiv) and triethylamine (1.14 g, 11.26 mmol, 24.52 equiv) in dichloromethane (15 mL) was added 3-methylbutanoyl chloride (67 mg, 0.56 mmol, 1.21 equiv). The resulting solution was stirred at room temperature for 2 h. The reaction was then quenched by the addition of 2 mL of water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give 250 mg of crude (*R/S*) *tert*-butyl methyl(2-(methyl((3-(1-(3-methylbutanoyl)piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate as a yellow solid. LCMS (method D, ESI): RT = 1.22 min, m/z = 520.0 $[M+H]^+$.

Step 4: 3-methyl-1-(4-(4-((methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)piperidin-1-yl)butan-1-one (Compound 40)

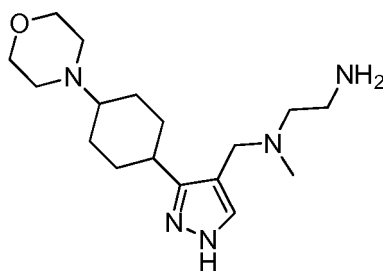


[00300] A solution of *tert*-butyl methyl(2-(methyl((3-(1-(3-methylbutanoyl)piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate (110 mg, 0.21 mmol, 1.00 equiv) in ethanol (2 mL), 1,4-dioxane (4 mL) and 12N hydrochloric acid (2 mL) was stirred at room temperature overnight. The resulting mixture was concentrated under vacuum and the residue was purified by Pre-HPLC with the following conditions (1#-Pre-HPLC-005 (Waters)): Column, XBridge Shield RP18 OBD Column, 5 μ m, 19x150mm; mobile phase, water with 10 mmol NH_4HCO_3 and CH_3CN (18% CH_3CN up to 58% in 10 min, up to 95% in 1 min, down to 18% in 2 min); Detector, UV 254/220 nm to give 17.7 mg

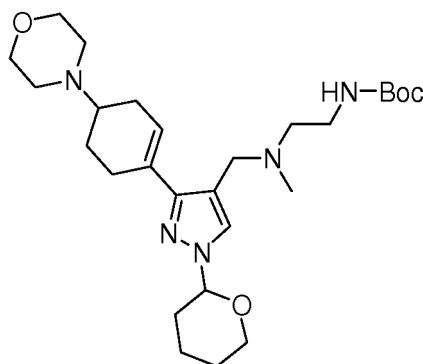
(25%) of 3-methyl-1-(4-(4-((methyl(2-(methylamino)ethyl)amino)methyl)-1*H*-pyrazol-3-yl)piperidin-1-yl)butan-1-one as a colorless solid. ¹H-NMR (300 MHz, D₂O): δ 7.53 (s, 1H), 4.50-4.40 (m, 1H), 4.10-4.00 (m, 1H), 3.44 (s, 2H), 3.25-3.10 (m, 1H), 3.09-2.95 (m, 1H), 2.80-2.65 (m, 3H), 2.53-2.43 (m, 2H), 2.40-2.20 (m, 5H), 2.13 (s, 3H), 2.00-1.75 (m, 3H), 1.72-1.43 (m, 2H), 0.88 (d, *J* = 6.8 Hz, 6H) ppm. LCMS (method R, ESI): RT = 1.26 min, *m/z* = 336.2 [M+H]⁺.

Compound 43

*N*¹-methyl-*N*¹-((3-(4-morpholinocyclohexyl)-1*H*-pyrazol-4-yl)methyl)ethane-1,2-diamine



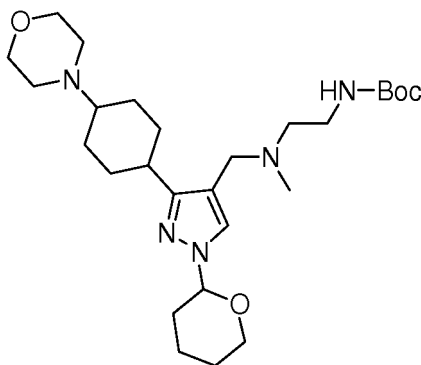
Step 1: (*R/S*) *tert*-butyl 2-(methyl((3-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)methyl)amino)ethyl)carbamate



[00301] A mixture of (*R/S*) *tert*-butyl *N*-[2-([3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl)(methyl)amino)ethyl]carbamate (400 mg, 0.86 mmol, 1.00 equiv), Pd(dppf)Cl₂ (66 mg, 0.09 mmol, 0.10 equiv), potassium carbonate (356 mg, 2.58 mmol, 2.99 equiv) and 4-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]morpholine (379 mg, 1.29 mmol, 1.50 equiv) in 1,4-dioxane (20 mL) and water (2 mL) was stirred under nitrogen at 100°C overnight. The resulting mixture was cooled to room temperature then concentrated under vacuum. The residue was purified on a silica gel column eluted with 0-3% of methanol in dichloromethane to give 320 mg (74%) of (*R/S*) *tert*-butyl 2-(methyl((3-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-

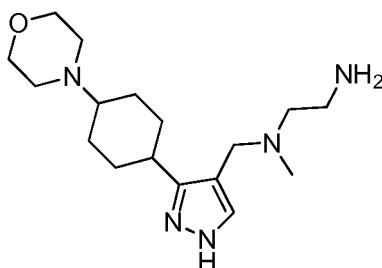
yl)methyl)amino)ethyl)carbamate as a brown oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.52 (s, 1H), 6.13-6.12 (m, 1H), 5.35-5.31 (m, 1H), 4.18-4.11 (m, 2H), 3.80-3.78 (m, 5H), 3.45-3.43 (m, 2H), 3.26-3.25 (m, 2H), 2.69-2.63 (m, 5H), 2.54-2.48 (m, 4H), 2.25-2.20 (m, 4H), 2.13-2.02 (m, 4H), 1.67-1.61 (m, 4H), 1.47 (s, 9H) ppm. LCMS (method A, ESI): RT = 1.00 min, m/z = 504.0 $[\text{M}+\text{H}]^+$.

Step 2: (*R/S*) *tert*-butyl 2-(methyl((3-(4-morpholinocyclohexyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)amino)ethyl)carbamate



[00302] A mixture of (*R/S*) *tert*-butyl 2-(methyl((3-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)amino)ethyl)carbamate (300 mg, 0.60 mmol, 1.00 equiv) and 10% palladium on carbon (20 mg) catalyst in acetic acid (15 mL) was stirred under 20 atm of hydrogen in a 50-mL high pressure reactor at 25°C for 3 days. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to give 300mg of crude (*R/S*) *tert*-butyl 2-(methyl((3-(4-morpholinocyclohexyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)amino)ethyl)carbamate as a yellow oil. The crude product was used in the next step without further purification. LCMS (method A, ESI): RT = 1.01 min, m/z = 506.0 $[\text{M}+\text{H}]^+$.

Step 3: *N*¹-methyl-*N*¹-((3-(4-morpholinocyclohexyl)-1H-pyrazol-4-yl)methyl)ethane-1,2-diamine (Compound 43)

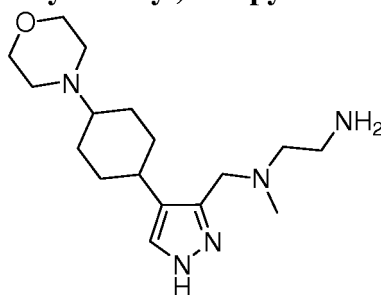


[00303] A solution of (*R/S*) *tert*-butyl 2-(methyl((3-(4-morpholinocyclohexyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)amino)ethyl)carbamate (300 mg, 0.59 mmol, 1.00 equiv) in 4N hydrochloric acid (15 mL) was stirred at 60°C for 2 h. The resulting mixture was cooled to room temperature then concentrated under vacuum. The crude product

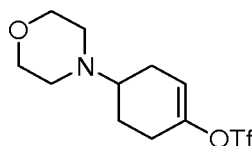
was purified by Prep-HPLC with the following conditions (Waters 2767-2(HPLC-08)): Column, XBridge Shield RP 18, 5 μ m, 19x150mm; mobile phase, water with 50 mmol CF₃COOH and CH₃CN (10.0% CH₃CN up to 28.0% in 2 min, up to 46.0% in 10 min, up to 100.0% in 1 min, down to 10.0% in 1 min); Detector, UV 254 nm to afford 36.5 mg (11%) of N¹-methyl-N¹-((3-(4-morpholinocyclohexyl)-1*H*-pyrazol-4-yl)methyl)ethane-1,2-diamine trifluoroacetate as a white solid. ¹H-NMR (300 MHz, CD₃OD): δ 7.47 (s, 1H), 3.78-3.71 (m, 4H), 3.47 (s, 2H), 2.88-2.80 (m, 2H), 2.80-2.70 (m, 1H), 2.70-2.62 (m, 4H), 2.57-2.50 (m, 2H), 2.45-2.27 (m, 1H), 2.23 (s, 3H), 2.16-1.93 (m, 4H), 1.75-1.57 (m, 2H), 1.50-1.34 (m, 2H) ppm. LCMS (method M, ESI): m/z = 322.2 [M+H]⁺.

Compound 44

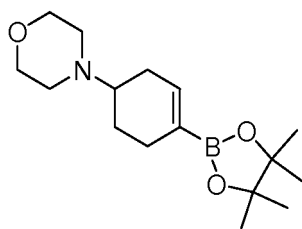
N¹-methyl-N¹-((4-(4-morpholinocyclohexyl)-1*H*-pyrazol-3-yl)methyl)ethane-1,2-diamine



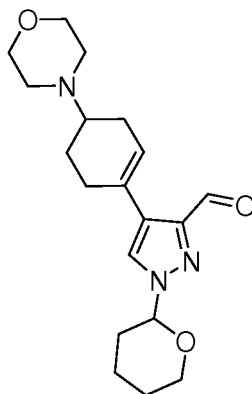
Step 1: 4-morpholinocyclohex-1-enyl trifluoromethanesulfonate



[00304] To a stirred solution of 4-(morpholin-4-yl)cyclohexan-1-one (920 mg, 5.02 mmol, 1.00 equiv) in anhydrous tetrahydrofuran (20 mL) maintained under nitrogen at -78°C was added dropwise a 1M solution of LiHMDS (6 mL) in tetrahydrofuran. After stirring for 1 h at -78 °C, a solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethane)-sulfonylmethanesulfonamide (1.97 g, 5.51 mmol, 1.10 equiv) in tetrahydrofuran (6 mL) was added. The reaction was warmed to room temperature and stirred for 12 h. The resulting solution was concentrated under vacuum and the residue was purified on a silica gel column eluted with 50-100% of ethyl acetate in petroleum ether to give 420 mg (27%) of 4-morpholinocyclohex-1-enyl trifluoromethanesulfonate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 5.80-5.70 (m, 1H), 3.90-3.75 (m, 4H), 2.75-2.00 (m, 10H), 1.70-1.50 (m, 1H) ppm.

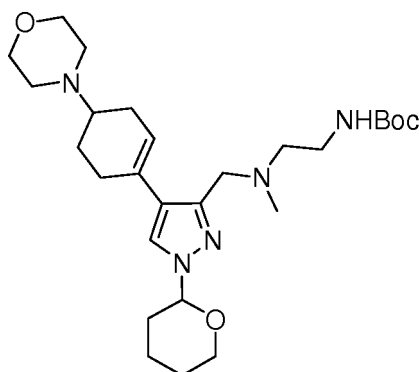
Step 2: 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)morpholine

[00305] A mixture of 4-morpholinocyclohex-1-enyl trifluoromethanesulfonate (4 g, 12.69 mmol, 1.00 equiv), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.87 g, 15.24 mmol, 1.20 equiv), potassium acetate (3.73 g, 38.01 mmol, 3.00 equiv) and Pd(dppf)Cl₂ (930 mg, 1.27 mmol, 0.10 equiv) in 1,4-dioxane (100 mL) was refluxed under nitrogen for 12 h. The reaction mixture was cooled to room temperature, filtered and then concentrated under vacuum. The residue was purified on a silica gel column eluted with 50-100% of ethyl acetate in petroleum ether to give 3.2 g (86%) of 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)morpholine as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 6.60-6.55 (m, 1H), 3.80-3.66 (m, 4H), 2.70-2.25 (m, 8H), 2.20-1.90 (m, 4H), 1.25 (s, 12H) ppm.

Step 3: (*R/S*) 4-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carbaldehyde

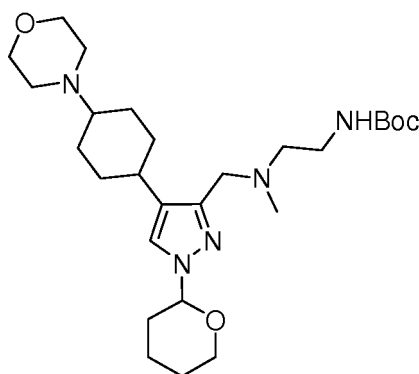
[00306] A mixture of 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enyl)morpholine (293 mg, 1.00 mmol, 1.00 equiv), (*R/S*) 4-iodo-1-(oxan-2-yl)-1*H*-pyrazole-3-carbaldehyde (306 mg, 1.00 mmol, 1.00 equiv), K₃PO₄ (640 mg, 3.02 mmol, 3.02 equiv) and Pd(dppf)Cl₂ (65.1 mg, 0.10 mmol, 0.10 equiv) in ethylene glycol dimethyl ether (5 mL) was stirred under nitrogen at 85°C for 12 h. The reaction was cooled to room temperature and concentrated under vacuum. The residue was purified on a silica gel column eluted with 50-100% of ethyl acetate in petroleum ether to give 280 mg (81%) of (*R/S*) 4-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carbaldehyde as a brown oil. LCMS (method C, ESI): RT = 0.70 min, m/z = 346.2 [M+H]⁺.

Step 4: (*R/S*) *tert*-butyl 2-(methyl((4-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)amino)ethyl)carbamate



[00307] To a solution of (*R/S*) 4-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carbaldehyde (500 mg, 1.45 mmol, 1.00 equiv) and *tert*-butyl *N*-[2-(methylamino)ethyl]carbamate (378 mg, 2.17 mmol, 1.50 equiv) in 1,2-dichloroethane (20 mL) was added NaBH(OAc)₃ (612 mg, 2.89 mmol, 1.99 equiv). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated NaHCO₃ solution (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with 20-100% of ethyl acetate in petroleum ether to give 300 mg (41%) of (*R/S*) *tert*-butyl 2-(methyl((4-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)amino)ethyl)carbamate as a brown oil. LCMS (method A, ESI): RT = 0.66 min, m/z = 504.4 [M+H]⁺.

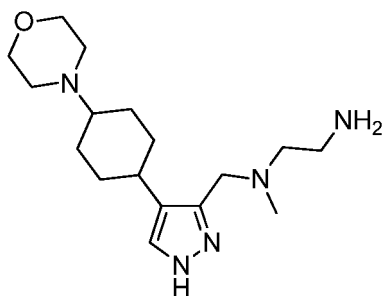
Step 5: (*R/S*) *tert*-butyl 2-(methyl((4-(4-morpholinocyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)amino)ethyl)carbamate



[00308] A mixture of (*R/S*) *tert*-butyl 2-(methyl((4-(4-morpholinocyclohex-1-enyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)amino)ethyl)carbamate (252 mg, 0.50 mmol, 1.00 equiv) and 10% palladium on carbon catalyst (25 mg) in acetic acid (10 mL) was stirred in a 30-mL pressure reactor under 20 atm. of hydrogen at 25°C for 12 h. The catalyst

was removed by filtration and the filtrate was concentrated to give 250 mg (99%) of (*R/S*) *tert*-butyl 2-(methyl((4-(4-morpholinocyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)amino)ethyl)carbamate as a yellow oil. LCMS (method C, ESI): RT = 0.66 min, m/z = 506.4 $[M+H]^+$.

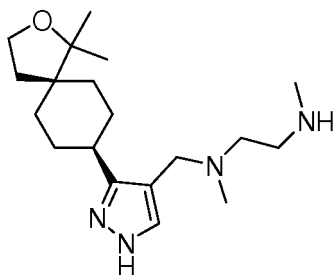
Step 6: *N*¹-methyl-*N*¹-((4-(4-morpholinocyclohexyl)-1*H*-pyrazol-3-yl)methyl)ethane-1,2-diamine (Compound 44)

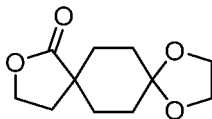


[00309] A mixture of (*R/S*) *tert*-butyl 2-(methyl((4-(4-morpholinocyclohexyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methyl)amino)ethyl)carbamate (253 mg, 0.50 mmol, 1.00 equiv) in a saturated solution of hydrogen chloride in 1,4-dioxane (20 mL) was stirred at 25°C for 24 h. The resulting mixture was concentrated under vacuum and the crude product (150 mg) was purified by Prep-HPLC with the following conditions (Prep-HPLC-005): Column, XBridge Prep C18 OBD Column, 5 μ m, 19x150 mm; mobile phase, water with 10 mmol NH_4HCO_3 and MeCN (hold 4% MeCN in 5 min, up to 5% in 10 min); Detector, UV 254/220 nm to give 30 mg (19%) of *N*¹-methyl-*N*¹-((4-(4-morpholinocyclohexyl)-1*H*-pyrazol-3-yl)methyl)ethane-1,2-diamine as a colorless oil. ¹H-NMR (300 MHz, CD_3OD): δ 7.40 (s, 1H), 3.75-3.65 (m, 4H), 3.58 (s, 2H), 2.80-2.72 (m, 2H), 2.69-2.27 (m, 8H), 2.19 (s, 3H), 2.12-1.93 (m, 4H), 1.55-1.28 (m, 4H) ppm. LCMS (method W): m/z = 322.2 $[M+H]^+$.

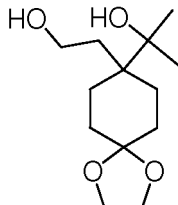
Compound 106

Methyl [2-(methylamino)ethyl]([3-[(5*R*,8*R*)-1,1-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine



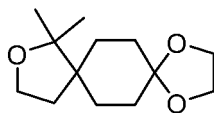
Step 1: 1,4,10-trioxadispiro[4.2.48.25]tetradecan-9-one

[00310] Into a 500-mL 3-necked round-bottom flask was placed THF (150 mL), LDA (1.3 equiv, prepared from 36 mL of n-BuLi (2.5 M in hexane) reacted with 13.8 mL of diisopropylamine for 30 min at -50°C). Then ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (15 g, 70.01 mmol, 1.0 equiv) was added and stirred for 30 min at -70°C, followed by oxirane (0.22g/mL in THF, 28 mL) at -78°C. The resulting solution was stirred for 2 h at -70°C. The reaction was quenched by 100 mL of NH₄Cl (sat. aq.), then treated with 100 mL of EtOAc. The organic phase was separated and then washed with 150 mL of brine. The organic phase was dried and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (1:2) as eluent to give 4.5 g (30%) of 1,4,10-trioxadispiro[4.2.4⁸.2⁵]tetradecan-9-one as a yellow solid. ¹H-NMR (300 MHz, CDCl₃): δ 4.28 (t, *J* = 6.6 Hz, 2H), 4.10-3.85 (m, 4H), 2.17 (t, *J* = 6.6 Hz, 2H), 2.15-1.85 (m, 4H), 1.80-1.50 (m, 4H).

Step 2: 2-[8-(2-hydroxyethyl)-1,4-dioxaspiro[4.5]decan-8-yl]propan-2-ol

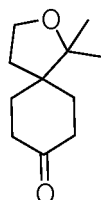
[00311] To a stirred solution of 1,4,10-trioxadispiro[4.2.4⁸.2⁵]tetradecan-9-one (3.18 g, 14.98 mmol, 1.0 equiv) in THF (100 mL) at 0°C was added dropwise a solution of MeMgBr (1M in ether, 75 mL, 5.0 equiv). The resulting solution was allowed to warm to room temperature and stirred for 12 h at room temperature. The reaction was quenched with 40 mL of NH₄Cl (sat. aq.), then treated with 300 mL of EtOAc. The organic phase was separated and then washed with 100 mL brine then dried with anhydrous Na₂SO₄. Concentration under reduced pressure afforded 4.9 g (crude) of 2-[8-(2-hydroxyethyl)-1,4-dioxaspiro[4.5]decan-8-yl]propan-2-ol as yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 4.00-3.90 (m, 4H), 3.80-3.40 (m, 4H), 1.95-1.50 (m, 10H), 1.40-1.10 (m, 6H).

Step 3: 9,9-dimethyl-1,4,10-trioxadispiro[4.2.48.25]tetradecane



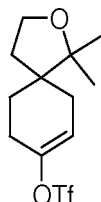
[00312] Into a 250-mL round-bottom flask was placed 2-[8-(2-hydroxyethyl)-1,4-dioxaspiro[4.5]decan-8-yl]propan-2-ol (4.91 g, 20.10 mmol, 1.00 equiv), dichloromethane (60 mL), 4-dimethylaminopyridine (300 mg, 2.46 mmol, 0.12 equiv) and triethylamine (20 mL). Tosylchloride (5.34 g, 28.01 mmol, 1.39 equiv) was added and the resulting solution was stirred for 12 h at room temperature then concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (1:2) as eluent to give 3.5 g (77%) of 9,9-dimethyl-1,4,10-trioxadispiro[4.2.4⁸.2⁵]tetradecane as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 3.84 (s, 4H), 3.66 (t, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.70-1.25 (m, 8H), 0.99 (s, 6H).

Step 4: 1,1-dimethyl-2-oxaspiro[4.5]decan-8-one



[00313] Into a 100-mL round-bottom flask purged and maintained with an atmosphere of nitrogen was placed 9,9-dimethyl-1,4,10-trioxadispiro[4.2.4⁸.2⁵]tetradecane (1.765 g, 7.80 mmol, 1.00 equiv), tetrahydrofuran (16 mL) and hydrochloric acid (12N, 16 mL). The resulting solution was stirred for 6 h at room temperature then extracted with 3 x 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 1.259 g (89%) of 1,1-dimethyl-2-oxaspiro[4.5]decan-8-one as a light yellow solid.

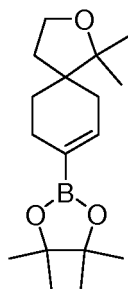
Step 5: 1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate



[00314] To a solution of 1,1-dimethyl-2-oxaspiro[4.5]decan-8-one (1.695 g, 9.30 mmol, 1.00 equiv) in THF (50 mL) at -70°C under dry nitrogen was added dropwise a solution of LiHMDS (1M in THF, 14 mL). The reaction mixture was stirred for 1 h at -70°C then treated with 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethane) sulfonylmethanesulfonamide (3.490 g, 9.77 mmol, 1.05 equiv) and stirred at -70°C for another 0.5 h. The resulting solution

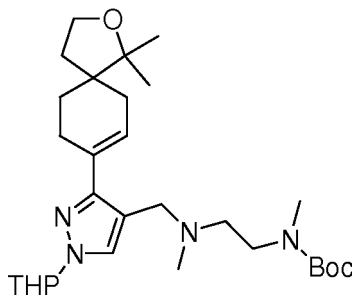
was allowed to warm to room temperature and stirred for another 12 hours then concentrated under vacuum. The residue was purified by flash chromatography on silica using ethyl acetate/petroleum ether (2:1) as eluent to afford 2.458 g (84%) of 1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate as a colorless oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.80-5.70 (m, 1H), 3.95-3.80 (m, 2H), 2.50-2.35 (m, 2H), 2.30-2.15 (m, 1H), 2.10-1.50 (m, 5H).

Step 6: 2-[1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



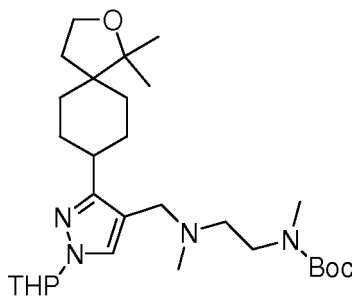
[00315] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (1.472 g, 4.68 mmol, 1.00 equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.786 g), 1,4-dioxane (20 mL), potassium acetate (1.378 g, 14.04 mmol, 3.00 equiv) and $\text{PdCl}_2(\text{dppf})$ (343 mg). The resulting solution was stirred for 12 h at 100°C then quenched by the addition of 10 mL of water/ice. The resulting solution was extracted with 200 mL of ethyl acetate and the combined organic layers washed with 50 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (2:1) as eluent to afford 715 mg (52%) of 2-[1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a white solid.

Step 7: (*R/S*) *tert*-butyl *N*-(2-[(3-[1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino)ethyl)-*N*-methylcarbamate



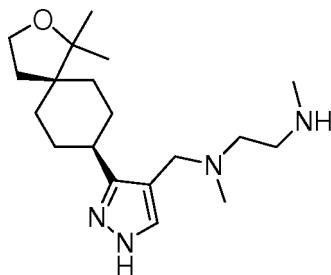
[00316] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 2-[1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.164 g, 3.98 mmol, 1.00 equiv), *tert*-butyl *N*-[2-([3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino)ethyl]-*N*-methylcarbamate (2.096 g, 4.38 mmol, 1.10 equiv), potassium carbonate (1.650 g, 11.94 mmol, 3.00 equiv), 1,4-dioxane (20 mL), water (2 mL) and PdCl₂(dppf) (292 mg). The resulting solution was stirred for 16 h at 100°C then quenched by the addition of 10 mL of water/ice. The resulting solution was extracted with 100 mL of ethyl acetate and the organic layer separated and washed with 50 mL of brine, dried over anhydrous sodium sulfate and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate/petroleum ether (1:1) as eluent to afford 1.081 g (53%) of (*R/S*) *tert*-butyl *N*-(2-[[3-[1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate as a yellow oil.

Step 8 (*R/S*) *tert*-butyl *N*-(2-[[3-[1,1-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate



[00317] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed (*R/S*) *tert*-butyl *N*-(2-[[3-[1,1-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate (1.081 g, 2.09 mmol, 1.00 equiv), tetrahydrofuran (25 mL), and 10% Pd(OH)₂/C (400 mg, 2.85 mmol, 1.36 equiv). The resulting solution was stirred for 5 h at room temperature under 3 atmospheres of hydrogen. The resulting mixture was filtered and the filtrate concentrated under vacuum to afford 860 mg (79%) of (*R/S*) *tert*-butyl *N*-(2-[[3-[1,1-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate as a light yellow oil.

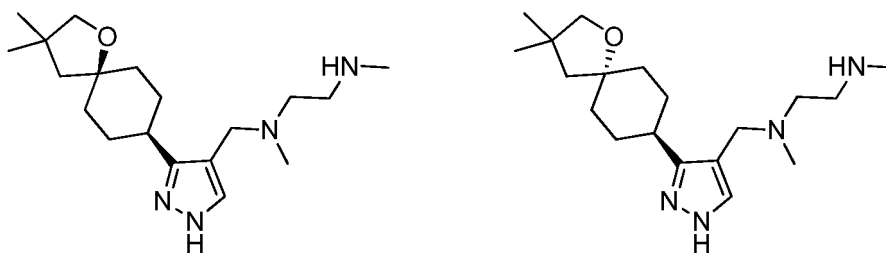
Step 9: Methyl[2-(methylamino)ethyl]([3-[(5*R*,8*S*)-1,1-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine (Compound 106)



[00318] A solution of (*R/S*) *tert*-butyl *N*-(2-[[[3-[1,1-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate (400 mg, 1.20 mmol, 1.00 equiv) in methanol (6 mL) was treated with hydrochloric acid (12*N*, 2 mL) and stirred for 1 h at room temperature then for an additional 2 h at 50°C. The reaction was then quenched by the addition of 20 mL of sodium bicarbonate (sat. aq.) and the resulting mixture concentrated under vacuum to remove the majority of the methanol. The resulting solution was extracted with 2x30 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product (200 mg) was purified by Chiral prep-HPLC. Column: IC4.6x100nm, Size: 0.46x10cm, 5µm; Mobile phase: Hex (0.2%IPA): IPA=85:15; Flow: 1.0 ml/min; Detector: UV-220nm; Instrument: LC-05; Temperature: 25°C. This resulted in 32.6 mg of methyl[2-(methylamino)ethyl]([3-[(5*R*,8*R*)-1,1-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine as a colorless solid. ¹H-NMR (300 MHz, D₂O): δ 7.50 (s, 1H), 3.76 (t, *J* = 7.5Hz, 2H), 3.42 (s, 2H), 2.80-2.45 (m, 5H), 2.31 (s, 3H), 2.12 (s, 3H), 2.01 (t, *J* = 7.5Hz, 2H), 1.80-1.25 (m, 8H), 1.05 (s, 6H) ppm. LCMS (method A11, ESI): RT = 1.44 min, *m/z* = 335.0 [M+H]⁺.

Compound 133 & 134

Methyl[2-(methylamino)ethyl]([3-[(5*s*,8*s*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine and methyl[2-(methylamino)ethyl]([3-[(5*r*,8*r*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine

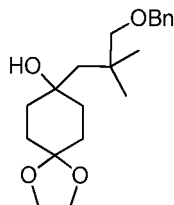


Step 1: 3-(benzyloxy)-2,2-dimethylpropan-1-ol

[00319] Into a 250-mL round-bottom flask, was placed 2,2-dimethylpropane-1,3-diol (10.4 g, 99.86 mmol) and N,N-dimethylformamide (100 mL). This was followed by the addition of 60% sodium hydride (4 g, 100.00 mmol), in portions at 0°C. To this was added (bromomethyl)benzene (13.68 g, 79.98 mmol) at 0°C. The resulting solution was stirred for 12 h at room temperature and then diluted with 200 mL of NH₄Cl (sat. aq). The resulting solution was extracted with 2x200 mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:10) to obtain 12 g (62%) of 3-(benzyloxy)-2,2-dimethylpropan-1-ol as light yellow oil. ¹H NMR (300 MHz, DMSO-d₆): δ 7.43-7.24 (m, 5H), 4.51-4.41 (m, 3H), 3.25-3.15 (m, 4H), 0.84 (s, 6H) ppm.

Step 2: [(3-iodo-2,2-dimethylpropoxy)methyl]benzene

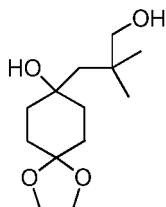
[00320] Into a 250-mL round-bottom flask, was placed 3-(benzyloxy)-2,2-dimethylpropan-1-ol (4 g, 20.59 mmol), imidazole (2.80 g, 41.18 mmol), triphenylphosphine (8.1 g, 30.88 mmol), and tetrahydrofuran (100 mL). This was followed by the addition of iodine (7.85 g, 30.93 mmol) in portions at 0°C. The resulting solution was stirred for 12 h at room temperature and then for an additional 4 hours at 80°C and then concentrated under vacuum. The residue was purified by silica gel column with petroleum ether to obtain 6 g (96%) of [(3-iodo-2,2-dimethylpropoxy)methyl]benzene as colorless oil. ¹H NMR (300 MHz, DMSO-d₆): δ 7.42-7.20 (m, 5H), 4.49 (s, 2H), 3.30 (s, 2H), 3.24 (s, 2H), 1.00 (s, 6H) ppm.

Step 3: 8-[3-(benzyloxy)-2,2-dimethylpropyl]-1,4-dioxaspiro[4.5]decan-8-ol

[00321] Into a 250-mL 3-necked round-bottom flask that was maintained with an atmosphere of nitrogen, was placed tetrahydrofuran (30 mL). This was followed by the addition of *t*-BuLi (1.3M in pentane, 40 mL) dropwise with stirring at -78°C. To this was added a solution of [(3-iodo-2,2-dimethylpropoxy)methyl]benzene (6.08 g, 20.00 mmol) in tetrahydrofuran (30 mL) dropwise with stirring at -78°C and the resulting mixture was stirred at -78°C for 1 h. To the mixture was added a solution of 1,4-dioxaspiro[4.5]decan-8-one (4.69

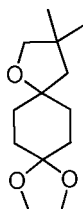
g, 30.00 mmol, 1.50 equiv) in tetrahydrofuran (30 mL) dropwise with stirring at -78°C . The resulting solution was stirred for 1 h at -78°C , and then was warmed to room temperature slowly. The reaction mixture was diluted with 120 mL of NH_4Cl (sat. aq). The organic layer was collected and the aqueous layer was extracted with 2x100 mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a C18 gel column with $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (3:7) to obtain 3.5 g (52%) of 8-[3-(benzyloxy)-2,2-dimethylpropyl]-1,4-dioxaspiro[4.5]decan-8-ol as light yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.42-7.20 (m, 5H), 4.46 (s, 2H), 3.92 (s, 1H), 3.82 (s, 4H), 3.21 (s, 2H), 1.80-1.67 (m, 2H), 1.66-1.55 (m, 2H), 1.55-1.45 (m, 2H), 1.5-1.35 (m, 4H), 1.00 (s, 6H) ppm.

Step 4: 8-(3-hydroxy-2,2-dimethylpropyl)-1,4-dioxaspiro[4.5]decan-8-ol



[00322] Into a 100-mL round-bottom flask, was placed 8-[3-(benzyloxy)-2,2-dimethylpropyl]-1,4-dioxaspiro[4.5]decan-8-ol (3.35 g, 10.02 mmol), tetrahydrofuran (40 mL), and 10% palladium/carbon (0.34 g). This was followed by the addition of formic acid (3.5 mL) dropwise with stirring. Hydrogen (3 atm) was then applied to the reaction mixture and the resulting solution stirred for 4 h at room temperature. The solids were removed by filtration and the solution was concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:1) to obtain 1.5 g (61%) of 8-(3-hydroxy-2,2-dimethylpropyl)-1,4-dioxaspiro[4.5]decan-8-ol as a white solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 4.85 (t, $J = 5.4$ Hz, 1H), 4.48 (s, 1H), 3.82 (s, 4H), 3.17 (d, $J = 5.4$ Hz, 2H), 1.83-1.58 (m, 4H), 1.58-1.35 (m, 6H), 0.90 (s, 6H) ppm.

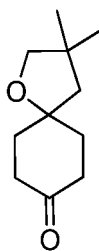
Step 5: 11,11-dimethyl-1,4,9-trioxadispiro[4.2.4[^][8].2[^][5]]tetradecane



[00323] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 8-(3-hydroxy-2,2-dimethylpropyl)-1,4-dioxaspiro[4.5]decan-8-ol (4 g, 16.37 mmol), tributylphosphane (6.62 g, 32.72 mmol), and tetrahydrofuran (60 mL). A

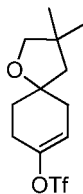
solution of TMAD (5.64 g, 32.75 mmol) in tetrahydrofuran (80 mL) was added dropwise with stirring at -40°C . The reaction mixture was stirred for 1 h at -40°C and then an additional 12 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:4) to obtain 3.2 g (86%) of 11,11-dimethyl-1,4,9-trioxadispiro[4.2.4[^][8].2[^][5]]tetradecane as colorless oil. ^1H NMR (400 MHz, DMSO- d_6): δ 3.83(s, 4H), 3.38(s, 2H), 1.78-1.63 (m, 4H), 1.63-1.42 (m, 6H), 1.03 (s, 6H) ppm.

Step 6: 3,3-dimethyl-1-oxaspiro[4.5]decan-8-one



[00324] Into a 100-mL round-bottom flask, was placed 11,11-dimethyl-1,4,9-trioxadispiro[4.2.4[^][8].2[^][5]]tetradecane (2.0 g, 8.84 mmol, 1.00 equiv), tetrahydrofuran (45 mL), and hydrochloric solution (15 mL of a 3M solution in tetrahydrofuran). The resulting solution was stirred for 24 h at room temperature and then the tetrahydrofuran was removed under vacuum. The resulting solution was extracted with 3x50 mL of ethyl acetate and the combined organic layers was washed with 1x25 mL of Na_2CO_3 (sat. aq.), dried over anhydrous sodium sulfate and concentrated under vacuum to obtain 1.4 g (87%) of 3,3-dimethyl-1-oxaspiro[4.5]decan-8-one as light yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 3.58(s, 2H), 2.78-2.60 (m, 2H), 2.32-2.17 (m, 2H), 2.17-2.05 (m, 2H), 1.92-1.75 (m, 2H), 1.88 (s, 2H) 1.15 (s, 6H) ppm.

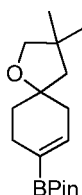
Step 7: 3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate



[00325] Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed LiHMDS (12 mL of a 1 M solution in tetrahydrofuran). A solution of 3,3-dimethyl-1-oxaspiro[4.5]decan-8-one (1.46 g, 8.01 mmol) in tetrahydrofuran (10 mL) was added at -50°C and the reaction mixture stirred at -50°C for 15 min. To this was added a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethane)sulfonylmethanesulfonamide (2.86 g, 8.01 mmol) in tetrahydrofuran (30 mL) at -50°C . The resulting solution was stirred for 1 h

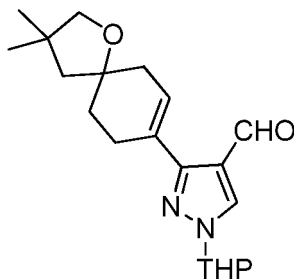
at -50°C and then for an additional 1 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:9) to obtain 1.23 g (49%) of 3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate as light yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 5.64(d, *J* = 2.7 Hz, 1H), 3.57-3.50 (m, 2H), 2.69-2.50 (m, 1H), 2.50-2.22 (m, 3H), 2.01-1.87 (m, 1H), 1.85-1.72 (m, 1H), 1.72-1.51 (m, 2H), 1.12 (s, 6H) ppm.

Step 8: 2-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[00326] Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (1.26 g, 4.01 mmol), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.22 g, 4.80 mmol), 1,4-dioxane (15 mL), potassium acetate (1.18 g, 12.02 mmol), and PdCl₂(dppf)CH₂Cl₂ (327 mg, 0.40 mmol). The resulting solution was stirred for 15 h at 100°C and then concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (10:1) to obtain 0.97 g (83%) of 2-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 6.46 (d, *J* = 1.6 Hz, 1H), 3.52 (s, 2H), 2.50-2.07 (m, 4H), 1.80-1.54 (m, 4H), 1.26 (s, 12H), 1.11 (s, 6H) ppm.

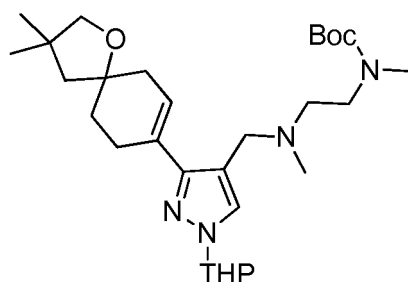
Step 9: 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1H-pyrazole-4-carbaldehyde



[00327] Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 3-iodo-1-(oxan-2-yl)-1H-pyrazole-4-carbaldehyde (964 mg, 3.15 mmol), 2-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (920 mg, 3.15 mmol), Cs₂CO₃ (3080 mg, 9.45 mmol), 1,4-dioxane/H₂O (v/v =

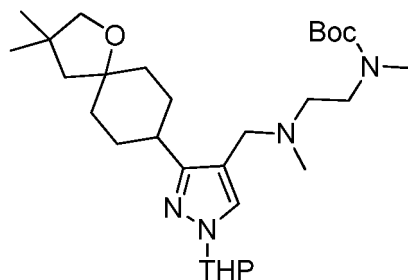
10:1) (10 mL), and $\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$ (257 mg, 0.31 mmol). The resulting solution was stirred for 15 h at 100°C and then concentrated under vacuum. The resulting residue was diluted with 50 mL of H_2O and then the mixture was extracted with 2x30 mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:2) to obtain 630 mg (58%) of 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1H-pyrazole-4-carbaldehyde as yellow oil. LCMS: $m/z = 345.2[\text{M}+1]$; ^1H NMR (400 MHz, CDCl_3): δ 9.90 (s, 1H), 8.13 (s, 1H), 6.30-6.20 (m, 1H), 5.40-5.30 (m, 1H), 4.15-4.00 (m, 1H), 3.78-3.64 (m, 1H), 3.57 (s, 2H), 2.86-2.30 (m, 4H), 2.20-1.86 (m, 4H), 1.86-1.60 (m, 6H), 1.13 (s, 6H) ppm.

Step 10: *tert*-butyl *N*-(2-[[3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1H-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



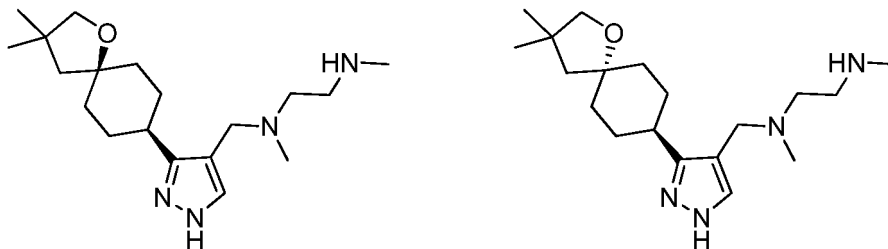
[00328] Into a 100-mL round-bottom flask, was placed 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1H-pyrazole-4-carbaldehyde (630 mg, 1.83 mmol), *tert*-butyl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate (516 mg, 2.74 mmol), $\text{ClCH}_2\text{CH}_2\text{Cl}$ (20 mL), and $\text{NaBH}(\text{AcO})_3$ (3.1 g, 14.62 mmol). The resulting solution was stirred for 5 h at 0°C and then quenched by the addition of 30 mL of Na_2CO_3 (sat. aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (3:2) to obtain 720 mg (76%) of *tert*-butyl *N*-(2-[[3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1H-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as light yellow oil. LCMS: $m/z = 517.5 [\text{M}+1]$; ^1H NMR (400 MHz, CDCl_3): δ 7.46 (s, 1H), 6.07 (s, 1H), 5.45-5.35 (m, 1H), 4.10-4.00 (m, 1H), 3.72-3.62 (m, 1H), 3.60-3.50 (m, 2H), 3.45-3.20 (m, 4H), 2.83 (s, 3H), 2.77-2.64 (m, 1H), 2.64-2.28 (m, 5H), 2.22 (s, 3H), 2.13-1.96 (m, 3H), 1.90-1.52 (m, 7H), 1.32 (s, 9H), 1.13 (s, 3H), 1.11 (s, 3H) ppm.

Step 11: *tert*-butyl N-(2-[[3-[3,3-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)-ethyl)-*N*-methylcarbamate



[00329] Into a 30-mL pressure tank reactor, was placed *tert*-butyl N-(2-[[3-[3,3-dimethyl-2-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (720 mg, 1.39 mmol), acetic acid (10 mL), and 10% palladium/carbon (100 mg). The reaction mixture was then subjected to hydrogen gas (pressure 10 atm) and stirred for 6 h at 50°C. The solids were removed by filtration and the solution was concentrated under vacuum to obtain 1 g (97%) of *tert*-butyl N-(2-[[3-[3,3-dimethyl-2-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)-ethyl)-*N*-methylcarbamate as light yellow oil.

Step 12: Methyl[2-(methylamino)ethyl]([3-[(5*s*,8*s*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine and methyl[2-(methylamino)ethyl]([3-[(5*r*,8*r*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine (Compound 134 & Compound 135)

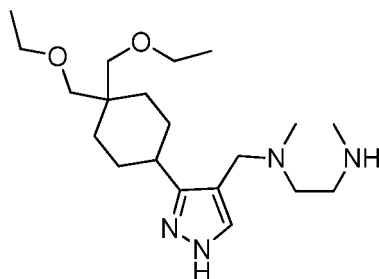


[00330] Into a 50-mL round-bottom flask, was placed *tert*-butyl N-(2-[[3-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (1 g, 1.93 mmol), and hydrogen chloride/methanol (saturated, 10 mL). The resulting solution was stirred for 5 h at room temperature and then concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Prep-HPLC-045): Column, Jupiter 4u Proteo 90A, AXIA Packed, 21.2 x250mm 4um 9nm; mobile phase, water with 0.05%TFA and ACN (5.0% ACN up to 30.0% in 8 min, hold 30.0% in 2 min); Detector, UV 220nm. This resulted in 480.8 mg (44%) of methyl[2-(methylamino)ethyl]([3-[(5*s*,8*s*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amine

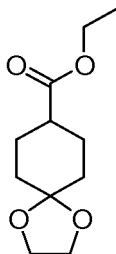
trifluoroacetate salt as a white semi-solid; LCMS: $m/z = 335.2$ $[M+1]$; ^1H NMR (300 MHz, D_2O): δ 7.73 (s, 1H), 4.28 (s, 2H), 3.50-3.40 (m, 6H), 2.74-2.68 (m, 7H), 1.90-1.86 (m, 2H), 1.68-1.42 (m, 8H) 1.00 (s, 6H) ppm. And 152.6 mg (14%) of methyl[2-(methylamino)ethyl]([3-[(5r,8r)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1H-pyrazol-4-yl)methyl)amine trifluoroacetate salt as a white semi-solid; LCMS: $m/z = 335.2$ $[M+1]$; ^1H NMR (300 MHz, D_2O): δ 7.73 (s, 1H), 4.28 (s, 2H), 3.46-3.34 (m, 6H), 2.74-2.69 (m, 7H), 1.83-1.75 (m, 4H), 1.70 (m, 2H), 1.57-1.46 (m, 4H), 1.00 (s, 6H) ppm.

Compound 158

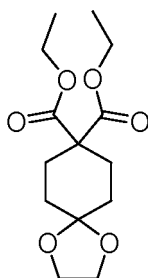
[(3-[4,4-bis(ethoxymethyl)cyclohexyl]-1H-pyrazol-4-yl)methyl](methyl)[2-(methylamino)ethyl]amine hydrochloride salt



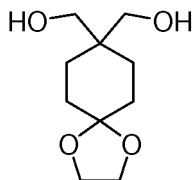
Step 1: ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate



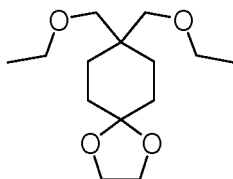
[00331] Into a 500-mL round-bottom flask was placed ethyl 4-oxocyclohexane-1-carboxylate (150 g, 881.29 mmol, 1.00 equiv), cyclohexane (300 mL), $\text{H}_2\text{NSO}_3\text{H}$ (3 g) and ethane-1,2-diol (65.7 g, 1.06 mol, 1.20 equiv). The resulting solution was stirred overnight at 100°C and then diluted with 300 mL of ethyl acetate. The resulting mixture was washed with 2x200 mL of brine and then concentrated under vacuum. This resulted in 152 g (80%) of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate as yellow oil. ^1H -NMR (300 MHz, CDCl_3): δ 4.05 (q, $J = 7.1\text{Hz}$, 2H), 3.95 (s, 4H), 2.44-2.23 (m, 1H), 2.00-1.70 (m, 6H), 1.65-1.47(m, 2H), 1.25(t, $J = 7.1\text{Hz}$, 3H) ppm.

Step 2: 8,8-diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate

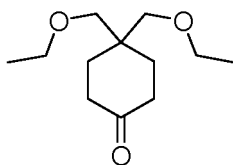
[00332] Into a 2-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed (i-Pr)₂NH (45.2 g) and tetrahydrofuran (1500 mL). Then n-BuLi (2.5M in hexane, 179.8 mL) was added dropwise at -50°C. The resulting mixture was reacted for 30 min at -50°C. Then ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (80 g, 373.38 mmol, 1.00 equiv) was added into mixture at -78°C. After 1 hour, chloro(ethoxy)methanone (60 g, 552.87 mmol, 1.48 equiv) was added dropwise at -78°C. The resulting solution was stirred for another 30 min at -78°C. The reaction was then quenched by the addition of 500 mL of water. The resulting solution was extracted with 3x800 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. This resulted in 82 g (77%) of 8,8-diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate as light yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ 4.18 (q, J = 7.1Hz, 4H), 3.94 (s, 4H), 2.18 (t, J = 6.2Hz, 4H), 1.69 (t, J = 6.2Hz, 4H), 1.25 (t, J = 7.1Hz, 6H) ppm.

Step 3: [8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methanol

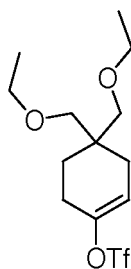
[00333] Into a 2500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed LiAlH₄ (47.9 g, 1.26 mol, 4.02 equiv) and tetrahydrofuran (1 L). This was followed by the addition of 8,8-diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate (90 g, 314.33 mmol, 1.00 equiv) in tetrahydrofuran (200 mL) dropwise with stirring at -20°C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 500 g of Na₂SO₄·10H₂O. The solids were filtered out. The resulting mixture was concentrated under vacuum to give 35 g (55%) of [8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methanol as a white solid. ¹H-NMR (300 MHz, MeOD): δ 3.94 (s, 4H), 3.49 (s, 4H), 1.69-1.59 (m, 4H), 1.59-1.44 (m, 4H) ppm.

Step 4: 8,8-bis(ethoxymethyl)-1,4-dioxaspiro[4.5]decane

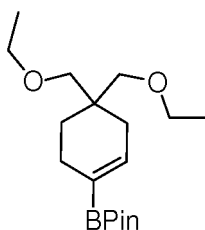
[00334] Into a 1000-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed [8-(hydroxymethyl)-1,4-dioxaspiro[4.5]decan-8-yl]methanol (35 g, 173.06 mmol, 1.00 equiv) and *N,N*-dimethylformamide (400 mL). This was followed by the addition of sodium hydride (21 g, 525.00 mmol, 3.03 equiv, 60%), in portions at 0°C. The mixture was stirred for 30 min at room temperature. To this was added iodoethane (108 g, 692.46 mmol, 4.00 equiv) dropwise with stirring. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 300 mL of water. The resulting solution was extracted with 3x200 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 300 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:20). This resulted in 30 g (67%) of 8,8-bis(ethoxymethyl)-1,4-dioxaspiro[4.5]decane as yellow oil. ¹H-NMR (300 MHz, CDCl₃) δ: 3.93 (s, 4H), 3.46(q, J = 7.0Hz, 4H), 3.29 (s, 4H), 1.65-1.50 (m, 8H), 1.16(t, J = 7.0Hz, 6H) ppm.

Step 5: 4,4-bis(ethoxymethyl)cyclohexan-1-one

[00335] Into a 1000-mL round-bottom flask, was placed 8,8-bis(ethoxymethyl)-1,4-dioxaspiro[4.5]decane (30 g, 116.12 mmol, 1.00 equiv), FeCl₃·6H₂O (62 g, 230.48 mmol, 1.98 equiv) and dichloromethane (300 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was washed with 3x150 mL of water and 150 mL of Na₂CO₃ (sat. aq.). The resulting mixture was washed with 150 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum to give 22.8 g (92%) of 4,4-bis(ethoxymethyl)cyclohexan-1-one as yellow oil. ¹H-NMR (300 MHz, CDCl₃) δ: 3.46(q, J = 7.0Hz, 4H), 3.37 (s, 4H), 2.36 (t, J = 14.1Hz, 4H), 1.77 (t, J = 14.1Hz, 4H), 1.18 (t, J = 7.0Hz, 6H) ppm.

Step 6: 4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate

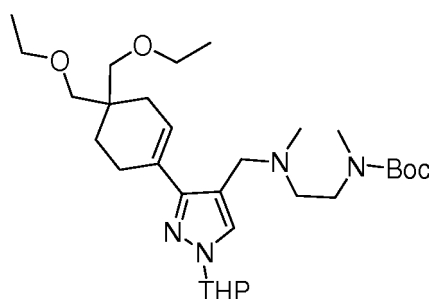
[00336] Into a 1-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 4,4-bis(ethoxymethyl)cyclohexan-1-one (22.8 g, 106.39 mmol, 1.00 equiv) and THF (400 mL). This was followed by the addition of LiHMDS (1M in THF, 117.2 mL) dropwise with stirring at -50°C . The resulting solution was stirred for 1 hr. at -30°C . To this was added a solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethane)sulfonylmethanesulfonamide (41.8 g, 117.00 mmol, 1.10 equiv) in tetrahydrofuran (40 mL) dropwise with stirring at -30°C . The resulting solution was allowed to react, with stirring, for an additional 4 hrs. at room temperature. The reaction was then quenched by the addition of 100 mL of NH_4Cl (sat. aq.). The resulting solution was extracted with 2x100 mL of ethyl acetate and the organic layers combined. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column with petroleum ether (100%) to give 29 g (79%) of 4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate as brown oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 5.78-5.61(m, 1H), 3.44(q, $J = 7.0\text{Hz}$, 4H), 3.27(q, $J = 7.0\text{Hz}$, 4H), 2.49-2.21(m, 2H), 2.20-2.00(m, 2H), 1.74(t, $J = 6.5\text{Hz}$, 2H), 1.18(t, $J = 7.0\text{Hz}$, 6H) ppm.

Step 7: 2-[4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00337] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (29 g, 83.8 mmol, 1.00 equiv), KOAc (32.4 g, 331 mmol, 3.95 equiv), $\text{Pd}(\text{dppf})\text{Cl}_2$ (6.13 g, 8.38 mmol, 0.10 equiv), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (25.5 g, 100.6 mmol, 1.19 equiv) and 1,4-dioxane (300 mL). The resulting solution was stirred overnight at 100°C in an oil bath. The reaction was then quenched by the

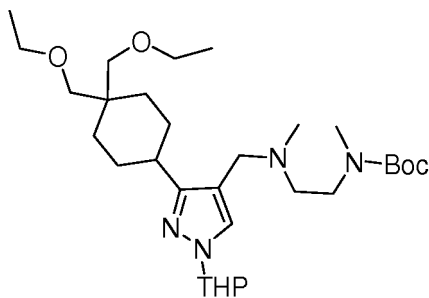
addition of 200 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate. The solids were filtered out and the solution concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:20). This resulted in 22 g (81%) of 2-[4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ: 6.67-6.35(m, 1H), 3.44(q, J = 7.0Hz, 4H), 3.24(q, J = 7.0Hz, 4H), 2.18-2.05(m, 2H), 2.03-1.84(m, 2H), 1.50(t, J = 6.3Hz, 2H), 1.15(t, J = 7.0Hz, 6H) ppm.

Step 8: *tert*-butyl *N*-[2-[(3-[4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl]-*N*-methylcarbamate



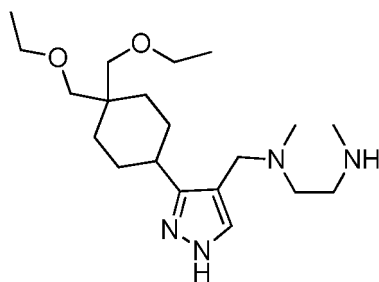
[00338] Into a 1-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 2-[4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22 g, 67.85 mmol, 1.00 equiv), Pd(dppf)Cl₂ (3.38 g, 4.62 mmol, 0.07 equiv), potassium carbonate (19.2 g, 138.92 mmol, 2.05 equiv), water (50 mL), *tert*-butyl *N*-[2-[(3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl]-*N*-methylcarbamate (18 g, 37.63 mmol, 0.55 equiv) and 1,4-dioxane (500 mL). The resulting solution was stirred overnight at 100°C in an oil bath. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (50%). This resulted in 18 g (48%) of *tert*-butyl *N*-[2-[(3-[4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl]-*N*-methylcarbamate as brown oil. ¹H-NMR (300 MHz, CDCl₃) δ: 7.46(s, 1H), 6.08(s, 1H), 5.40-5.22(m, 1H), 4.12-4.00(m, 1H), 3.76-3.60(m, 1H), 3.58-3.20(m, 8H), 2.83(s, 3H), 2.57(s, 3H), 2.45(s, 2H), 2.15-1.95(m, 4H), 1.82-1.52(m, 6H), 1.44(s, 6H), 1.35(s, 9H), 1.15(t, J = 7.0Hz, 6H) ppm.

Step 9: *tert*-butyl *N*-[2-[[[3-[4,4-bis(ethoxymethyl)cyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl](methyl)amino]ethyl]-*N*-methylcarbamate



[00339] Into a 1-L round-bottom flask, was placed *tert*-butyl *N*-[2-[[[3-[4,4-bis(ethoxymethyl)cyclohex-1-en-1-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl](methyl)amino]ethyl]-*N*-methylcarbamate (18.0 g, 32.85 mmol, 1.00 equiv), 10% Pd(OH)₂/C (20 g) and tetrahydrofuran (400 mL). Hydrogen (3 atm) was then applied to the reaction mixture. The resulting solution was stirred for 7 h at room temperature. The solids were filtered out and the solution concentrated under vacuum. The residue was purified by silica gel column with dichloromethane/methanol (3.5%). This resulted in 8.8 g (49%) of *tert*-butyl *N*-[2-[[[3-[4,4-bis(ethoxymethyl)cyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl](methyl)amino]ethyl]-*N*-methylcarbamate as yellow oil. ¹H-NMR (400 MHz, CDCl₃) δ : 7.36(s, 1H), 5.30-5.10(m, 1H), 4.00-3.85(m, 1H), 3.68-3.50(m, 2H), 3.56-3.46(m, 6H), 3.35-3.27(m, 4H), 3.14(s, 2H), 2.77(s, 3H), 2.69-2.37(m, 3H), 1.94(s, 3H), 1.80-1.46(m, 9H), 1.37(s, 9H), 1.30-1.15(m, 4H), 1.10(t, J = 7.0Hz, 6H) ppm.

Step 10: ([3-[4,4-bis(ethoxymethyl)cyclohexyl]-1*H*-pyrazol-4-yl]methyl)(methyl)[2-(methylamino)ethyl]amine hydrochloride salt (Compound 158)

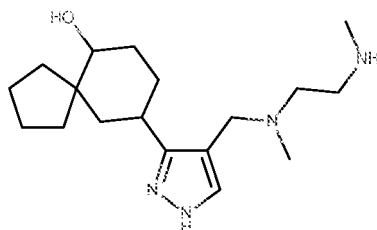


[00340] Into a 500-mL round-bottom flask was placed *tert*-butyl *N*-[2-[[[3-[4,4-bis(ethoxymethyl)cyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl](methyl)amino]ethyl]-*N*-methylcarbamate (8.8 g, 15.98 mmol, 1.00 equiv) and dichloromethane (300 mL). Hydrogen chloride gas was bubbled into the reaction mixture. The resulting solution was stirred for 4 h at room temperature and then concentrated under vacuum. The resulting residue was washed with 1 L of hexane. The solids were collected by filtration. This resulted

in 5.90 g (84%) of ([3-[4,4-bis(ethoxymethyl)cyclohexyl]-1*H*-pyrazol-4-yl]methyl)(methyl)[2-(methylamino)ethyl]amine hydrochloride salt as an off-white solid. ¹H-NMR (300 MHz, D₂O) δ: 7.75(s, 1H), 4.30(s, 2H), 3.57-3.43(m, 10H), 3.23(s, 2H), 2.80-2.67(m, 7H), 1.64-1.54(m, 6H), 1.35-1.20(m, 2H), 1.15-1.05(m, 6H) ppm. LCMS (method M, ESI), RT=1.25min, *m/z* =367.3 [M-2HCl+H]⁺.

Compound 182

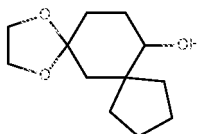
9-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]spiro[4.5]decan-6-ol



Step 1: 1,4-dioxadispiro[4.1.4⁷.3⁵]tetradecan-12-one

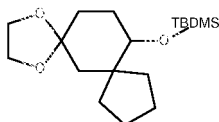
[00341] To a solution of 1,4-dioxaspiro[4.5]decan-8-one (5 g, 32.01 mmol) in toluene (90 ml) was added ^tBuOK (632.26 mg, 5.63 mmol) and the reaction mixture stirred at room temperature for 5 mins. 1,4-Dibromobutane (4 ml, 33.62 mmol) was added and the reaction was heated at reflux for 20 hours. The reaction was monitored by TLC (heptane:EtOAc 80/20, PMA). The reaction was cooled at room temperature, quenched with an aqueous saturated NH₄Cl solution and then diluted with EtOAc. The two layers were separated and the aqueous layer was further extracted with EtOAc (1×). The combined organic layers were washed with water (1×) and brine (1×), dried (MgSO₄) and concentrated to give a crude oil. This product was dissolved in a minimum amount of DCM and loaded on a 340g SNAP KP column and eluted with heptane:EtOAc 6% to 40% on Biotage to give: 3.9 g (58%) of 1,4-dioxadispiro[4.1.4⁷.3⁵] tetradecan-12-one. ¹H-NMR (500 MHz, Chloroform-*d*) δ 4.02 – 3.88 (m, 4H), 2.59 – 2.50 (m, 2H), 2.05 (dd, *J* = 7.9, 4.7 Hz, 2H), 1.99 – 1.95 (m, 2H), 1.93 (s, 2H), 1.60 – 1.46 (m, 6H).

Step 2: 1,4-dioxadispiro[4.1.4⁷.3⁵]tetradecan-12-ol



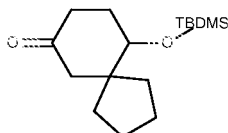
[00342] A solution of 1,4-dioxadispiro[4.1.4^{7.3}⁵]tetradecan-12-one (3.9 g, 18.55 mmol) in MeOH (100 ml) was cooled to 0 °C. NaBH₄ (1.75 g, 46.37 mmol) was added in small portions. The reaction was left to stir at 0°C for 1 hour and then quenched with water. The resulting mixture was stirred for 10 mins at room temperature and then diluted with water and EtOAc. The aqueous layer was back extracted with EtOAc and the combined organic layers were washed with water (1×) and brine (2×), dried (MgSO₄) filtered and the filtrate was concentrated in *vacuo* to give an oil, 2.96 g (75%) of 1,4-dioxadispiro[4.1.4^{7.3}⁵]tetradecan-12-ol. This material was used in the next step without further purification. ¹H-NMR (500 MHz, Chloroform-d) δ 3.93 (s, 4H), 3.52 (dd, J = 6.7, 2.4 Hz, 1H), 1.90 – 1.76 (m, 3H), 1.77 – 1.42 (m, 12H).

Step 3: *tert*-butyl({1,4-dioxadispiro[4.1.4^{7.3}⁵]tetradecan-12-yloxy})dimethylsilane



[00343] To a solution of 1,4-dioxadispiro[4.1.4^{7.3}⁵]tetradecan-12-ol (2.96 g, 13.94 mmol) in DMF (40 ml) was added *tert*-butyl(chloro)dimethylsilane (2.31 g, 15.34 mmol) and 1*H*-imidazole (1.9 g, 27.89 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with ether (3×). The combined organic layers were washed with water (2×) and brine (2×), dried (MgSO₄), filtered and concentrated to give an oil. This was purified by dissolving in a minimum amount of DCM, loading on a 25g KP SNAP column, eluting with 5% - 35% of EtOAc in heptane to give 3.73 g (82%) of *tert*-butyl({1,4-dioxadispiro[4.1.4^{7.3}⁵]tetradecan-12-yloxy}) dimethylsilane. ¹H-NMR (500 MHz, Chloroform-d) δ 3.97 – 3.83 (m, 4H), 3.44 (dd, J = 5.5, 2.2 Hz, 1H), 1.89 (td, J = 12.1, 4.0 Hz, 1H), 1.83 (d, J = 13.5 Hz, 1H), 1.79 – 1.46 (m, 9H), 1.43 – 1.30 (m, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

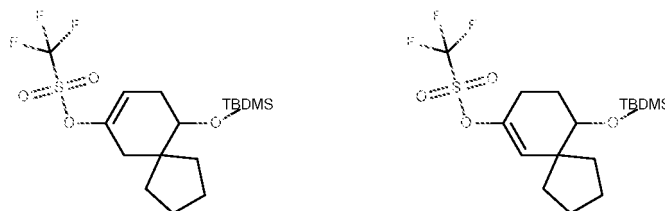
Step 4: 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]decan-7-one



[00344] To a solution of *tert*-butyl({1,4-dioxadispiro[4.1.4^{7.3}⁵]tetradecan-12-yloxy})dimethylsilane (3.7 g, 11.33 mmol) in DCM (120 ml) was added trichloroiron hexahydrate (15.31 g, 56.65 mmol) and the resulting suspension was stirred at room temperature for 2 hours. The reaction was monitored by TLC (9:1 heptane/EtOAc, DNP

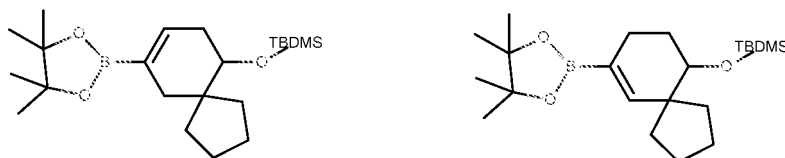
stain). The reaction mixture was diluted with DCM, decanted to remove most of the solid inorganics and washed with aqueous saturated NaHCO_3 (1 $\times$), water (1 $\times$), brine (1 $\times$), dried over MgSO_4 , filtered and the filtrate was concentrated *in vacuo* to give a clear oil: 3.22 g (99%) of 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]decan-7-one. This material was used in the next step. ^1H -NMR (500 MHz, Chloroform- d) δ 3.62 (t, J = 3.3 Hz, 1H), 2.67 – 2.54 (m, 2H), 2.16 (dtd, J = 14.2, 4.6, 2.1 Hz, 1H), 2.06 (d, J = 13.4 Hz, 1H), 1.90 (dt, J = 8.1, 4.2 Hz, 2H), 1.76 – 1.48 (m, 5H), 1.38 (ddd, J = 12.1, 6.7, 5.2 Hz, 1H), 1.28 (ddd, J = 19.8, 7.7, 4.8 Hz, 2H), 0.92 (s, 9H), 0.10 (d, J = 2.9 Hz, 6H).

Step 5: 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec-6-en-7-yl trifluoromethane sulfonate and 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec-7-en-7-yl trifluoromethane sulfonate



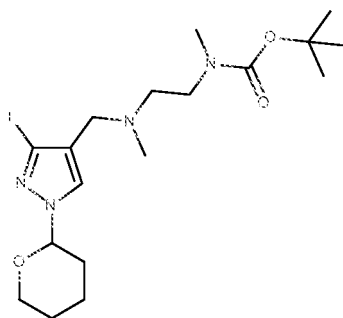
[00345] A solution of 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]decan-7-one (3.2 g, 11.33 mmol) in THF (45 ml) was cooled to -78°C under nitrogen. A 2M solution of LDA in heptanes-THF (7.9 ml) was added and the resulting solution was stirred at -78°C for 1 hour. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (4.45 g, 12.46 mmol) was added at -78°C to the reaction as a solution in THF (15 ml) and the reaction was stirred at -78°C for 1 hour and then left to warm to room temperature and stir overnight. The reaction was quenched by addition of water and diluted with EtOAc. The combined organic layers were washed with water (1 $\times$) and brine (2 $\times$), dried (MgSO_4), filtered and the filtrate was concentrated *in vacuo* to give an oil. This material was dissolved in a minimum amount of DCM and was loaded on a 100g KP SNAP column and eluted with heptane-EtOAc 0% to 25%, to give 2.81 g (60%) of a mixture of 10-[(*tert*-butyldimethylsilyl)oxy] spiro[4.5]dec-6-en-7-yl trifluoromethanesulfonate and 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec- 7-en-7-yl trifluoromethanesulfonate as a clear oil. NMR showed a ratio of 9:1 for the two isomers. ^1H -NMR (500 MHz, Chloroform- d) δ 5.59 (t, J = 3.8 Hz, 0.9H), 5.53 (s, 0.1H), 3.60 (dd, J = 6.2, 3.3 Hz, 0.1H), 3.56 (t, J = 4.2 Hz, 0.9H), 2.46 – 2.40 (m, 1H), 2.40 – 2.32 (m, 1H), 2.13 (ddq, J = 17.9, 4.2, 2.2 Hz, 1H), 2.07 (d, J = 16.6 Hz, 1H), 1.70 – 1.57 (m, 5H), 1.46 – 1.32 (m, 3H), 0.87 (s, 9H), 0.06 (d, J = 4.3 Hz, 6H).

Step 6: *tert*-butyldimethyl{[9-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[4.5]dec-8-en-6-yl]oxy}silane and *tert*-butyldimethyl{[9-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[4.5]dec-9-en-6-yl]oxy}silane



[00346] A suspension of 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec-6-en-7-yl trifluoromethanesulfonate and 10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec-7-en-7-yl trifluoromethanesulfonate (0.74 g, 2.89 mmol), potassium acetate (1.78 g, 18.09 mmol), bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron; dichloromethane, dichloropalladium (99 mg, 0.12 mmol) in 1,4-dioxane (10 ml) was purged with nitrogen for 5 minutes and then heated at 80°C in a pressure tube overnight. The mixture was allowed to cool at room temperature and diluted with EtOAc and filtered through Celite®. The filtrate was washed with water (1×), brine (1×) and dried over MgSO₄. The solvent was evaporated and the residue purified on a 50g KP SNAP column on Biotage eluting with a gradient of heptane:EtOAc (0% to 20%) to give 0.41 g (43%) of a mixture of *tert*-butyldimethyl {9-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[4.5]dec-8-en-6-yl]oxy}silane and *tert*-butyldimethyl {9-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[4.5]dec-9-en-6-yl]oxy}silane, 409 mg (43%) in a 9:1 ratio as shown by NMR. ¹H-NMR (500 MHz, Chloroform-d) δ 6.45 – 6.38 (m, 0.9H), 6.28 (t, J = 1.8 Hz, 0.1H), 3.67 – 3.57 (m, 1H), 2.29 (dtt, J = 18.7, 4.2, 2.0 Hz, 1H), 2.20 (dd, J = 17.4, 1.7 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.94 (dt, J = 17.5, 2.5 Hz, 1H), 1.71 – 1.45 (m, 8H), 1.26 (s, 12H), 0.87 (s, 9H), 0.02 (d, J = 3.7 Hz, 6H).

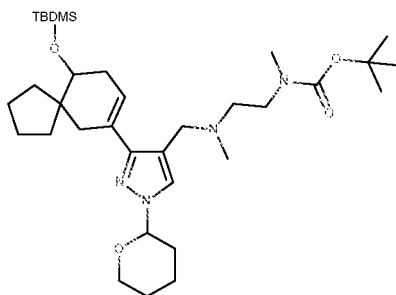
Step 7A: *tert*-butyl *N*-[2-({[3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl})(methyl)amino)ethyl]-*N*-methylcarbamate



[00347] To a solution of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde (7.42 g, 24.25 mmol) in 1,2-dichloroethane (160 ml) was added *tert*-butyl *N*-methyl-*N*-[2-

(methylamino)ethyl]carbamate (90%, 6.14 g, 29.34 mmol) followed by the addition of $\text{NaBH}(\text{OAc})_3$ (10.28 g, 48.49 mmol). The resulting mixture was stirred at room temperature. The reaction mixture was diluted with DCM, washed with brine (2 $\times$), dried over MgSO_4 , and dried *in vacuo*. Purification by flash chromatography using a Biotage Isolera system with a 100 g KP SNAP cartridge, eluting with a gradient of MeOH in DCM (0 to 10%,) afforded *tert*-butyl *N*-[2-({[3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl}(methylamino)ethyl)-*N*-methyl carbamate as a white solid after crystallization from heptane - ether 8.4 g (72%). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.88 – 7.35 (m, 1H), 5.32 (dd, *J* = 9.5, 2.6 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.72 – 3.58 (m, 1H), 3.55 – 3.23 (m, 4H), 2.85 (s, 3H), 2.69 – 2.43 (m, 2H), 2.39 – 2.16 (m, 3H), 2.14 – 1.92 (m, 3H), 1.73 – 1.49 (m, 3H), 1.44 (s, 9H).

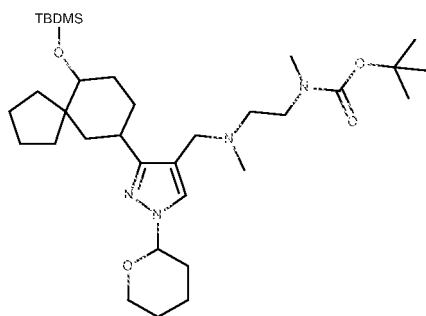
Step 7B: *tert*-butyl *N*-(2-({[3-({10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec-7-en-7-yl}-1-(oxan-2-yl) pyrazol-4-yl)methyl}(methylamino)ethyl)-*N*-methylcarbamate



[00348] A suspension of *tert*-butyl *N*-[2-({[3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl}(methylamino)ethyl)-*N*-methylcarbamate (488 mg, 1.02 mmol), *tert*-butyldimethyl{[9-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[4.5]dec-8-en-6-yl]oxy}silane and *tert*-butyldimethyl{[9-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[4.5]dec-9-en-6-yl]oxy}silane (400 mg, 1.02 mmol) in 1,4-dioxane (2 ml) and aqueous 2M sodium carbonate (1.53 ml) was degassed by bubbling nitrogen for 5 mins. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron, dichloromethane, and dichloropalladium (42 mg, 0.05 mmol) was added and the reaction was heated at 80 °C overnight. The reaction mixture was left to cool to room temperature and then diluted with EtOAc, filtered through Celite® and the solids were washed with EtOAc. The combined filtrates were washed with water (1 $\times$) and brine (2 $\times$), dried (MgSO_4), filtered and concentrated to give an orange oil. This material was purified by loading as a solution in DCM on a 25g SNAP column on Biotage and elution with a gradient of heptane-EtOAc 35% to 100% to give *tert*-butyl *N*-(2-({[3-({10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]dec-7-en-7-yl}-1-(oxan-2-yl)pyrazol-4-yl)methyl}(methylamino)ethyl)-*N*-methylcarbamate, 0.45 g (72%). LC-MS: 2.42 min (3 min method), m/z =617.35. ^1H -NMR (500 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 3.9 Hz, 1H), 5.91

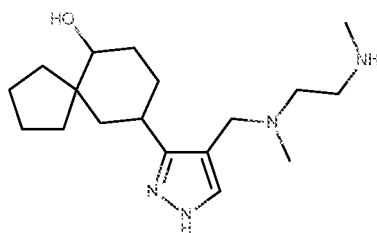
(d, $J = 21.6$ Hz, 1H), 5.26 (dd, $J = 8.9, 2.8$ Hz, 1H), 4.04 – 3.97 (m, 1H), 3.69 – 3.56 (m, 2H), 3.27 (d, $J = 49.4$ Hz, 4H), 2.77 (s, 3H), 2.53 – 2.37 (m, 3H), 2.33 (d, $J = 18.3$ Hz, 1H), 2.25 (d, $J = 16.6$ Hz, 1H), 2.17 (s, 3H), 2.14 – 2.05 (m, 1H), 1.98 (dd, $J = 10.2, 2.9$ Hz, 3H), 1.67 – 1.46 (m, 11H), 1.38 (s, 9H), 0.84 – 0.80 (m, 9H), 0.00 (s, 6H).

Step 8: *tert*-butyl *N*-(2-{[(3-{10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]decan-7-yl}-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate



[00349] A suspension of *tert*-butyl *N*-(2-{[(3-{10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]decan-7-en-7-yl)-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate (453 mg, 0.73 mmol) and Pd/C (10%, 156 mg, 0.147 mmol) in EtOH (10 ml) was stirred at room temperature under an atmosphere of hydrogen for 2 days. The reaction mixture was filtered through Celite® and the filtrate concentrated to give an oil that was purified on Biotage using a SNAP KP 25g column, eluting with a gradient of heptane - EtOAc 25% to 100% to give *tert*-butyl *N*-(2-{[(3-{10-[(*tert*-butyldimethylsilyl)oxy]spiro[4.5]decan-7-yl)-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate, 120 mg (26%). LC-MS: 2.16 min (3 min method), $m/z=619.35$. $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 7.46 (d, $J = 10.4$ Hz, 1H), 5.31 – 5.24 (m, 1H), 4.05 (d, $J = 11.5$ Hz, 1H), 3.67 (td, $J = 11.2, 2.2$ Hz, 1H), 3.48 – 3.21 (m, 5H), 2.88 – 2.73 (m, 4H), 2.55 – 2.38 (m, 2H), 2.22 (s, 3H), 2.07 – 1.88 (m, 6H), 1.70 – 1.48 (m, 12H), 1.43 (d, $J = 10.5$ Hz, 11H), 0.92 (s, 9H), 0.05 (s, 6H).

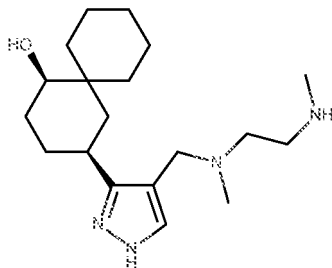
Step 9: 9-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]spiro[4.5]decan-6-ol (Compound 182)



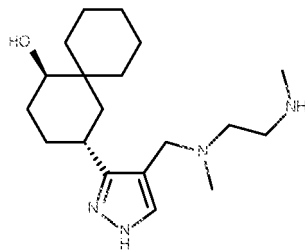
[00350] A suspension of *tert*-butyl *N*-(2-((3-((10-((*tert*-butyldimethylsilyl)oxy)spiro[4.5]decan-7-yl)-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl)-*N*-methylcarbamate (77 mg, 0.12 mmol) in aqueous 6M HCl (0.56 ml) was stirred at room temperature overnight. It was diluted with water and extracted with DCM (2×). The combined organic layers were concentrated to give an oily residue that was dissolved in 1ml DMSO - CH₃CN (1:1) and purified on the Gilson3 using a high pH prep-HPLC method to give 9-[4-((methyl[2-(methylamino)ethyl]amino)methyl)-1*H*-pyrazol-3-yl]spiro[4.5] decan-6-ol, 13 mg (33%) as a white solid. LC-MS: 4.3 min (7 min, high pH), *m/z*=321.3. ¹H-NMR (500 MHz, Methanol-*d*₄) δ 7.47 (s, 0.1H), 7.42 (s, 0.9H), 3.49 (s, 1H), 3.42 (s, 2H), 2.93 (tt, *J* = 12.7, 3.4 Hz, 1H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.37 (s, 3H), 2.20 (s, 3H), 1.99 – 1.85 (m, 2H), 1.86 – 1.72 (m, 3H), 1.72 – 1.50 (m, 6H), 1.47 – 1.30 (m, 3H).

Compounds 183 & 184

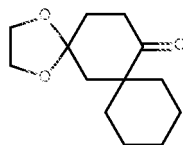
Racemic mixture of (1*R*,4*S*)-4-[4-((methyl[2-(methylamino)ethyl]amino)methyl)-1*H*-pyrazol-3-yl] spiro[5.5]undecan-1-ol (Compound 183):



Racemic mixture of (1*S*,4*S*)-4-[4-((methyl[2-(methylamino)ethyl]amino)methyl)-1*H*-pyrazol-3-yl] spiro[5.5]undecan-1-ol (Compound 184):

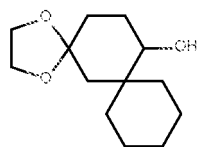


Step 1: 1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-one



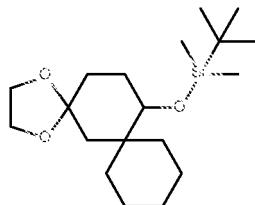
[00351] To a solution of 1,4-dioxaspiro[4.5]decan-8-one (5 g, 32.01 mmol) and 1,5-dibromopentane (7.36 g, 32 mmol) in toluene (120 ml) was added tBuOK (3.59 g, 32 mmol) at RT. The solution was refluxed overnight. The reaction was cooled to RT and quenched with HCl (0.5N, 10ml). The phases were separated and the aqueous was extracted with DCM (3x30ml). The organic extracts were combined and dried over Na₂SO₄ and evaporated to dryness. The residue was purified by Biotage (SNAP 340g, eluent heptane/EtOAc 95/5 to 60/40) to afford 2.35 g of the title compound (33%) as a light colourless oil. ¹H-NMR (500 MHz, Chloroform-d) δ 4.08 – 3.91 (m, 4H), 2.61 – 2.42 (m, 2H), 2.01 – 1.95 (m, 2H), 1.93 (s, 2H), 1.83 – 1.72 (m, 2H), 1.58 – 1.38 (m, 7H), 1.38 – 1.28 (m, 1H). R_f = 0.47 (heptane/EtOAc 7/3).

Step 2: 1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-ol



[00352] Sodium borohydride (0.99 g, 26.19 mmol) was added at 0°C and under nitrogen to 1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-one (2.35 g, 10.48 mmol) in MeOH (120 ml). The reaction was stirred at 0°C until completion (6h). The reaction was quenched slowly with water (100 mL). DCM (50 mL) was added and the layers separated. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford 2.18 g of desired 1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-ol (92%). ¹H-NMR (500 MHz, Chloroform-d) δ 3.97 – 3.86 (m, 4H), 3.52 – 3.44 (m, 1H), 1.90 – 1.79 (m, 3H), 1.77 – 1.62 (m, 2H), 1.61 – 1.34 (m, 10H), 1.35 – 1.18 (m, 2H). R_f = 0.35 (heptane/EtOAc 7/3).

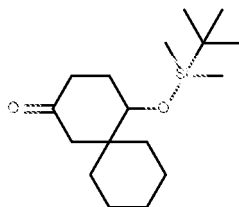
Step 3: *tert*-butyl({1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-yloxy})dimethylsilane



[00353] To a solution of 1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-ol (2.18 g, 9.63 mmol) in DMF (20 ml) was added *tert*-butyl(chloro)dimethylsilane (2.18 g, 14.45 mmol) and 1*H*-imidazole (1.32 g, 19.27 mmol). The reaction was stirred at RT overnight. The reaction mixture was diluted with water and extracted with EtOAc (3x50 ml). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by Biotage (SNAP

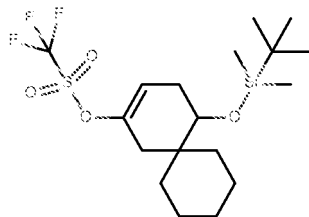
100g, eluent heptane/EtOAc 95/5 to 80/20) to afford 2.45 g of desired material (75%). ¹H-NMR (500 MHz, Chloroform-d) δ 4.02 – 3.80 (m, 4H), 3.49 – 3.38 (m, 1H), 1.89 (td, J = 12.2, 4.2 Hz, 1H), 1.84 – 1.71 (m, 2H), 1.64 – 1.15 (m, 13H), 0.89 (s, 9H), 0.04 (d, J = 2.2 Hz, 6H). R_f = 0.60 (EtOAc/heptane 10/90).

Step 4: 5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undecan-2-one



[00354] To a solution of *tert*-butyl({1,4-dioxadispiro[4.1.5⁷.3⁵]pentadecan-13-yl oxy})dimethylsilane (2.45 g, 7.19 mmol) in DCM (100ml) was added iron trichloride hexahydrate (1.94 g, 7.19 mmol). After 2h, no more starting material was detected by TLC. The reaction mixture was washed with water (50ml), aq sat NaHCO₃ (50ml), brine (50ml), the organic layer was dried over Na₂SO₄ and evaporated to dryness to afford 2.08g of ketone as a clear oil (97%). ¹H-NMR (500 MHz, Chloroform-d) δ 3.67 (s, 1H), 2.67 – 2.48 (m, 2H), 2.26 – 2.11 (m, 2H), 2.00 (dddd, J = 14.5, 12.2, 5.4, 2.5 Hz, 1H), 1.87 (ddt, J = 14.2, 7.1, 3.7 Hz, 1H), 1.64 – 1.17 (m, 10H), 0.92 (s, 9H), 0.10 (t, J = 2.9 Hz, 6H). R_f = 0.40 (EtOAc/heptane 10/90).

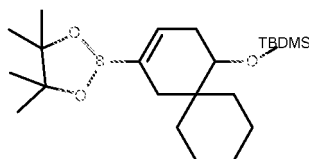
Step 5: 5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undec-2-en-2-yl trifluoromethanesulfonate



[00355] A stirred solution of 5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undecan-2-one (2 g, 6.8 mmol) was dissolved in dry THF (160 mL) and cooled to -78°C. To this 0.18M LHMDS in THF (73.5 mL) was added dropwise. The reaction was stirred for 45 min and a solution of *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-[(trifluoromethyl)sulfonyl]methane sulfonamide (5g, 12.75 mmol) in THF (60 mL) was added dropwise over 10 minutes, the reaction was stirred at -78°C for 1 hr, then allowed to warm to RT over 3 hr. The reaction was quenched by addition of sat. NH₄Cl (100 mL). EtOAc (100 mL) was added and the organic layer separated. The aqueous layer was washed (2 x 100mL EtOAc), and the organics combined, dried (Na₂SO₄), filtered, and solvent removed under reduced pressure to leave 8.4 g yellow

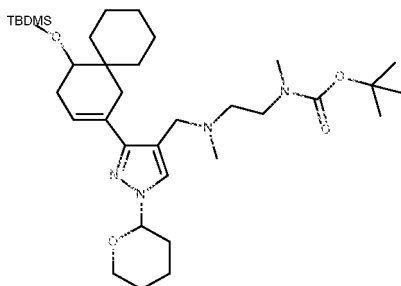
crude material. The crude product was purified using silica gel column chromatography (Biotage SNAP-HP 100g cartridge, dry loaded, eluent heptane:EtOAc 99:1 to 9:1) to afford 2.16 g of the target material as a colourless free flowing oil (71%, 95% purity). ¹H-NMR (500 MHz, Chloroform-*d*) δ 5.54 (d, *J* = 4.1 Hz, 1H), 3.51 (t, *J* = 3.9 Hz, 1H), 2.48 – 2.30 (m, 2H), 2.16 – 2.06 (m, 2H), 1.64 – 1.17 (m, 10H), 0.88 (s, 9H), 0.05 (s, 6H). R_f = 0.61 (EtOAc/heptane 5/95). LC-MS: 2.72 min (hydrophobic LC-MS method), no ionisation.

Step 6: *tert*-butyldimethyl[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[5.5]undec-3-en-1-yl]oxy}silane



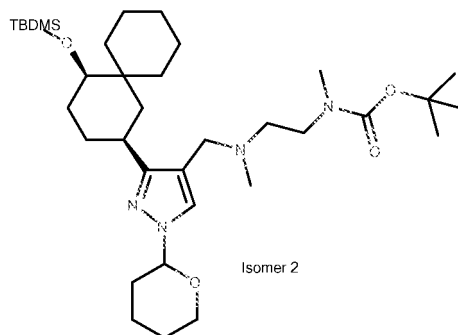
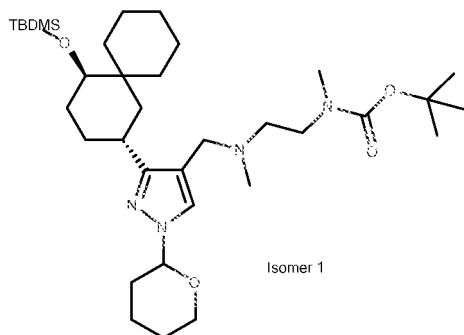
[00356] 5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undec-2-en-2-yl trifluoromethanesulfonate (90%, 500 mg, 1.05 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (320 mg, 1.26 mmol), Pd(dppf)Cl₂ (43 mg, 0.05 mmol) and potassium acetate (770 mg, 7.87 mmol) were suspended in dioxane (5ml). The solution was degassed with nitrogen for 10min and then heated to 80°C. After 2h, no SM was visible by LCMS but still a trace by TLC. The reaction was allowed to cool to RT and stirred O/N. Water (10ml) was added and the reaction was extracted with EtOAc (2x20ml). The combined organic layers were washed with water (10ml) and was dried over Na₂SO₄ and evaporated to dryness. The residue was purified by Biotage (SNAP 50g, eluent heptane/EtOAc 100/0 to 90/10) to afford 310 mg of desired boronic ester (65%) as a colourless oil. ¹H-NMR (500 MHz, Chloroform-*d*) δ 6.57 (s, 0H), 6.45 – 6.32 (m, 1H), 3.58 – 3.40 (m, 1H), 2.36 (dd, *J* = 17.6, 1.9 Hz, 1H), 2.30 – 2.20 (m, 1H), 2.05 (ddd, *J* = 18.8, 5.9, 3.1 Hz, 1H), 1.79 (dd, *J* = 17.6, 2.2 Hz, 1H), 1.60 – 1.06 (m, 22H), 0.91 – 0.83 (m, 9H), 0.01 (d, *J* = 1.4 Hz, 6H). R_f = 0.47 (EtOAc/heptane 5/95). LC-MS: 2.85 min (hydrophobic LC-MS method), no ionisation.

Step 7: *tert*-butyl *N*-(2-[(3-{5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undec-2-en-2-yl}-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate



[00357] *tert*-Butyldimethyl{[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[5.5]undec-3-en-1-yl]oxy}silane (90%, 200 mg, 0.44 mmol), *tert*-butyl-*N*-(2-[(3-iodo-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (140 mg, 0.29 mmol), Pd(dppf)Cl₂ (24 mg, 29 μmol) and dipotassium carbonate (122 mg, 0.88 mmol) were suspended in a mixture of dioxane (14ml) and water (1ml). The reaction was degassed with nitrogen for 10min and then heated to 100°C under nitrogen. After overnight, TLC and LCMS showed the presence of desired material. The solvent was removed under reduced pressure and the residue was purified by Biotage (SNAP 50g, eluent heptane /EtOAc 83/17 to 0/100) to afford 140 mg of desired alkene (87%) as a yellow oil. ¹H-NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.40 (m, 1H), 6.00 – 5.85 (m, 1H), 5.32 (dd, *J* = 9.2, 2.9 Hz, 1H), 4.06 (d, *J* = 9.9 Hz, 1H), 3.72 – 3.64 (m, 1H), 3.60 (t, *J* = 5.4 Hz, 1H), 3.43 – 3.21 (m, 3H), 2.82 (s, 2H), 2.62 (d, *J* = 14.6 Hz, 1H), 2.46 (s, 2H), 2.34 (d, *J* = 17.8 Hz, 1H), 2.19 (d, *J* = 19.2 Hz, 4H), 1.93 (d, *J* = 15.1 Hz, 1H), 1.76 – 1.34 (m, 18H), 1.24 (s, 9H), 0.88 (s, 9H), 0.04 (d, *J* = 2.3 Hz, 6H). LCMS: 1.59 min (2min method), *m/z* = 631.25. *R_f* = 0.30 (heptane/EtOAc, 3/7, UV and PMA).

Step 8: Racemic *tert*-butyl *N*-{2-[(3-[(2*S*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undecan-2-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl}-*N*-methylcarbamate and racemic *tert*-butyl *N*-{2-[(3-[(2*S*,5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undecan-2-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl}-*N*-methylcarbamate



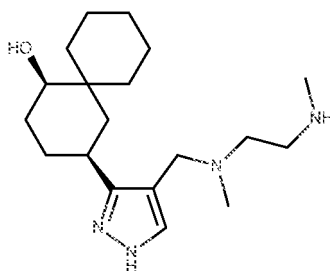
[00358] *tert*-Butyl *N*-(2-[(3-{5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undec-2-en-2-yl}-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (140 mg, 0.26 mmol) and palladium on carbon (10%) (27 mg, 0.26 mmol) were suspended in EtOH (5ml). The reaction was stirred at RT under hydrogen atmosphere. LCMS after overnight shows only starting material. The solution was filtered on Celite and washed with MeOH (2x 10ml). The filtrate was evaporated and the residue was dissolved in EtOH (5ml) and palladium on carbon (10%) (27 mg, 0.26 mmol) added. The reaction was stirred at RT under hydrogen atmosphere for 36h. The solution was filtered on Celite and washed with MeOH (2x 10ml). The filtrate

was evaporated and the residue was purified by Biotage (SNAP HP 10g, eluent heptane/EtOAc 95/5 to 0/100) to afford 40 mg of deaminated side product (43%) as a yellow oil, 10 mg of isomer 1 (7%) as a yellow oil and 40 mg of isomer 2 (28%) as a yellow oil.

Deaminated side product: $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 7.30 – 7.27 (m, 1H), 5.31 – 5.23 (m, 1H), 4.10 – 4.00 (m, 1H), 3.73 – 3.62 (m, 1H), 3.56 – 3.50 (m, 1H), 2.97 – 2.85 (m, 1H), 2.08 (s, 3H), 2.06 – 1.96 (m, 4H), 1.85 – 1.72 (m, 2H), 1.72 – 1.62 (m, 4H), 1.62 – 1.51 (m, 4H), 1.43 (dd, J = 10.3, 5.5 Hz, 4H), 1.40 – 1.19 (m, 4H), 0.91 (d, J = 3.3 Hz, 9H), 0.05 (d, J = 3.9 Hz, 6H). R_f = 0.80 (heptane/EtOAc 3/7). LC-MS: 2.73 min (hydrophobic LC-MS method), m/z = 447.2. Isomer 1: $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 7.53 – 7.39 (m, 1H), 5.35 – 5.22 (m, 1H), 4.04 (d, J = 9.9 Hz, 1H), 3.75 – 3.61 (m, 1H), 3.56 – 3.21 (m, 5H), 2.96 – 2.78 (m, 4H), 2.61 – 2.38 (m, 2H), 2.30 – 2.15 (m, 3H), 2.11 – 1.88 (m, 5H), 1.84 – 1.50 (m, 12H), 1.50 – 1.39 (m, 14H), 1.30 – 1.16 (m, 13H), 0.92 (s, 9H), 0.09 – -0.00 (m, 6H). R_f = 0.44 (heptane/EtOAc 3/7). LC-MS: 1.72 min (2.5 minute LC-MS method), m/z = 633.25.

Isomer 2: $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 7.56 – 7.37 (m, 1H), 5.32 – 5.24 (m, 1H), 4.04 (d, J = 9.9 Hz, 1H), 3.67 (td, J = 10.1, 8.9, 4.3 Hz, 1H), 3.55 – 3.18 (m, 5H), 2.90 (t, J = 12.9 Hz, 1H), 2.82 (s, 3H), 2.58 – 2.39 (m, 2H), 2.29 – 2.18 (m, 3H), 2.05 – 1.91 (m, 4H), 1.83 – 1.50 (m, 9H), 1.50 – 1.39 (m, 13H), 1.36 – 1.20 (m, 5H), 0.92 (s, 9H), 0.05 (d, J = 4.9 Hz, 6H). R_f = 0.35 (heptane/EtOAc 3/7). LC-MS: 1.66 min (2.5 minute LC-MS method), m/z = 633.25.

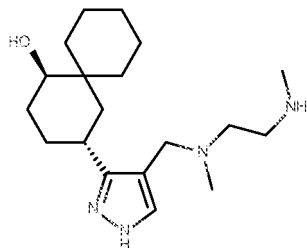
Step 9 (isomer 2): Racemic mixture of (1*R*,4*S*)-4-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl] spiro[5.5]undecan-1-ol (Compound 183)



[00359] *tert*-Butyl *N*-(2-[[[(3-{5-[(*tert*-butyldimethylsilyl)oxy]spiro[5.5]undecan-2-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl]-*N*-methylcarbamate (40 mg, 0.06 mmol) was dissolved in dioxane (1ml) and HCl (6M, 1ml) was added. The reaction was monitored by LCMS. After 2h, no more starting material was left and full conversion to the desired mass detected (mass trace only). The solvent was removed under reduced pressure and the residue was purified by SCX (2g) column eluting with MeOH (10ml) then

MeOH/NH₃ (10ml) to afford 20 mg (85%) of the desired material at 90% purity (assessed by ¹H-NMR). ¹H-NMR (500 MHz, Chloroform-d) δ 7.40 (s, 1H), 3.67 (s, 1H), 3.36 (s, 2H), 2.99 (tt, J = 13.0, 3.7 Hz, 1H), 2.68 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 5.9 Hz, 2H), 2.41 (s, 3H), 2.18 – 2.15 (m, 1H), 2.14 (s, 3H), 2.09 – 1.97 (m, 1H), 1.95 – 1.84 (m, 1H), 1.83 – 1.69 (m, 3H), 1.62 (d, J = 10.2 Hz, 4H), 1.54 – 1.26 (m, 9H).

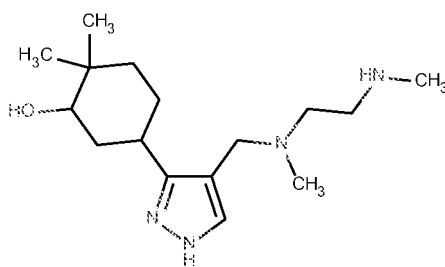
Step 9 (isomer 1): Racemic mixture of (1*S*,4*S*)-4-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl] spiro[5.5]undecan-1-ol (Compound 184)



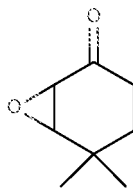
[00360] Similarly, 5 mg of title compound were isolated from 10 mg reaction (85% yield, 80% purity). ¹H-NMR (500 MHz, Chloroform-d) δ 7.47 – 7.32 (m, 1H), 3.68 (s, 1H), 3.41 – 3.34 (m, 2H), 3.05 – 2.91 (m, 1H), 2.89 – 2.75 (m, 3H), 2.64 – 2.55 (m, 2H), 2.53 – 2.44 (m, 3H), 2.31 – 2.20 (m, 1H), 2.19 – 2.14 (m, 2H), 2.08 – 1.96 (m, 1H), 1.94 – 1.83 (m, 1H), 1.81 – 1.70 (m, 2H), 1.70 – 1.55 (m, 4H), 1.55 – 1.19 (m, 10H).

Compound 185

2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol



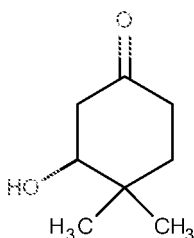
Step 1: 5,5-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one



[00361] To an ice-cold solution of 4,4-dimethyl-cyclohex-2-enone (1.00 g, 8.05 mmol) in methanol (8 mL) was added 35% hydrogen peroxide (4.6 mL, 40.91 mmol) followed by 0.5

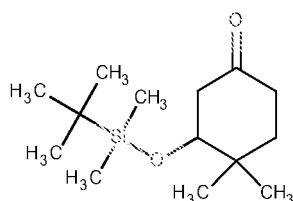
N NaOH (2.2 mL, 1.1 mmol). The mixture was stirred at 0 °C for 5 h, stored in a fridge (4 °C) overnight and then stirred at 0 °C for another 5 h. After this time the reaction mixture was concentrated *in vacuo*, then water (15 mL) was added, and the mixture extracted with dichloromethane (3 x 50 mL). The organic layers were combined, washed with 10% Na₂SO₃ (2 x 40 mL) and brine, dried over Na₂SO₄, filtered and concentrated at reduced pressure to afford 5,5-dimethyl-7-oxa-bicyclo[4.1.0]heptan-2-one as a colourless oil (1.18 g, quant): MS (ESI+) for C₈H₁₂O₂ *m/z* 141.0 (M+H)⁺; HPLC purity 88 % (ret. time, 1.00 min); ¹H-NMR (500 MHz, Chloroform-d) δ 3.23 (d, J = 4.0 Hz, 1H), 3.18 (dd, J = 4.0, 1.1 Hz, 1H), 2.41 (ddd, J = 18.9, 6.4, 3.0 Hz, 1H), 2.19 (ddd, J = 18.9, 11.7, 7.0 Hz, 1H), 1.91 (ddd, J = 13.5, 11.9, 6.4 Hz, 1H), 1.34 (dddd, J = 13.6, 7.0, 3.0, 1.2 Hz, 1H), 1.22 (s, 3H), 1.07 (s, 3H).

Step 2: 3-hydroxy-4,4-dimethylcyclohexan-1-one



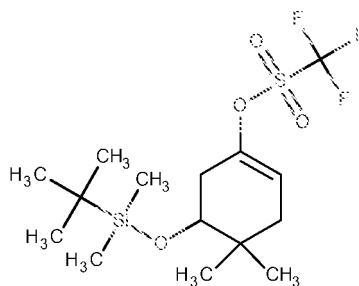
[00362] Lithium (sticks) metal (74.27 mg, 10.70 mmol) was added to a solution of naphthalene (1.83 g, 14.27 mmol) in dry THF (25 ml) at RT and stirred until the metal was dissolved (~ 3 h) before cooling to -78 °C. A solution of 5,5-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one (0.50 g, 3.57 mmol) in dry THF (10 ml) was then added and stirred for 20 min. Water (5 ml) was added and the reaction was allowed to warm to RT. Water (20 ml) was added to the reaction mixture and the product extracted with Et₂O (2 x 50 ml). This was dried over Na₂SO₄, filtered and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 25 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes + 1 % TEA (1:9 - 9:1), gave the desired product as a colourless oil (210 mg, 41 %): ¹H-NMR (500 MHz, Chloroform-d) δ 3.72 (dd, J = 8.1, 4.3 Hz, 1H), 2.67 (ddd, J = 14.9, 4.3, 1.0 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.39 – 2.32 (m, 2H), 1.89 (dt, J = 13.3, 6.6 Hz, 1H), 1.51 (ddd, J = 14.3, 8.3, 6.4 Hz, 1H), 1.15 (s, 3H), 1.10 (s, 3H).

Step 3: 3-[(tert-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexan-1-one



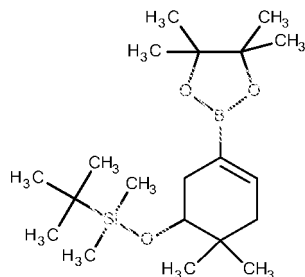
[00363] *tert*-Butyldimethylsilylchloride (0.43 g, 2.84 mmol) was added to a solution of 3-hydroxy-4,4-dimethylcyclohexan-1-one (0.34 g, 2.37 mmol) and imidazole (0.39 g, 5.69 mmol) in DCM (10 ml) at RT and stirred over the weekend. The reaction mixture was diluted with DCM (50 ml) and washed with water (50 ml) and then brine (50 ml), dried over Na₂SO₄, filtered and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 25 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (1:9 - 2:8 - 1) gave the desired product as a colourless oil (193 mg, 31 %): ¹H-NMR (500 MHz, Chloroform-d) δ 3.64 (dd, *J* = 7.4, 4.2 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.39 – 2.25 (m, 3H), 1.90 – 1.81 (m, 1H), 1.47 – 1.40 (m, 1H), 1.07 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 6.0 Hz, 6H).

Step 4: 5-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate



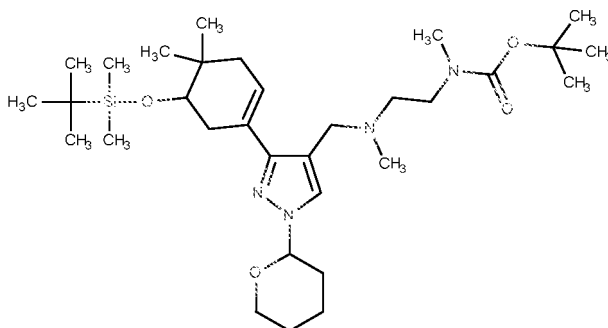
[00364] 2 M LDA in THF (0.96 ml, 1.92 mmol) was added to a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexan-1-one (0.35 g, 1.37 mmol) in dry THF (10 ml) at -78 °C and stirred for 1 hr under N₂. 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (0.59 g, 0.53 mmol) was added to the reaction as a solution in THF (1 ml) and the reaction was stirred at -78 °C for 1 hour and then left to warm to RT and stirred overnight. The reaction was quenched by the addition of water (1 ml) and diluted with ethyl acetate (30 ml). This was washed with water (30 ml) then brine (30 ml), dried over Na₂SO₄, filtered and evaporated *in vacuo*, to give an oil. This was dissolved in minimum amount of DCM and was loaded on a 25g KP SNAP column and eluted with heptane-EtOAc 0 % to 6 % to give 335 mg (62 %) of the desired product as a colourless oil: ¹H-NMR (500 MHz, Chloroform-d) δ 5.62 – 5.48 (m, 1H), 3.54 – 3.44 (m, 1H), 2.50 – 2.42 (m, 1H), 2.24 – 2.15 (m, 1H), 2.11 – 2.03 (m, 1H), 1.85 – 1.77 (m, 1H), 0.85 – 0.81 (m, 15H), -0.01 (d, *J* = 7.3 Hz, 6H).

Step 5: *tert*-butyl({[6,6-dimethyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]oxy})dimethylsilane



[00365] A suspension of 5-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (0.34 g, 0.86 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (0.33 g, 1.29 mmol) and KOAc (0.59 g, 6.04 mmol) in 1,4-dioxane (5 ml) was degassed with a nitrogen sparge for 10 min whilst stirring at RT. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron, dichloromethane and dichloro palladium (0.07 g, 0.09 mmol) was added to this suspension and stirred at 90 °C for 3.5 h before allowing to cool to RT overnight. The reaction mixture was diluted with EtOAc (10 ml) and water (10 ml). The organic layer was separated and the aqueous was extracted with EtOAc (10 ml). The combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 25 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (0 - 1), gave the desired product as a colourless oil (250 mg, 79 %): ¹H-NMR (500 MHz, Chloroform-d) δ 6.49 – 6.15 (m, 1H), 3.52 – 3.42 (m, 1H), 2.32 – 2.21 (m, 1H), 2.12 – 1.98 (m, 2H), 1.93 – 1.83 (m, 1H), 1.25 (d, J = 3.3 Hz, 12H), 0.91 (s, 3H), 0.87 (d, J = 3.8 Hz, 9H), 0.82 (d, J = 3.4 Hz, 3H), 0.07 – 0.02 (m, 6H).

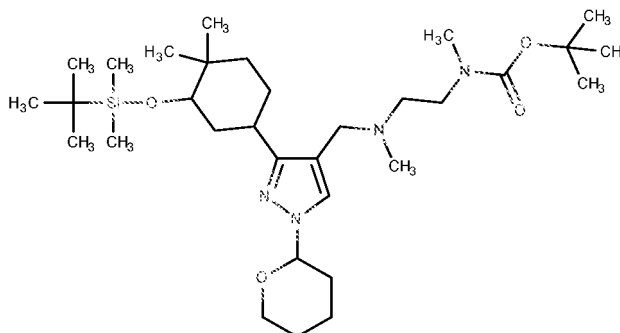
Step 6: *tert*-butyl *N*-(2-({[3-(5-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate



[00366] A suspension of *tert*-butyl({[6,6-dimethyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]oxy})dimethylsilane (0.15 g, 0.41 mmol), *tert*-butyl *N*-[2-({[3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl}(methyl)amino)ethyl]-*N*-methylcarbamate (0.13 g, 0.27

mmol) and KOAc (0.11 g, 0.82 mmol) in 1,4-dioxane (10 ml) and water (1 ml) was degassed with a nitrogen sparge for 10 min whilst stirring. Pd(dppf)Cl₂.DCM (0.02 g, 0.03 mmol) was added to the reaction mixture which was then stirred at 100 °C for 18 hr in a sealed tube. The reaction was then allowed to cool to RT and evaporated *in vacuo*. The residue was absorbed onto silica gel (~ 5 ml). Purification by silica gel column chromatography, on a Biotage Isolera system, using a 25 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (+1 % TEA, 1:9 - 1), gave the desired product as a yellow oil (120 mg, 75 %): MS (ESI+) for C₃₂H₅₈N₄O₄Si *m/z* 591.25 (M+H)⁺; HPLC purity 100 % (ret. time, 1.39 min); ¹H-NMR (500 MHz, Chloroform-d) δ 7.68 – 7.40 (m, 1H), 6.06 – 5.73 (m, 1H), 5.37 – 5.27 (m, 1H), 4.09 – 4.02 (m, 1H), 3.72 – 3.64 (m, 1H), 3.61 (dd, J = 8.0, 5.4 Hz, 1H), 3.48 – 3.31 (m, 2H), 3.27 (s, 1H), 3.18 – 3.05 (m, 1H), 2.94 – 2.75 (m, 3H), 2.71 – 2.61 (m, 1H), 2.54 – 2.40 (m, 2H), 2.40 – 2.30 (m, 1H), 2.27 – 2.16 (m, 2H), 2.13 – 1.95 (m, 5H), 1.66 (d, J = 8.9 Hz, 2H), 1.49 – 1.39 (m, 9H), 0.96 – 0.79 (m, 15H), 0.13 – -0.01 (m, 6H).

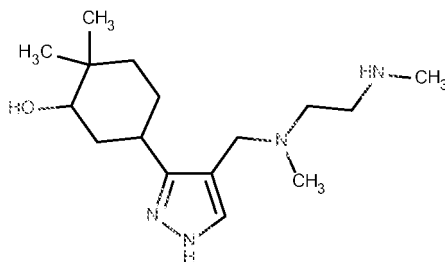
Step 7: *tert*-butyl *N*-(2-[[3-{3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexyl}-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate



[00367] A mixture of *tert*-butyl *N*-(2-[[3-{3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl}-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino}ethyl)-*N*-methylcarbamate (120 mg, 0.20 mmol) and 10 % Pd-C (0.01 g) in EtOH (10 ml) was stirred under an atmosphere of hydrogen for 18 hrs. This was filtered and recharged with another portion of 10 % Pd-C and hydrogen and stirred overnight. The reaction mixture was filtered and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 10 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (1:9 - 1), gave the desired product as a colourless glass (49 mg, 40 %): MS (ESI+) for C₃₂H₆₀N₄O₄Si *m/z* 593.25 (M+H)⁺; HPLC purity 99% (ret. time, 1.41 min); ¹H-NMR (500 MHz, Chloroform-d) δ 7.44 (d, J = 25.2 Hz, 1H), 5.34 – 5.23 (m, 1H), 4.09 – 4.00 (m, 1H), 3.74 – 3.62 (m, 1H), 3.53 – 3.22 (m, 5H), 2.91 – 2.78 (m, 3H), 2.74 – 2.63 (m, 1H), 2.45 (s, 2H), 2.19 (d, J = 19.7 Hz, 3H), 2.07 – 1.96 (m, 3H), 1.76 (tt, J = 13.0, 7.9 Hz, 3H), 1.70 –

1.48 (m, 5H), 1.48 – 1.39 (m, 10H), 1.34 – 1.16 (m, 3H), 0.95 – 0.90 (m, 7H), 0.86 (s, 9H).

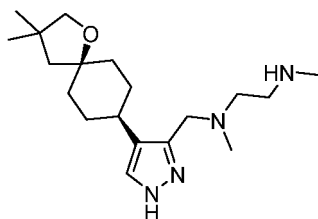
Step 8: 2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol (Compound 185)



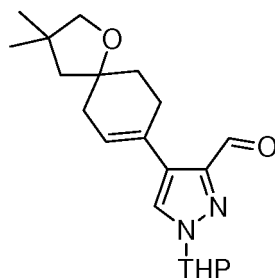
[00368] 6 N HCl (2 ml) was added to a solution of *tert*-butyl *N*-(2-{[(3-{3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexyl}-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl] (methyl)amino}ethyl)-*N*-methylcarbamate (49 mg, 0.08 mmol) in 1,4-dioxane (2 ml) at 0 °C and stirred whilst allowing to warm to RT. The reaction was stirred overnight then evaporated to dryness, then evaporated from MeOH (2 x 10 ml). The product was dissolved in MeOH (5 ml) and eluted onto a 2 g Isolute SCX-2 cartridge. MeOH (2 x 10 ml) was eluted then the product was released with 7 N NH₃ in MeOH (2 x 10 ml). This was evaporated to dryness to give ~20 mg of the product. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 10 g KP-Sil SNAP cartridge, eluting with DCM:MeOH (1:9) and then 7 N NH₃ in MeOH:DCM (1:99 - 1:9) gave the desired product as a colourless glass (16 mg, 66 %): ¹H-NMR (500 MHz, Methanol-d₄) δ 7.44 (s, 1H), 3.43 (d, *J* = 8.9 Hz, 2H), 3.40 – 3.35 (m, 1H), 2.84 (ddt, *J* = 12.5, 7.9, 4.0 Hz, 1H), 2.76 – 2.64 (m, 2H), 2.52 (td, *J* = 6.5, 2.5 Hz, 2H), 2.38 (d, *J* = 6.3 Hz, 3H), 2.20 (d, *J* = 3.4 Hz, 3H), 1.76 (ddd, *J* = 24.8, 12.4, 4.2 Hz, 3H), 1.63 – 1.50 (m, 2H), 1.41 – 1.26 (m, 2H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 4.2 Hz, 3H); MS (ESI+) for C₁₆H₃₀N₄O *m/z* 295.05 (M+H)⁺.

Compound 200

Methyl[2-(methylamino)ethyl]([4-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-3-yl)methyl)amine trifluoroacetic acid salt

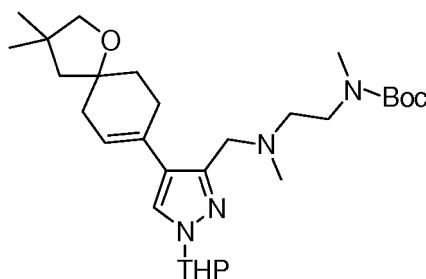


Step 1: (*R/S*)-4-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazole-

3-carbaldehyde

[00369] Into a 50-mL round-bottom flask purged and maintained with an atmosphere of nitrogen was added 2-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 1.71 mmol, 1.00 equiv), 4-iodo-1-(oxan-2-yl)-1*H*-pyrazole-3-carbaldehyde (523 mg, 1.71 mmol, 1.00 equiv), Pd(dppf)Cl₂ (124 mg, 0.17 mmol, 0.10 equiv), K₃PO₄ (1.087 g, 5.12 mmol, 2.99 equiv), ethylene glycol dimethyl ether (10 mL) and water (1 mL). The resulting solution was stirred overnight at 75°C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) as eluent to afford 270 mg (46%) of (*R/S*) 4-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazole-3-carbaldehyde as a yellow oil.

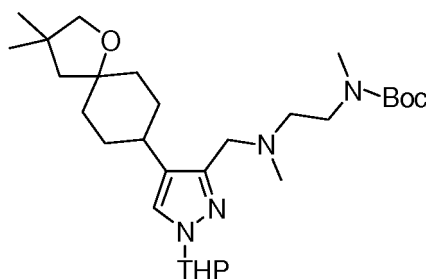
Step 2: (*R/S*) *tert*-butyl *N*-(2-[[4-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



[00370] Into a 50-mL round-bottom flask was placed 4-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazole-3-carbaldehyde (270 mg, 0.78 mmol, 1.00 equiv), *tert*-butyl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate (220 mg, 1.17 mmol, 1.49 equiv) and dichloroethane (10 mL). NaBH(OAc)₃ (496 mg, 2.34 mmol, 2.98 equiv) was added portionwise and the resultant mixture stirred overnight at room temperature. The reaction was quenched with 15 mL of water and extracted with 3x15 mL of dichloromethane. The combined organic layers were washed with 20 mL of brine and dried over anhydrous sodium sulfate and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol (20:1) to afford 300 mg (74%) of (*R/S*) *tert*-butyl *N*-(2-[[4-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-

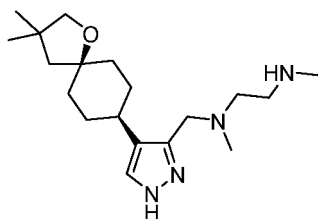
yl)-1*H*-pyrazol-3-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.43 (s, 1H), 5.78-5.50 (m, 1H), 4.79-4.58 (m, 1H), 4.15-3.77 (m, 2H), 3.77-3.40 (m, 4H), 3.40-3.05 (m, 2H), 3.00-2.68 (m, 4H), 2.68-1.99 (m, 10H), 1.99-1.82 (m, 2H), 1.82-1.50 (m, 6H), 1.44 (s, 9H), 1.13 (s, 6H) ppm.

Step 3: (*R/S*) *tert*-butyl *N*-(2-[[4-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



[00371] Into a 100-mL round-bottom flask was placed *tert*-butyl *N*-(2-[[4-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (300 mg, 0.58 mmol, 1.00 equiv), 10% Pd(OH)₂/C (300 mg) and tetrahydrofuran (30 mL). The resulting reaction mixture was stirred for 1 h at room temperature under 3 atmospheres of hydrogen. The reaction vessel was purged with an inert gas and the mixture filtered under a blanket of inert gas. The filtrate was concentrated under vacuum to provide 300 mg (100%) of (*R/S*) *tert*-butyl *N*-(2-[[4-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.45 (s, 1H), 5.74-5.53 (m, 1H), 4.10-3.98 (m, 1H), 3.40-3.25 (m, 3H), 2.79 (s, 3H), 2.60-2.30 (m, 5H), 2.30-2.15 (m, 3H), 1.99-1.75 (m, 8H), 1.75-1.50 (m, 10H), 1.42 (s, 9H), 1.10 (s, 6H).

Step 4: Methyl[2-(methylamino)ethyl]([4-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-3-yl)methyl)amine trifluoroacetic acid salt (Compound 200)

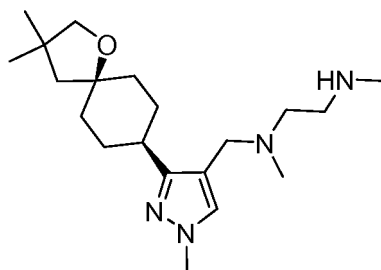


[00372] Into a 50-mL round-bottom flask was placed (*R/S*) *tert*-butyl *N*-(2-[[4-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (300 mg, 0.58 mmol, 1.00 equiv), trifluoroacetic acid (5 mL) and dichloromethane (5 mL). The resulting solution was stirred for 30 min at room temperature and then concentrated under vacuum. The crude product (307

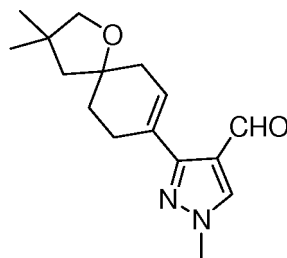
mg) was purified by Prep-HPLC with the following conditions (Prep-HPLC-005(Waters): Column, Atlantis Prep OBD T3 Column, 19x150mm, 5 μ m; mobile phase, water with 0.05% trifluoroacetic acid and CH₃CN (up to 3.0% in 10 min, up to 100% in 1 min, hold at 100% for 1 min); Detector, UV 220 nm. This resulted in 154.5 mg (50%) of (*R/S*) methyl[2-(methylamino)ethyl]([4-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-3-yl)methyl)amine trifluoroacetic acid salt as a colorless solid. ¹H-NMR (300 MHz, D₂O) δ : 7.71 (s, 1H), 4.49 (s, 2H), 3.70-3.50 (m, 6H), 2.94 (s, 3H), 2.80 (s, 3H), 2.62-2.49 (m, 1H), 2.05-1.87 (m, 2H), 1.79-1.52 (m, 8H), 1.10 (s, 6H) ppm.

Compound 205

Methyl([1-methyl-3-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)[2-(methylamino)ethyl]amine hydrochloride



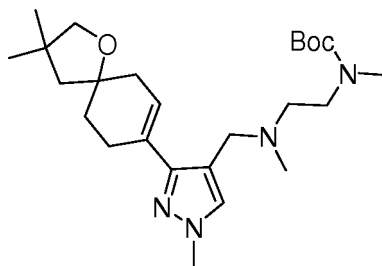
Step 1: 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazole-4-carbaldehyde



[00373] To a stirred mixture of 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1*H*-pyrazole-4-carbaldehyde (2 g, 7.68 mmol, 1.00 equiv) and potassium carbonate (3.18 g, 23.01 mmol, 2.99 equiv) in CH₃CN (40 mL) at 0°C was added CH₃I (5.46 g, 38.47 mmol, 5.01 equiv) dropwise. The resulting mixture was stirred overnight at room temperature then filtered and concentrated under vacuum. The resultant residue was dissolved in H₂O (30mL) and extracted with 3 x 20 mL of dichloromethane. The combined organic layers were washed with 3 x 20 mL of brine then dried over anhydrous sodium sulfate. The residue was partially purified by flash chromatography on silica gel column using ethyl acetate/petroleum ether (gradient: 1:9-1:2) as eluent. The resultant material was re-purified by Prep-HPLC with

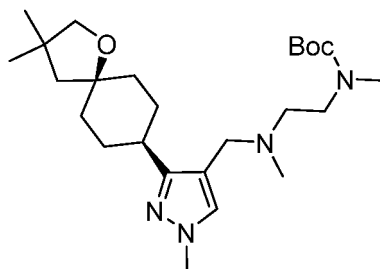
the following conditions: Column: XBridge C18, 19x150 mm, 5 μ m; Mobile Phase A: Water / 0.05% NH_4HCO_3 , Mobile Phase B: ACN; Flow rate: 30 mL / min; Gradient: 20% B to 85% B in 10 min; 254nm. This resulted in 1.04 g (49%) of 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazole-4-carbaldehyde as a white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 9.88(s, 1H), 7.86(s, 1H), 6.18-6.16(m, 1H), 3.90(s, 3H), 3.59-3.54(m, 3H), 2.78-2.70(m, 1H), 2.59-2.35(m, 3H), 2.63-2.56(m, 1H), 1.96-1.90(m, 1H), 1.75-1.61(m, 2H), 1.13(s, 6H) ppm. And another isomer, 0.45 g (21.2%) of 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-2-methyl-pyrazole-4-carbaldehyde. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 9.70(s, 1H), 7.91(s, 1H), 5.84-5.82(m, 1H), 3.80(s, 3H), 3.60-3.54(m, 3H), 2.57-2.26(m, 4H), 2.01-1.94(m, 1H), 1.85-1.80(m, 1H), 1.78-1.60(m, 1H), 1.15(s, 6H) ppm.

Step 2: *tert*-butyl *N*-(2-[(3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



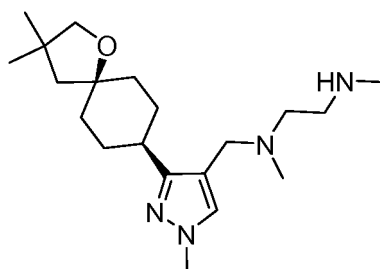
[00374] To a solution of 3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazole-4-carbaldehyde (1.04 g, 3.79 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-(2-(methylamino)ethyl)carbamate (1.07 g, 5.68 mmol, 1.50 equiv) in dichloroethane (20 mL) was added $\text{NaBH}(\text{OAc})_3$ (2.41 g) portionwise. The resulting mixture was stirred overnight at 50°C in an oil bath then cooled to room temperature and quenched by the addition of 5 mL of NH_4Cl (sat. aq.). The resulting mixture was dissolved in dichloromethane (40mL) and washed with 3 x 20 mL of brine then dried over anhydrous sodium sulfate. The residue was purified by flash chromatography on silica gel column using dichloromethane/methanol (20:1) as eluent to afford 1.50 g (89%) of *tert*-butyl *N*-(2-[(3-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as a yellow oil. $^1\text{H-NMR}$ (300 MHz, D_2O) δ : 8.12 (s, 1H), 5.72-5.70(m, 1H), 4.25-3.94(m, 4H), 3.75-3.34(m, 5H), 3.16-2.88(m, 4H), 2.51-2.04(m, 7H), 1.93-1.62(m, 5H), 1.45(s, 9H), 1.13(s, 6H).

Step 3: *N*-methyl-*N*-[2-[methyl([1-methyl-3-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amino]ethyl]carbamate



[00375] Into a 250-mL round-bottom flask was placed *tert*-butyl *N*-(2-[[3-[(3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl)-1-methyl-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (1.50 g, 3.36 mmol, 1.00 equiv), tetrahydrofuran (30 mL), and 10% Pd(OH)₂ / C (1.50 g). The resulting mixture was stirred overnight at room temperature under 3 atmospheres of hydrogen. The resulting mixture was filtered then concentrated under vacuum. The residue was partially purified by flash chromatography on silica gel column using dichloromethane/methanol (20:1) as eluent. The partially purified material was then repurified under the following conditions: Column: XBridge C18, 19 x 150 mm, 5 μm; Mobile Phase A: Water / 0.05% NH₄HCO₃, Mobile Phase B: ACN; Flow rate: 30 mL / min; Gradient: 20% B to 85% B in 10 min; 254 nm. This resulted in 1.0 g (66%) of *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-methyl-3-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amino]ethyl]carbamate as a yellow oil. ¹H-NMR (400 MHz, CD₃Cl) δ : 7.14(s, 1H), 3.80-3.78(m, 4H), 3.51(s, 3H), 3.36-3.28(m, 3H), 2.85(s, 3H), 2.58-2.46(m, 2H), 2.28-2.22(m, 3H), 2.01-1.84(m, 4H), 1.68-1.53(m, 4H), 1.55(s, 2H), 1.43(s, 9H), 1.13(s, 6H).

Step 4: Methyl([1-methyl-3-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)[2-(methylamino)ethyl]amine hydrochloride (Compound 205)

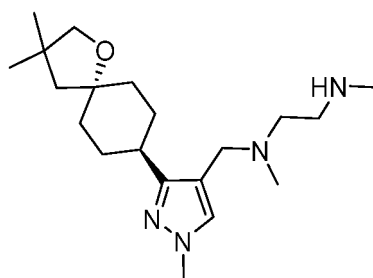


[00376] Into a 25-mL round-bottom flask was placed *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-methyl-3-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amino]ethyl]carbamate (230 mg, 0.51 mmol, 1.00 equiv) and dichloromethane (10 mL). Hydrogen chloride gas was bubbled through the reaction mixture. The reaction mixture was then stirred for 0.5 h at room temperature then extracted with 3x10 mL of water and the

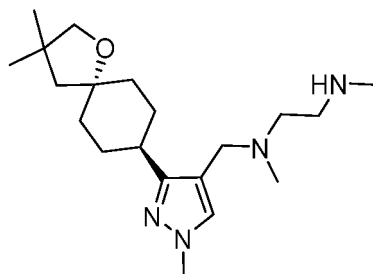
aqueous layers combined and concentrated under vacuum. This resulted in 131 mg (61%) of methyl([1-methyl-3-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl]methyl)[2-(methylamino)ethyl]amine hydrochloride as a colorless solid. ¹H-NMR (400 MHz, D₂O) : 7.66 (s, 1H), 4.25 (s, 2H), 3.74 (s, 3H), 3.50-3.40 (m, 6H), 2.74 (s, 3H), 2.70 (s, 3H), 2.64-2.54 (m, 1H), 2.60 (s, 1H), 1.89 (d, 2H, *J* = 16 Hz), 1.70-1.42 (m, 8H), 0.99 (s, 6H). LCMS (method A5, ESI): RT = 1.33 min, *m/z* = 349.2 [M+H]⁺.

Compound 206

Methyl([1-methyl-3-[(5*R*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl]methyl)[2-(methylamino)ethyl]amine hydrochloride



Step 1: Methyl([1-methyl-3-[(5*R*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl]methyl)[2-(methylamino)ethyl]amine hydrochloride (Compound 206)

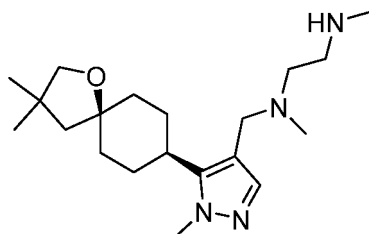


[00377] Into a 25-mL round-bottom flask was placed *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-methyl-3-[(5*R*,8*R*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl]methyl)amino]ethyl]carbamate (80 mg, 178.32 μmol, 1.00 equiv) and dichloromethane (10 mL). Hydrogen chloride (gas) was bubbled through the reaction mixture. The reaction mixture was then stirred overnight at room temperature and then extracted with 3 x 10 mL of water and the aqueous layers combined and concentrated under vacuum. This resulted in 23.1 mg of methyl([1-methyl-3-[(5*R*,8*R*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl]methyl)[2-(methylamino)ethyl]amine hydrochloride as a colorless solid. ¹H-NMR (400 MHz, D₂O) δ : 7.66 (s, 1H), 4.25 (s, 2H), 3.74 (s, 3H), 3.50-3.40 (m, 6H), 2.74 (s, 3H), 2.70 (s, 3H), 2.67-2.55 (m, 1H), 1.87-1.68 (m, 6H), 1.52-1.42 (m, 4H), 1.02 (s, 6H). LCMS

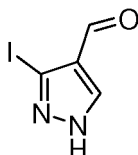
(method A5, ESI): RT = 1.32 min, m/z = 349.15 [M+H]⁺.

Compound 245

Methyl ([2-[methyl([1-methyl-5-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl)amino]ethyl)]amine trifluoroacetic acid salt

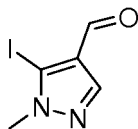


Step 1: 3-Iodo-1*H*-pyrazole-4-carbaldehyde



[00378] To stirred solution of 3-iodo-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde (3 g, 9.80 mmol, 1.00 equiv) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The resulting solution was stirred for 3 h at room temperature then concentrated under vacuum and the resulting residue was treated with sufficient sodium carbonate (sat. aq.) solution to afford a mixture of pH 8. The resulting solution was extracted with 50 mL of dichloromethane and the organic layer washed with brine (3x50 mL) and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using dichloromethane/petroleum ether (1:3) as eluent to afford 1.4 g (64%) of 3-iodo-1*H*-pyrazole-4-carbaldehyde as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 9.89 (s, 1H), 8.04(s, 1H) ppm.

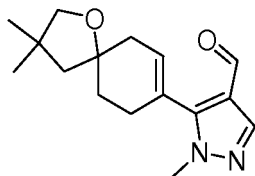
Step 2: 5-iodo-1-methyl-1*H*-pyrazole-4-carbaldehyde



[00379] To a stirred solution of 3-iodo-1*H*-pyrazole-4-carbaldehyde (1.4 g, 6.31 mmol, 1.00 equiv) in CH₃CN (20 mL) at 0°C was added potassium carbonate (2.5 g, 18.09 mmol, 2.87 equiv) followed by dropwise addition of CH₃I (980 mg, 6.90 mmol, 1.09 equiv). The resulting mixture was stirred for 3 h at room temperature, then filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl

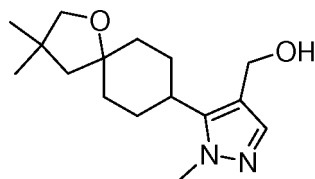
acetate / petroleum ether (1:10) as eluent to afford 400 mg (27%) of 5-iodo-1-methyl-1*H*-pyrazole-4-carbaldehyde as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 9.61 (s, 1H), 8.02 (s, 1H), 3.92 (s, 3H) ppm.

Step 3: 5-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazole-4-carbaldehyde



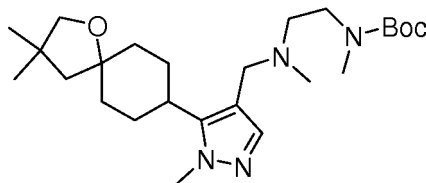
[00380] Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 2-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (686 mg, 2.35 mmol, 1.00 equiv), 1,4-dioxane (20 mL), 5-iodo-1-methyl-1*H*-pyrazole-4-carbaldehyde (370 mg, 1.57 mmol, 0.67 equiv), Pd(dppf)Cl₂ (115 mg, 0.16 mmol, 0.07 equiv), water (2 mL) and potassium carbonate (650 mg, 4.70 mmol, 2.00 equiv). The resulting mixture was stirred overnight at 80°C then concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate/petroleum ether (1:7) as eluent to afford 340 mg (53%) of 5-[3,3-dimethyl-1-oxaspiro[4.5]dec-7-en-8-yl]-1-methyl-1*H*-pyrazole-4-carbaldehyde as a light yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 9.70 (s, 1H), 7.92 (s, 1H), 5.84-5.83 (m, 1H), 3.80 (s, 3H), 3.60 (s, 2H), 2.57-2.26 (m, 4H), 2.04-1.68 (m, 4H), 1.21-1.10 (m, 6H) ppm.

Step 4: (5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methanol



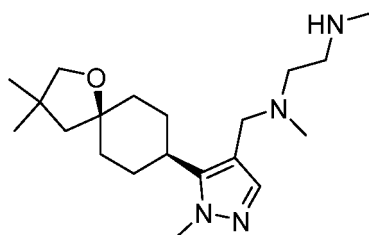
[00381] Into a 50-mL round-bottom flask was placed 5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazole-4-carbaldehyde (340 mg, 1.23 mmol, 1.00 equiv), tetrahydrofuran (20 mL) and 10% Pd(OH)₂/C (680 mg). The resulting mixture was stirred overnight at room temperature under 3 atmospheres of hydrogen then filtered and concentrated under vacuum to afford 340 mg of (5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methanol as light yellow oil.

Step 5: *tert*-butyl *N*-(2-[[5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate



[00382] To a solution of (5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methanol (340 mg, 1.22 mmol, 1.00 equiv) and triethylamine (371 mg, 3.67 mmol, 3.00 equiv) in dichloromethane (8 mL) at 0°C was added methanesulfonyl chloride (167.3 mg) dropwise with stirring. The resulting solution was stirred for 30 min at room temperature then treated with *tert*-butyl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate (276 mg, 1.47 mmol, 1.20 equiv). The resulting solution was stirred for 2 h at room temperature then quenched by the addition of 20 mL of water. The resulting mixture was extracted with 3x50 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum to afford 128 mg (23%) of *tert*-butyl *N*-(2-[[5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate as a light yellow oil. ¹H-NMR (300 MHz, CD₃OD): δ 7.30 (s, 1H), 3.83 (s, 3H), 3.53 (s, 2H), 3.43-3.31 (m, 4H), 2.91-2.83 (m, 4H), 2.53-2.50 (m, 2H), 2.25-2.07 (m, 5H), 1.97-1.93 (m, 2H), 1.63-1.49 (m, 15H), 1.18-1.10 (m, 6H) ppm.

Step 6: Methyl ([2-[methyl([1-methyl-5-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl]amino]ethyl)]amine trifluoroacetic acid salt (Compound 245)

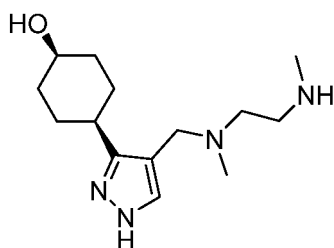


[00383] Into a 8-mL sealed tube was placed *tert*-butyl *N*-(2-[[5-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1-methyl-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate (37 mg, 0.08 mmol, 1.00 equiv), dichloromethane (1 mL) and CF₃COOH (1 mL). The resulting solution was stirred for 30 min at room temperature then concentrated under vacuum. The resultant residue was purified by reverse phase HPLC using the following conditions: Column: Sunfire C18, 19x150 mm, 5 μm; Mobile Phase A: Water /

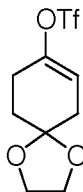
0.05% TFA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 5% B to 55% B in 10 min; 254 nm. This resulted in 18.9 mg (40%) of methyl ([2-[methyl([1-methyl-5-[(5*S*,8*S*)-3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-4-yl)methyl]amino]ethyl])amine trifluoroacetic acid salt as a colorless oil. ¹H-NMR (300 MHz, D₂O): δ 7.53 (s, 1H), 4.33 (s, 2H), 3.81 (s, 3H), 3.52-3.40 (m, 6H), 2.91-2.69 (m, 7H), 2.00-1.72 (m, 4H), 1.69-1.45 (m, 6H), 1.00 (s, 6H). LCMS (method W, ESI): RT = 1.37 min, m/z = 349.1 [M+H].

Compound 217

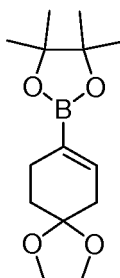
4-[4-([methyl[2-(methylanino)ethyl]amino]methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol trifluoroacetate



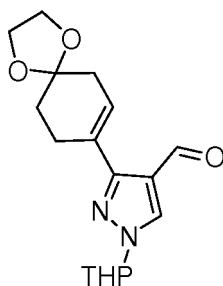
Step 1: 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate



[00384] To a solution of 1,4-dioxaspiro[4.5]decan-8-one (80 g, 512.23 mmol, 1.00 equiv) in THF (500 mL) at -78°C was added LiHMDS (615 mL of a 1 M solution in THF) dropwise over approximately 25 min then stirred for 2h at -40°C. The reaction mixture was then cooled to -78°C and treated with 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethane)sulfonylmethanesulfonamide (220 g, 615.82 mmol, 1.20 equiv) dropwise. The resulting solution was allowed to warm to room temperature and stirred overnight then quenched by the addition of 100 mL of NH₄Cl (sat. aq.). The resulting mixture was extracted with 500 mL of ethyl acetate and the organic extract washed with 3 x 500 mL of brine and dried over anhydrous sodium sulfate. The crude product was purified by flash chromatography on silica gel column using ethyl acetate / petroleum ether (gradient: 1% to 3% EA) as eluent to afford 166 g of 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): 5.68-5.64 (m, 1H), 3.99(s, 4H), 2.56-2.51(m, 2H), 2.42-2.41(m, 2H), 1.90(t, *J*=6.6Hz, 2H) ppm.

Step 2: 2-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

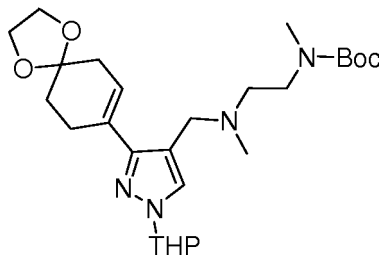
[00385] Into a 3-L 4-necked round-bottom flask was placed 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (80 g, 277.55 mmol, 1.00 equiv), B_2Pin_2 (85 g, 334.65 mmol, 1.21 equiv), $Pd(dppf)Cl_2$ (20 g, 27.33 mmol, 0.10 equiv), KOAc (82 g, 835.54 mmol, 3.01 equiv) and 1,4-dioxane (800 mL). The resulting solution was stirred overnight at 80°C using an oil bath then cooled to room temperature and concentrated under vacuum. The residue was extracted with 1 L of ethyl acetate and the organic layer washed with 3x1 L of brine and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate / petroleum ether (gradient: 5% to 10% ethyl acetate) to afford 36 g (49%) of 2-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a yellow solid. ^1H -NMR (300 MHz, $CDCl_3$): 6.46-6.47 (m, 1H), 3.98(s, 4H), 2.39-2.35(m, 4H), 1.73(t, $J=4.8Hz$, 2H), 1.26(s, 12H) ppm.

Step 3: 3-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1H-pyrazole-4-carbaldehyde

[00386] Into a 2-L 4-necked round-bottom flask was placed 2-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (44 g, 165.33 mmol, 1.00 equiv) and 3-iodo-1-(oxan-2-yl)-1H-pyrazole-4-carbaldehyde (45.5 g, 148.64 mmol, 0.90 equiv). This was followed by the addition of $Pd(dppf)Cl_2$ (12 g, 16.40 mmol, 0.10 equiv). To this was added K_3PO_4 (105 g, 494.66 mmol, 2.99 equiv), ethylene glycol dimethyl ether (500 mL) and water (50 mL). The resulting mixture was stirred overnight at 75°C in an oil bath then cooled to room temperature and concentrated under vacuum. The residue was extracted with 500 mL of ethyl acetate and the organic layer washed with 3 x 500 mL of brine and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate / petroleum ether (gradient: 20% to

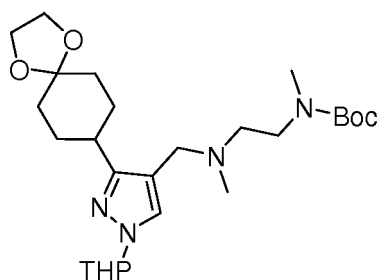
30% EA) as eluent to afford 35.5 g (67%) of (*R/S*) 3-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde as a light yellow solid. ¹H-NMR (300 MHz, CDCl₃): 9.91(s, 1H), 8.26(s, 1H), 6.29-6.26(m, 1H), 5.38-5.34 (m, 1H), 4.09-4.01(m, 5H), 3.74-3.63(m, 1H), 2.79-2.74(m, 2H), 2.50-2.49(d, *J*=3.6Hz, 2H), 2.12-1.89(m, 5H), 1.72-1.60(m, 3H) ppm.

Step 4: (*R/S*) *tert*-butyl *N*-(2-[[3-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



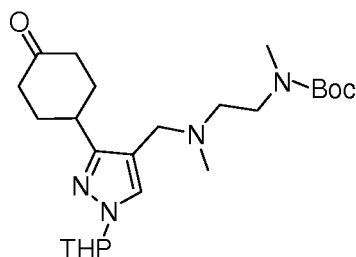
[00387] To a stirred solution of (*R/S*) 3-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazole-4-carbaldehyde (25 g, 78.53 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-(2-(methylamino)ethyl)carbamate (17.7 g, 94.02 mmol, 1.20 equiv) in dichloroethane (250 mL) at 0°C was added NaBH(OAc)₃ (50 g, 235.91 mmol, 3.00 equiv) portionwise. The resulting mixture was allowed to warm to room temperature, stirred overnight and then quenched by the addition of 50 mL of NH₄Cl (sat. aq.). The resulting mixture was extracted with 500 mL of CH₂Cl₂ and the organic phase washed with 3x500 mL of brine and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate / petroleum ether (1:2) as eluent to afford 30.3 g (79%) of (*R/S*) *tert*-butyl *N*-(2-[[3-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as a yellow oil. ¹H-NMR (300 MHz, CDCl₃) : 7.50(s, 1H), 6.26 (br, 1H), 5.38-5.34 (m, 1H), 4.09-3.99(m, 5H), 3.74-3.69(m, 1H), 3.42(br, 2H), 2.86(s, 3H), 2.84-2.07(m, 8H), 2.04(s, 3H), 1.85(t, *J*=6.6Hz, 2H), 1.68-1.52(m, 6H), 1.58(s, 9H) ppm.

Step 5: (*R/S*) *tert*-butyl *N*-(2-[[3-[1,4-dioxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



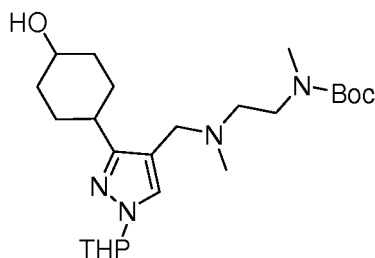
[00388] Into a 1-L round-bottom flask was placed (*R/S*) *tert*-butyl *N*-(2-[[3-[1,4-dioxaspiro[4.5]dec-7-en-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (15 g, 30.57 mmol, 1.00 equiv), THF (500 mL) and 10% Pd(OH)₂/C (9 g). The resulting mixture was stirred for 2 h at room temperature under 3 atmospheres of hydrogen. The resulting mixture was filtered and concentrated under vacuum to afford 11.5 g (76%) of (*R/S*) *tert*-butyl *N*-(2-[[3-[1,4-dioxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as yellow oil. ¹H-NMR (300 MHz, CDCl₃) : 7.41(s, 1H), 5.30-5.25 (m, 1H), 4.11-3.95(m, 5H), 3.70-3.62(m, 1H), 3.36(br, 4H), 2.83(s, 3H), 2.74-2.66(m, 1H), 2.47(s, 3H), 2.04(s, 3H), 2.04-1.82(m, 10H), 1.68-1.52(m, 6H), 1.48(s, 9H) ppm.

Step 6: (*R/S*) *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-(oxan-2-yl)-3-(4-oxocyclohexyl)-1*H*-pyrazol-4-yl)methyl])amino]ethyl]carbamate



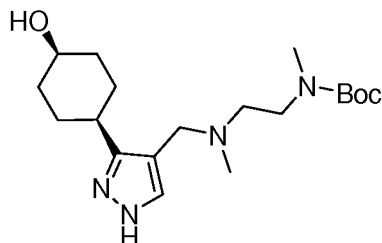
[00389] Into a 250-mL round-bottom flask was placed *tert*-butyl *N*-(2-[[3-[1,4-dioxaspiro[4.5]decan-8-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate (13.5 g, 27.40 mmol, 1.00 equiv), dichloromethane (130 mL) and FeCl₃·6H₂O (26 g, 96.30 mmol, 3.51 equiv). The resulting solution was stirred for 2 h at room temperature then extracted with dichloromethane (200 mL). The organic phase was washed sequentially with 3 x 100 mL of brine, 3 x 100 mL sodium bicarbonate (sat. aq.) and then again with 3 x 100 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using methanol / dichloromethane (gradient: 1% to 5% MeOH) to afford 7.5 g (61%) of *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-(oxan-2-yl)-3-(4-oxocyclohexyl)-1*H*-pyrazol-4-yl)methyl])amino]ethyl]carbamate as a yellow oil.

Step 7: (*R/S*) *N*-[2-([3-(4-hydroxycyclohexyl)-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl]-*N*-methylcarbamate



[00390] To a stirred solution of (*R/S*) *tert*-butyl *N*-methyl-*N*-[2-[methyl([1-(oxan-2-yl)-3-(4-oxocyclohexyl)-1*H*-pyrazol-4-yl)methyl])amino]ethyl]carbamate (500 mg, 1.11 mmol) in methanol (5 mL) at 0°C was added NaBH₄ (85 mg, 2.24 mmol) portionwise. The resulting mixture was stirred for 1 h at room temperature then quenched by the addition of 5 mL of NH₄Cl (sat. aq.). The resulting mixture was concentrated under vacuum to afford 380 mg (76%) of (*R/S*) *tert*-butyl *N*-[2-([3-(4-hydroxycyclohexyl)-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl]-*N*-methylcarbamate as a light yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ 7.41 (s, 1H), 5.28 (t, *J* = 6.0 Hz, 1H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.74-3.62 (m, 2H), 3.41-3.25 (m, 3H), 2.84 (s, 3H), 2.68-2.56 (m, 2H), 2.20 (s, 3H), 2.09-1.82 (m, 6H), 1.74-1.52 (m, 7H), 1.51-1.29 (m, 13H) ppm.

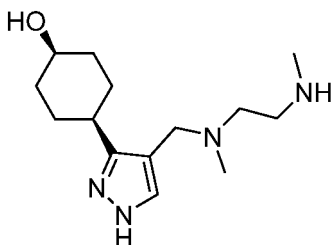
Step 8: *tert*-butyl 2-(((3-((1*S*,4*S*)-4-hydroxycyclohexyl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl(methyl)carbamate



[00391] A solution of (*R/S*) *tert*-butyl *N*-[2-([3-(4-hydroxycyclohexyl)-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl]-*N*-methylcarbamate (380 mg, 0.84 mmol, 1.00 equiv) in methanol (30 mL) was treated with aqueous hydrochloric acid (12N, 0.06 mL) and stirred overnight at room temperature. The pH value of the solution was adjusted to 7-8 with ammonia and the mixture dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase HPLC with the following conditions: Column: Sunfire C18, 19 x 150 mm, 5 μm; Mobile Phase A: Water / 0.05% ammonium hydroxide Mobile Phase B: ACN; Flow rate: 30 mL / min; Gradient: 5% B to 55% B in 10 min; Detector: 254 nm. This resulted in the *cis*-isomer 30 mg of *tert*-butyl 2-(((3-((1*S*,4*S*)-4-hydroxycyclohexyl)-1*H*-pyrazol-4-yl)methyl)(methylamino)ethyl(methyl)carbamate. LCMS

(method D, ESI): RT= 1.12 min, m/z = 367.0 $[M+H]^+$. And the *trans*-isomer 130 mg of *tert*-butyl 2-(((3-((1*R*,4*R*)-4-hydroxycyclohexyl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl(methyl)carbamate as a light yellow oil.

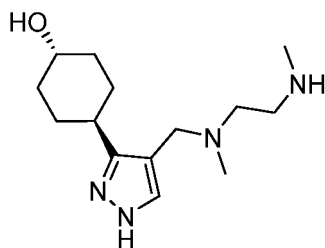
Step 9: 4-[4-([methyl[2-(methylamino)ethyl]amino]methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol trifluoroacetate (Compound 217)



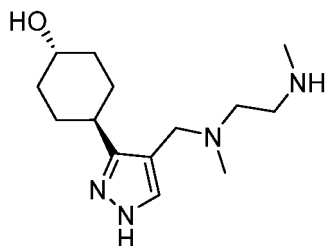
[00392] A solution of *tert*-butyl 2-(((3-((1*S*,4*S*)-4-hydroxycyclohexyl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl(methyl)carbamate (30 mg, 0.08 mmol, 1.00 equiv) in dichloromethane (2 mL) was treated with trifluoroacetic acid (2 mL) and stirred for 5 min at room temperature. The resulting mixture was concentrated under vacuum to afford 28.6 mg (71%) of 4-[4-([methyl[2-(methylamino)ethyl]amino]methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol trifluoroacetate salts as a light yellow oil. $^1\text{H-NMR}$ (300 MHz, D_2O): δ 7.70 (s, 1H), 4.30 (s, 2H), 4.70-4.00 (m, 1H), 3.51-3.40 (m, 4H), 2.82-2.66 (m, 7H), 1.86-1.52 (m, 8H) ppm. LCMS (method A6, ESI): RT = 2.78 min, m/z = 267.05 $[M+H]^+$.

Compound 227

4-[4-([methyl[2-(methylamino)ethyl]amino]methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol trifluoroacetate



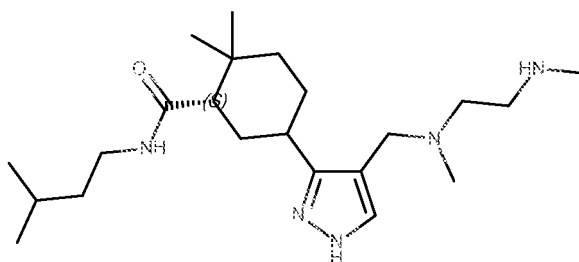
Step 1: 4-[4-([methyl[2-(methylamino)ethyl]amino]methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol trifluoroacetate (Compound 227)



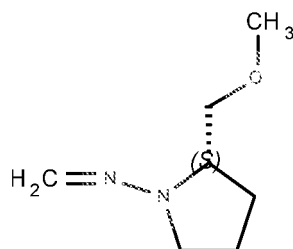
[00393] A solution of *tert*-butyl 2-(((3-((1*R*,4*R*)-4-hydroxycyclohexyl)-1*H*-pyrazol-4-yl)methyl)(methyl)amino)ethyl(methyl)carbamate (130 mg, 0.35 mmol, 1.00 equiv)) in dichloromethane (2 mL) was treated with trifluoroacetic acid (2 mL) and stirred for 5 min at room temperature. The resulting mixture was concentrated under vacuum to afford 120.9 mg (69%) of 4-[4-([methyl[2-(methylamino)ethyl]amino]methyl)-1*H*-pyrazol-3-yl]cyclohexan-1-ol trifluoroacetate as a light yellow oil. ¹H-NMR (300 MHz, D₂O): δ 7.70 (s, 1H), 4.30 (s, 2H), 3.71-3.60 (m, 1H), 3.51-3.41 (m, 4H), 2.78-2.60 (m, 7H), 2.01-1.91 (m, 2H), 1.87-1.75 (m, 2H), 1.61-1.45 (m, 2H), 1.40-1.22 (m, 2H) ppm. LCMS (method A6, ESI): RT = 2.83 min, *m/z* = 267.1 [M+H]⁺.

Compound 263

(1*S*)-2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]-N-(3-methylbutyl)cyclohexane-1-carboxamide



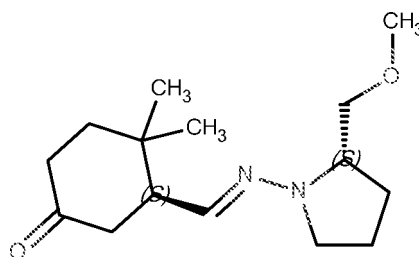
Step 1: (2*S*)-2-(methoxymethyl)-*N*-methylidenepyrrolidin-1-amine



[00394] To an ice cold solution of (2*S*)-2-(methoxymethyl)pyrrolidin-1-amine (5.0 g, 38.41

mmol) in DCM (75 mL) was added paraformaldehyde (1.38 g, 46.09 mmol). The mixture was left to stir at RT over the weekend. Water (25 mL) was added, and the phases were separated. The aqueous phase was extracted with DCM (3 x 30 mL). The combined organics were washed with water (20 ml), brine (20 ml), dried over Na₂SO₄, filtered and evaporated to dryness. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 100 g HP-Sil SNAP cartridge, eluting with EtOAc:heptane (1:99 - 4:6), gave the desired product as a colourless oil (4.19 g, 76 %): MS (ESI⁺) for C₇H₁₄N₂O *m/z* 143.0 (M+H)⁺; HPLC purity 100 % (ret. time, 0.81 min); ¹H-NMR (500 MHz, Chloroform-*d*) δ 6.13 (d, *J* = 11.6 Hz, 1H), 6.02 (d, *J* = 11.6 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.49 – 3.42 (m, 1H), 3.38 (s, 3H), 3.33 (ddd, *J* = 9.9, 7.3, 3.4 Hz, 1H), 2.83 (q, *J* = 7.9 Hz, 1H), 2.04 – 1.87 (m, 3H), 1.86 – 1.75 (m, 1H).

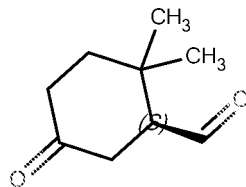
Step 2: (3*S*)-3-[(*E*)-*N*-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carboximidoyl]-4,4-dimethylcyclohexan-1-one



[00395] To a cooled (-78 °C) solution of 4,4-dimethylcyclohex-2-en-1-one (4.57 g, 36.83 mmol) in dry THF (100 mL) were sequentially added *tert*-butyl(dimethyl)silyl trifluoromethanesulfonate (7.45 ml, 32.41 mmol) and pre-cooled (-78 °C) (2*S*)-2-(methoxymethyl)-*N*-methylidenepyrrolidin-1-amine (4.19 g, 29.47 mmol) under a N₂ atmosphere. After 45 min 1M *N,N,N*-tributylbutan-1-aminium fluoride (44.20 ml, 44.20 mmol) was added and the mixture was allowed to warm to RT and stirred until LC/MS indicated total consumption of the silyl enol ether (overnight). The reaction mixture was diluted with *t*-butylmethylether (100 ml) and washed with water (2 x 100 ml). The aqueous was then extracted with *t*-butylmethylether (100 ml). The combined organic layers were washed with brine (100 ml), dried over Na₂SO₄, filtered and evaporated *in vacuo* to give a dark brown oil. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 340 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (1:9 - 6:4), gave the desired product as a yellow oil (4.6 g, 59 %): MS (ESI⁺) for C₁₅H₂₆N₂O₂ *m/z* 266.95 (M+H)⁺; HPLC purity 100 % (ret. time, 1.11 min); ¹H-NMR (500 MHz, Chloroform-*d*) δ 6.60 – 6.51 (m, 1H), 3.56 – 3.49 (m, 1H), 3.47 – 3.41 (m, 1H), 3.40 – 3.28 (m, 5H), 2.73 (q, *J*

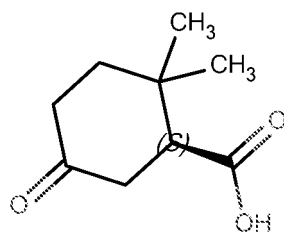
= 8.0 Hz, 1H), 2.56 – 2.25 (m, 5H), 2.01 – 1.84 (m, 3H), 1.83 – 1.70 (m, 2H), 1.67 – 1.60 (m, 1H), 1.07 (d, J = 11.2 Hz, 6H).

Step 3: 3 (1*S*)-2,2-dimethyl-5-oxocyclohexane-1-carbaldehyde



[00396] A solution of (3*S*)-3-[(*E*)-*N*-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carboximidoyl]-4,4-dimethylcyclohexan-1-one (13.7 g, 51.43 mmol) in DCM (250 ml) was cooled to -78 °C and dry ozone was bubbled through until appearance of a permanent green/blue colour (~4 h) and then continued for a further 30 min. The reaction mixture was sparged with nitrogen for 20 min. Dimethylsulfide (3.9 ml, 62.13 mmol) was added and the reaction mixture stirred at RT for 30 min before evaporating *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 340 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (1:9 - 7:3), gave the desired product as a yellow oil (4.02 g, 46 %): ¹H-NMR (500 MHz, Chloroform-*d*) δ 9.85 (d, J = 1.5 Hz, 1H), 2.67 – 2.62 (m, 1H), 2.61 – 2.54 (m, 1H), 2.48 – 2.40 (m, 1H), 2.39 – 2.29 (m, 2H), 1.78 – 1.71 (m, 2H), 1.32 (s, 3H), 1.15 (s, 3H).

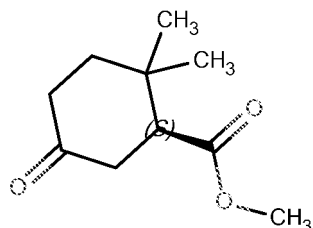
Step 4: (1*S*)-2,2-dimethyl-5-oxocyclohexane-1-carboxylic acid



[00397] (1*S*)-2,2-Dimethyl-5-oxocyclohexane-1-carbaldehyde (4.02 g, 23.46 mmol) in ether (200 ml) was cooled to -30 °C and treated with 2M trioxochromium - sulfuric acid (1:1) (58.66 ml, 117.31 mmol Jones' Reagent). After 30min at -30 °C the mixture was stirred for a further 2 hr whilst allowing to warm to RT. The reaction mixture was cooled to 0° C and basified with 1N NaOH (~ 650 ml) and washed with t-butylmethylether (~2 x 500 ml). The aqueous layer was acidified to acid pH with 2 N H₂SO₄ (~ 160 ml) and the product was extracted with EtOAc (3 x 800 ml). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and co-evaporated with heptane (~ 50 ml). Purification by silica gel

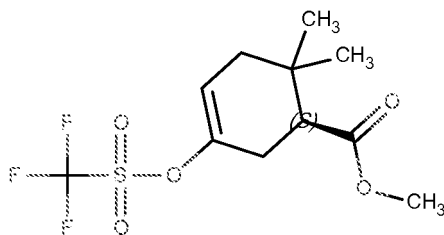
column chromatography, on a Biotage Isolera system, using a 100 g KP-Sil SNAP cartridge, eluting with MeOH:DCM (1:99 - 1:9), gave the desired product as an off-white solid (3.04 g, 76 %): $^1\text{H-NMR}$ (500 MHz, Chloroform-*d*) δ 2.73 – 2.57 (m, 2H), 2.51 – 2.40 (m, 2H), 2.38 – 2.31 (m, 1H), 1.95 – 1.86 (m, 1H), 1.72 – 1.63 (m, 1H), 1.22 (s, 3H), 1.17 (s, 3H).

Step 5: methyl (1*S*)-2,2-dimethyl-5-oxocyclohexane-1-carboxylate



[00398] MeI (1.22 mL, 19.65 mmol) was added to a suspension of (1*S*)-2,2-dimethyl-5-oxocyclohexane-1-carboxylic acid (3.04 g, 17.86 mmol) and K_2CO_3 (2.72 g, 19.65 mmol) in acetone (45 mL) and heated to 60 °C for 18 h. This was then allowed to cool to RT, filtered using additional DCM 2 x 20 mL, and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 100 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (1:9 - 1), gave the desired product as a colourless oil (2.80 g, 85 %): $^1\text{H-NMR}$ (250 MHz, Chloroform-*d*) δ 3.69 (s, 3H), 2.73 – 2.54 (m, 2H), 2.53 – 2.24 (m, 3H), 1.95 – 1.80 (m, 1H), 1.74 – 1.59 (m, 1H), 1.16 (s, 3H), 1.11 (s, 3H).

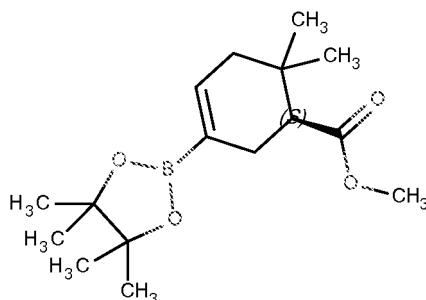
Step 6: methyl (1*S*)-6,6-dimethyl-3-(trifluoromethanesulfonyloxy)cyclohex-3-ene-1-carboxylate



[00399] To a cold [0°C] solution of methyl (1*S*)-2,2-dimethyl-5-oxocyclohexane-1-carboxylate (1.7 g, 9.27 mmol) in 1,2-dichloroethane (50 mL) was added 2,6-di-*tert*-butylpyridine (2.28 mL, 10.15 mmol) followed by slow addition of a solution of Tf_2O (1.65 mL, 9.79 mmol). The reaction was allowed to warm to RT overnight. The solvent was evaporated and the residue was partitioned between water (50 mL) and *t*-butylmethylether-EtOAc (120 mL, ~10:1). The organic layer was separated, washed with water (25 mL), sat NaHCO_3 (25 mL), brine (25 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was absorbed onto silica gel, and purified by silica gel column chromatography, eluting with EtOAc:heptanes (0 – 1:4) to give the desired product as a yellow oil (2.1 g, 72 %): $^1\text{H-NMR}$

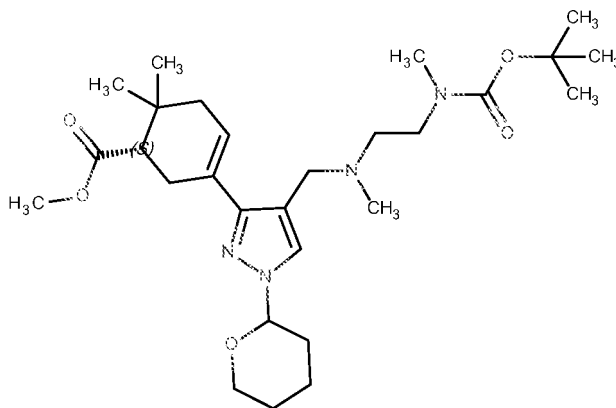
(500 MHz, Chloroform-*d*) δ 5.71 (t, J = 3.9 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.60 – 2.53 (m, 1H), 2.50 – 2.39 (m, 1H), 2.12 – 2.04 (m, 2H), 1.04 (s, 3H), 1.01 (s, 3H).

Step 7: methyl (1*S*)-6,6-dimethyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate



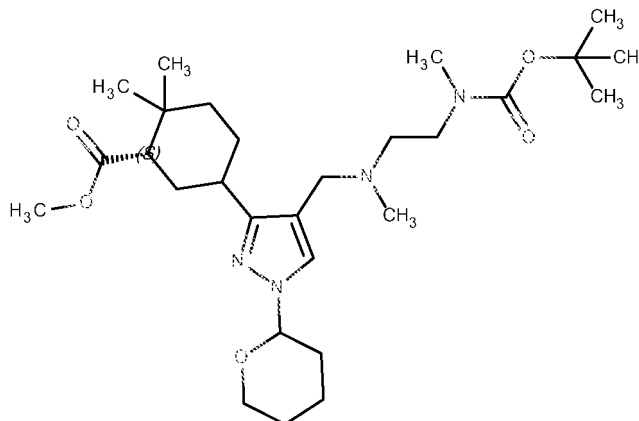
[00400] A suspension of methyl (1*S*)-6,6-dimethyl-3-(trifluoromethanesulfonyloxy)cyclohex-3-ene-1-carboxylate (2.10 g, 6.64 mmol), KOAc (4.89 g, 49.80 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.02 g, 7.97 mmol) in 1,4-dioxane (120 ml) was degassed for 10 min under a nitrogen sparge at RT. Pd(dppf).Cl₂ (0.04 g, 0.05 mmol) was added to the reaction mixture and stirred at 90 °C for 3 h, then allowed to stir whilst cooling to RT. The reaction mixture was diluted with EtOAc (130 ml) and washed with water (130 ml). The aqueous layer was extracted with EtOAc (130 ml), the combined organics washed with brine (50 ml), dried over Na₂SO₄, filtered and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 100 g KP-Sil SNAP cartridge, eluting with EtOAc:heptanes (1:99 - 3:7), gave the desired product as a white solid (1.62 g, 83 %): ¹H-NMR (250 MHz, Chloroform-*d*) δ 6.59 – 6.39 (m, 1H), 3.64 (s, 3H), 2.36 (s, 3H), 2.07 – 1.90 (m, 2H), 1.25 (s, 12H), 0.96 (d, J = 4.2 Hz, 6H).

Step 8: methyl (1S)-3-(4-[[2-[[*tert*-butoxy)carbonyl](methyl)amino]ethyl)(methyl)amino]methyl)-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)-6,6-dimethylcyclohex-3-ene-1-carboxylate



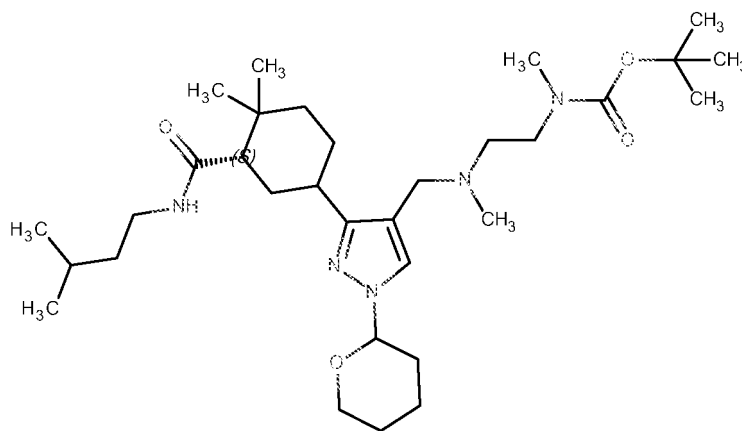
[00401] A suspension of methyl (1*S*)-6,6-dimethyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (1.62 g, 5.51 mmol), *tert*-butyl *N*-[2-([3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl)(methyl)amino)ethyl]-*N*-methylcarbamate (2.63g, 5.51 mmol), K_2CO_3 (2.30 g, 16.63 mmol) and $Pd(dppf)Cl_2 \cdot DCM$ (0.45 g, 0.55 mmol) in 1,4-dioxane (100 ml) and water (10 ml) was stirred under a N_2 sparge for 10 min at RT. This was then heated to 90 °C and stirred overnight under N_2 . The reaction mixture was allowed to cool to RT before evaporating to dryness. MeOH (2 x 20 ml) was added to the residue and evaporated to dryness *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 100 g KP-Sil SNAP cartridge, eluting with THF:heptanes (1:99 - 12:88), gave the desired product as a tan oil (1.89 g, 57 %): MS (ESI+) for $C_{28}H_{46}N_4O_5$ m/z 519.10 ($M+H$)⁺; HPLC purity 86 % (ret. time, 1.14 min); ^1H -NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.38 (m, 1H), 6.12 (s, 1H), 5.34 – 5.23 (m, 1H), 4.05 (d, $J = 10.0$ Hz, 1H), 3.73 – 3.59 (m, 4H), 3.45 – 3.22 (m, 4H), 2.82 (s, 3H), 2.77 – 2.63 (m, 2H), 2.57 – 2.39 (m, 3H), 2.21 (s, 3H), 2.16 – 1.95 (m, 5H), 1.73 – 1.56 (m, 3H), 1.44 (s, 9H), 1.03 (m, 6H).

Step 9: methyl (1*S*)-5-(4-{{(2-{{(tert-butoxy)carbonyl}(methyl)amino}ethyl)(methyl)amino}methyl}-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)-2,2-dimethylcyclohexane-1-carboxylate



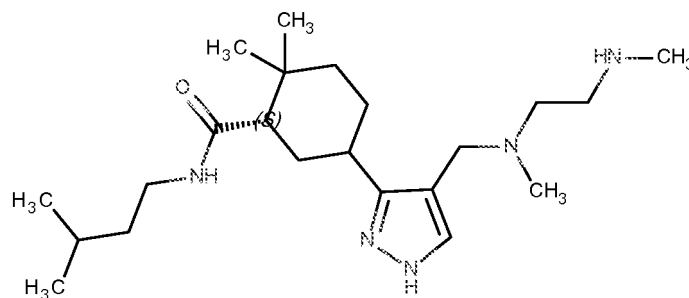
[00402] 10% Pd-C (189 mg) was added to a solution of methyl (1*S*)-3-(4-{{(2-{{(tert-butoxy)carbonyl}(methyl)amino}ethyl)(methyl)amino}methyl}-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)-6,6-dimethylcyclohex-3-ene-1-carboxylate (1.89 mg, 3.13 mmol) in EtOH (30 ml) and stirred under an atmosphere of hydrogen for 3 h. An additional 189 mg of 10% Pd-C was added and the reaction continued overnight. After stirring overnight an additional 189 mg of 10% Pd-C was added and the reaction continued for 3 h. This was then filtered and re-treated with 10% Pd-C (190 mg) and hydrogen for 4 h. The reaction mixture was filtered and allowed to stand over the weekend. The reaction mixture was then treated with 10% Pd-C (0.5 g) and hydrogen for a further 48 hrs before filtering through Celite and evaporating to dryness. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 100 g KP-Sil SNAP cartridge, eluting with THF:heptanes (1:9 - 1), gave the desired product as a colourless oil (1.11 g, 68 %): MS (ESI+) for C₂₈H₄₈N₄O₅ *m/z* 521.30 (M+H)⁺.; HPLC purity 95 % (ret. time, 1.07 min); ¹H-NMR (500 MHz, Chloroform-*d*) δ 7.41 (s, 1H), 5.28 (dt, *J* = 9.3, 4.2 Hz, 1H), 4.05 (d, *J* = 10.1 Hz, 1H), 3.71 – 3.64 (m, 1H), 3.64 (s, 3H), 3.31 (d, *J* = 31.3 Hz, 4H), 2.83 (s, 3H), 2.66 (ddt, *J* = 12.5, 7.4, 3.7 Hz, 1H), 2.46 (s, 2H), 2.35 – 2.28 (m, 1H), 2.20 (s, 3H), 2.13 – 1.95 (m, 4H), 1.92 – 1.76 (m, 3H), 1.75 – 1.49 (m, 5H), 1.44 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 6H).

Step 10: *tert*-butyl *N*-{2-[(3-[(3*S*)-4,4-dimethyl-3-[(3-methylbutyl)carbamoyl]cyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate



[00403] To a solution of 2 M Me₃Al in toluene (230 μ l, 0.46 mmol) was added a solution of 3-methylbutan-1-amine (53.5 μ l, 0.46 mmol) in toluene (1 ml) in a sealed tube. After 5 min, a solution of methyl (1*S*)-5-(4-[(2-[(*tert*-butoxy)carbonyl](methyl)amino)ethyl](methyl)amino)methyl}-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)-2,2-dimethylcyclohexane-1-carboxylate (200 mg, 0.038 mmol) in toluene (3 ml) was added. The reaction was sealed and heated to 110 °C for 18 h. The reaction was allowed to cool to RT and MeOH (25 ml) was added. The mixture was stirred at RT with Celite (~5 g) filtered and the pad washed with MeOH (10 ml). The filtrates were concentrated. The crude product was absorbed onto silica gel (2 ml). Purification by silica gel column chromatography, on a Biotage Isolera system, using a 10 g HP-Sil SNAP cartridge, eluting with THF:heptanes (1:9 - 1), gave the desired product as a colourless glass (160 mg, 72 %): MS (ESI+) for C₃₂H₅₇N₅O₄ m/z 576.3 (M+H)⁺.; HPLC purity 100 % (ret. time, 1.14 min); ¹H-NMR (500 MHz, Chloroform-*d*) δ 7.57 – 7.34 (m, 1H), 5.84 – 5.39 (m, 1H), 5.28 (s, 1H), 4.05 (d, J = 11.9 Hz, 1H), 3.72 – 3.62 (m, 1H), 3.41 – 3.14 (m, 4H), 2.82 (s, 2H), 2.77 – 2.36 (m, 2H), 2.18 (s, 2H), 2.03 (d, J = 17.2 Hz, 5H), 1.92 – 1.73 (m, 2H), 1.66 (s, 3H), 1.55 (s, 9H), 1.52 – 1.42 (m, 9H), 1.41 – 1.30 (m, 3H), 1.13 – 1.06 (m, 2H), 1.03 (s, 3H), 0.93 – 0.86 (m, 6H).

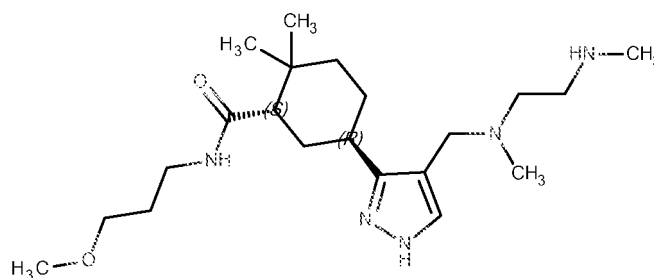
Step 11: (1S)-2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1H-pyrazol-3-yl]-N-(3-methylbutyl)cyclohexane-1-carboxamide (Compound 263)



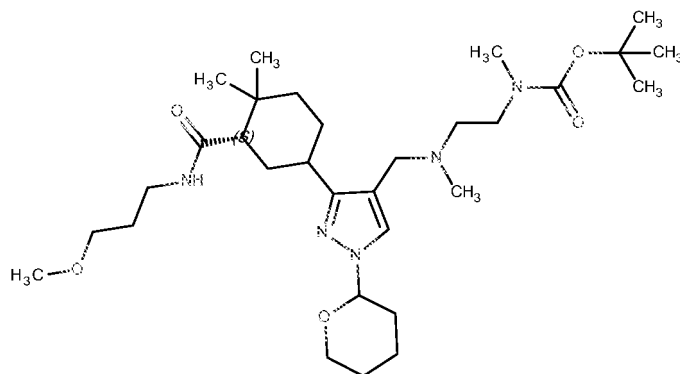
[00404] 6 N HCl (2 ml) was added to a solution of *tert*-butyl *N*-{2-[(3-[(3*R*)-4,4-dimethyl-3-[(3-methylbutyl)carbamoyl]cyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl}-*N*-methylcarbamate (160 mg, 0.28 mmol) in 1,4-dioxane (1 ml) at 0 °C and stirred for 5 min. This was then allowed to continue at RT for 18 hr before evaporating *in vacuo*. MeOH (10 ml) was added to the residue and evaporated to dryness again. MeOH (5 ml) was added to the residue and this solution was passed through an Isolute SCX 2 cartridge (2 g) followed by MeOH (2 x 5 ml). The product was eluted with 7 N NH₃ in MeOH (15 ml). This was then evaporated to dryness to give 90 mg (83 %, 8:1 *cis:trans* mixture) the desired product as a colourless glass: MS (ESI+) for C₂₂H₄₁N₅O *m/z* 392.2 (M+H)⁺; HPLC purity 100 % (ret. time, 2.47 min); ¹H-NMR (500 MHz, Methanol-*d*₄) δ 7.43 (s, 1H), 3.42 (d, *J* = 4.5 Hz, 2H), 3.27 – 3.18 (m, 1H), 3.18 – 3.08 (m, 1H), 2.85 – 2.75 (m, 1H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.44 – 2.35 (m, 3H), 2.24 – 2.13 (m, 4H), 2.07 (q, *J* = 12.8 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.75 – 1.58 (m, 3H), 1.58 – 1.51 (m, 1H), 1.49 – 1.31 (m, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 18.6 Hz, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Compound 271

(1*S*,5*R*)-*N*-(3-methoxypropyl)-2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]cyclohexane-1-carboxamide

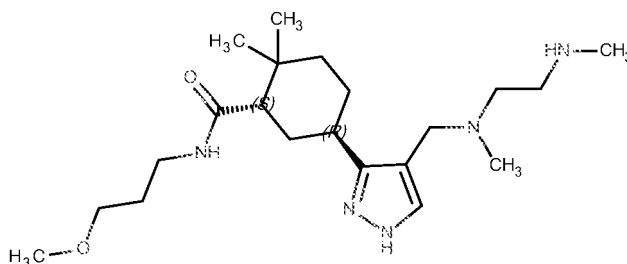


Step 1: *tert*-butyl *N*-{2-[(3-[(3*S*)-3-[(3-methoxypropyl)carbamoyl]-4,4-dimethylcyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate



[00405] To a solution of 2 M Me₃Al in toluene (230 μ l, 0.46 mmol) was added a solution of 3-methoxypropylamine (47.0 μ l, 0.46 mmol) in toluene (1 ml) in a sealed tube. After 5 min, a solution of methyl (1*S*)-5-(4-{[(2-{[(*tert*-butoxy)carbonyl](methyl)amino}ethyl)(methyl)amino]methyl}-1-(oxan-2-yl)-1*H*-pyrazol-3-yl)-2,2-dimethylcyclohexane-1-carboxylate (200 mg, 0.38 mmol) in toluene (3 ml) was added. The reaction was sealed and heated to 110 °C for 18 h. The reaction was allowed to cool to RT and MeOH (25 ml) was added. The mixture was stirred at RT with Celite (~5 g) and filtered and the pad washed with MeOH (10 ml). The filtrates were concentrated. The crude product was absorbed onto silica gel (2 ml). Purification by silica gel column chromatography, on a Biotage Isolera system, using a 25 g KP-Sil SNAP cartridge, eluting with THF:heptanes (1:9 - 1), gave the desired product as a colourless glass (130 mg, 58 %): MS (ESI+) for C₃₁H₅₅N₅O₅ *m/z* 578.35 (M+H)⁺; HPLC purity 100 % (ret. time, 1.11 min); ¹H-NMR (500 MHz, Chloroform-*d*) δ 7.67 – 7.30 (m, 1H), 5.37 – 5.18 (m, 1H), 4.04 (d, *J* = 11.0 Hz, 1H), 3.67 (t, *J* = 11.4 Hz, 1H), 3.45 (t, *J* = 5.5 Hz, 2H), 3.39 – 3.20 (m, 8H), 3.02 – 2.77 (m, 3H), 2.70 (s, 1H), 2.46 (s, 2H), 2.19 (s, 2H), 2.10 – 1.96 (m, 5H), 1.85 (s, 1H), 1.80 – 1.73 (m, 3H), 1.72 – 1.62 (m, 3H), 1.57 (s, 6H), 1.45 (s, 9H), 1.09 (s, 3H), 1.06 – 1.01 (m, 3H).

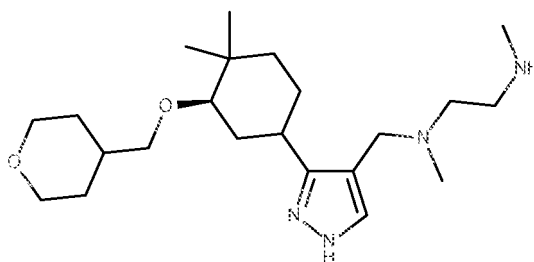
Step 2: (1*S*,5*R*)-*N*-(3-methoxypropyl)-2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]cyclohexane-1-carboxamide (Compound 271)

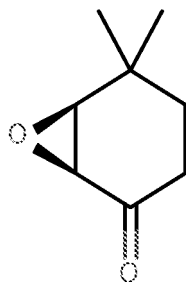


[00406] 6 N HCl (2 ml) was added to a solution of *tert*-butyl *N*-{2-[(3-[(3*S*)-3-[(3-methoxypropyl)carbamoyl]-4,4-dimethylcyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methylamino)ethyl}-*N*-methylcarbamate (130 mg, 0.23 mmol) in 1,4-dioxane (1 ml) at 0 °C and stirred for 5 min. This was then allowed to continue at RT for 18 hr before evaporating *in vacuo*. MeOH (10 ml) was added to the residue and evaporated to dryness again. MeOH (5 ml) was added to the residue and this solution was passed through an Isolute SCX 2 cartridge (2 g) followed by MeOH (2 x 5 ml). The product was eluted with 7 N NH₃ in MeOH (15 ml). This was then evaporated to dryness to give 69 mg (78 %) of the desired product as a colourless glass. The diastereoisomers were separated by prep HPLC under high pH conditions to give 3 mg of the desired product: MS (ESI+) for C₂₁H₃₉N₅O₂ *m/z* 394.5 (M+H)⁺; HPLC purity 91 % (ret. time, 1.00 min); ¹H-NMR (500 MHz, Methanol-*d*₄) δ 7.43 (s, 1H), 3.69 (s, 1H), 3.51 – 3.39 (m, 4H), 3.32 (d, *J* = 1.0 Hz, 3H), 3.31 – 3.24 (m, 1H), 3.22 – 3.12 (m, 1H), 2.92 (t, *J* = 5.8 Hz, 2H), 2.63 – 2.50 (m, 5H), 2.20 (d, *J* = 10.8 Hz, 4H), 2.15 – 1.99 (m, 2H), 1.87 – 1.65 (m, 5H), 1.38 – 1.27 (m, 1H), 1.13 (s, 3H), 0.99 (s, 3H) (plus 51 mg of (1*S*,5*S*)-*N*-(3-methoxypropyl)-2,2-dimethyl-5-[4-({methyl[2-(methylamino)ethyl]amino}methyl)-1*H*-pyrazol-3-yl]cyclohexane-1-carboxamide).

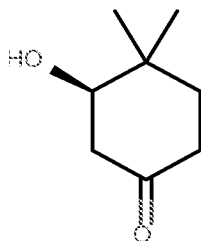
Compound 273

(3-[(3*R*)-4,4-dimethyl-3-(oxan-4-ylmethoxy)cyclohexyl]-1*H*-pyrazol-4-yl)methyl(methyl)[2-(methylamino)ethyl]amine



Step 1: (1*S*,6*S*)-5,5-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one

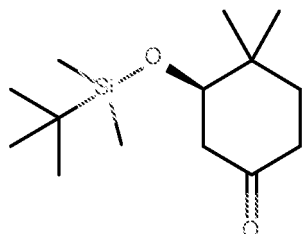
[00407] (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (3.42 g, 16.11 mmol) and trifluoroacetic acid (1.2 ml, 16.11 mmol) were dissolved in 1,4-dioxane (150 ml). The solution was stirred for 30 min before adding 4,4-dimethylcyclohex-2-en-1-one (10 g, 80.53 mmol) and hydrogen peroxide (10.58 ml, 120.79 mmol 35 % in water). The reaction was stirred and heated to 50 °C for 72 h after which time the reaction was quenched with NH₄Cl (saturated, 100 ml). The solution was extracted with DCM (4 x 100 ml). The combined organic extracts were dried over Na₂SO₄ and evaporated to dryness to afford 12.5 g of desired material (containing ~10% 1,4-dioxane w/w). ¹H-NMR (250 MHz, Chloroform-*d*) δ 3.23 (d, *J* = 4.0 Hz, 1H), 3.17 (dd, *J* = 4.0, 1.2 Hz, 1H), 2.41 (ddd, *J* = 18.8, 6.5, 3.2 Hz, 1H), 2.19 (ddd, *J* = 18.7, 11.5, 6.9 Hz, 1H), 1.90 (td, *J* = 12.5, 11.5, 6.5 Hz, 1H), 1.35 (dtd, *J* = 9.9, 3.1, 1.2 Hz, 1H), 1.22 (s, 3H), 1.06 (s, 3H). *R*_f = 0.30 (3 % 7 N NH₃ in MeOH in DCM).

Step 2: (3*R*)-3-hydroxy-4,4-dimethylcyclohexan-1-one

[00408] At RT under nitrogen, lithium (1.63 g, 235 mmol) was added to a solution of naphthalene (40 g, 314 mmol) in dry THF (600 ml). The solution quickly turned dark green and the reaction was stirred at RT until full dissolution of the lithium (~5 h). The solution was cooled to -78 °C and a solution of (1*S*,6*S*)-5,5-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one (11 g, 78.47 mmol) in dry THF (300 ml) was added. The reaction was stirred for 1 h then quenched with water (30 ml) and allowed to warm to RT. A further 300 ml of water was added and the solution was extracted with Et₂O (2 x 500 ml). The combined organic extracts were dried over Na₂SO₄ and evaporated to dryness. The residue was purified by Biotage (SNAP 340g, eluent heptane/EtOAc/NEt₃ 90/10/1 to 10/90/1) to afford 5.81 g of title

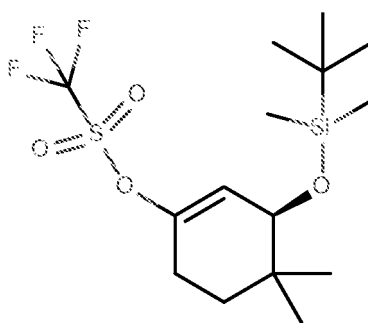
compound (52 %) as an orange oil. $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 3.77 – 3.62 (m, 1H), 2.64 (ddd, J = 14.9, 4.3, 1.0 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.36 – 2.25 (m, 2H), 1.94 – 1.82 (m, 1H), 1.83 – 1.76 (m, 1H), 1.54 – 1.44 (m, 1H), 1.13 (s, 3H), 1.07 (s, 3H). R_f = 0.30 (EtOAc/heptane/ NEt_3 (6/4/0.1)).

Step 3: (3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexan-1-one



[00409] (3*R*)-3-hydroxy-4,4-dimethylcyclohexan-1-one (5.81 g, 40.86 mmol), *tert*-butyl(chloro)dimethylsilane (9.24 g, 61.29 mmol) and 1*H*-imidazole (6.95 g, 102.15 mmol) were dissolved in DMF (50 ml). The reaction was stirred at RT overnight; no starting material was detected by TLC. The reaction was quenched with saturated aqueous ammonium chloride solution (30 ml) and was extracted with EtOAc (3 x 30 ml); the combined organic layers were washed with water (30 ml) and dried over Na_2SO_4 , evaporated and co-evaporated with toluene (4 x 50 ml) to dryness affording 8.4 g of the title compound isolated as a yellow oil (80 %). $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 3.64 (dd, J = 7.4, 4.1 Hz, 1H), 2.63 – 2.49 (m, 1H), 2.39 – 2.25 (m, 3H), 1.95 – 1.78 (m, 1H), 1.43 (dt, J = 13.8, 7.1 Hz, 1H), 1.07 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.04 (d, J = 6.0 Hz, 6H). R_f = 0.53 (heptane/EtOAc 85/15).

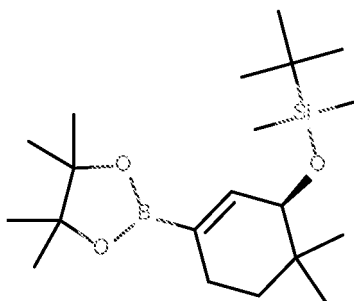
Step 4: (3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate



(3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,4-dimethylcyclohexan-1-one (3 g, 11.7 mmol) was dissolved in dry THF (250 ml). The solution was cooled to -78°C and 1 M lithium 1,1,1,3,3,3-hexamethyldisilazan-2-ide (23.4 ml) was slowly added. The reaction was stirred for 45 min and a solution of *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-

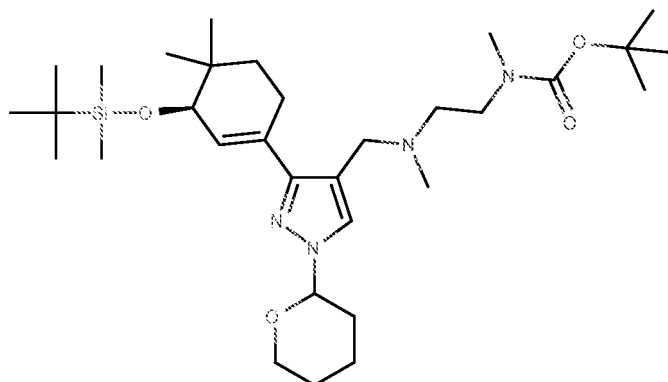
[(trifluoromethyl)sulfonyl]methanesulfonamide (8.59 g, 21.88 mmol) in dry THF (60 ml) was slowly added. The reaction was allowed to warm to RT and stirred for 3 h. The reaction was quenched with NH_4Cl (saturated, 100 ml) and extracted with EtOAc (3 x 100 ml). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness and the residue purified by Biotage (SNAP HP 100 g, eluent heptane/EtOAc 100/0 to 90/10) to afford 3.1 g of title compound as a 1:1 mix of isomers (61 %). ^1H -NMR (500 MHz, Chloroform- d) δ 5.74 – 5.52 (m, 1H), 3.57 (t, J = 5.3 Hz, 1H), 2.53 (dd, J = 17.3, 2.2 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.13 (ddt, J = 17.6, 4.4, 2.5 Hz, 1H), 1.88 (ddt, J = 17.5, 4.4, 2.4 Hz, 1H), 0.96 – 0.84 (m, 15H), 0.06 (d, J = 7.4 Hz, 6H).

Step 5: *tert*-butyl({[(1*R*)-6,6-dimethyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-yl]oxy})dimethylsilane



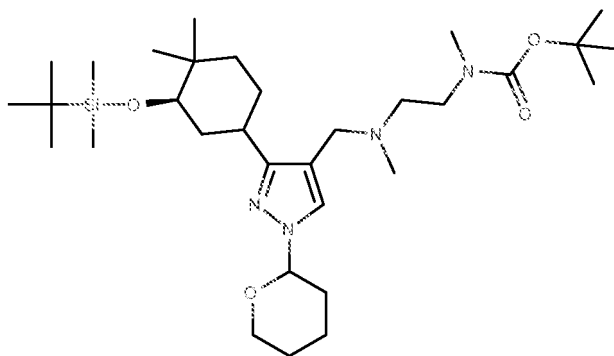
[00410] A suspension of (3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (90 %, 3.11 g, 7.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.74 g, 10.81 mmol) and potassium acetate (3.15 ml, 50.43 mmol) in 1,4-dioxane (100 ml) was degassed with a N_2 sparge for 10 min whilst stirring at RT. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron; dichloromethane; dichloropalladium (0.59 g, 0.72 mmol) was added to this suspension and stirred at 90 °C for 3.5 h before allowing to cool to RT overnight. The reaction mixture was diluted with EtOAc (50 ml) and water (50 ml). The organic layer was separated and the aqueous was extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over Na_2SO_4 , filtered and evaporated *in vacuo*. Purification by silica gel column chromatography, on a Biotage Isolera system, using a 100 g HP-Sil SNAP cartridge, eluting with EtOAc:heptanes (0 - 5:95), gave the desired product as an orange oil (2.02 g, 76 %). ^1H -NMR (500 MHz, Chloroform- d) δ 6.50 – 6.12 (m, 1H), 3.90 – 3.41 (m, 1H), 2.34 – 2.18 (m, 1H), 2.18 – 1.96 (m, 2H), 1.96 – 1.82 (m, 1H), 1.25 (d, J = 3.2 Hz, 12H), 0.95 – 0.80 (m, 15H), 0.11 – -0.01 (m, 6H).

Step 6: *tert*-butyl *N*-{2-[(3-[(3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate



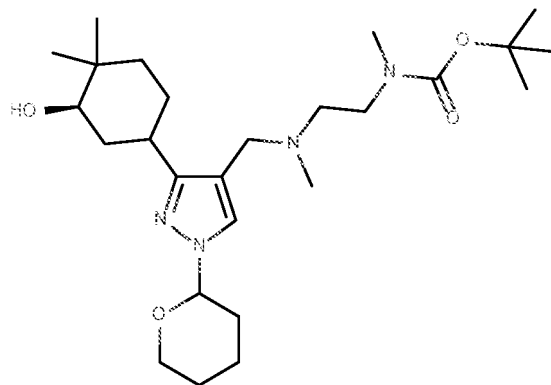
[00411] *tert*-Butyl({[(1*R*)-6,6-dimethyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-yl]oxy}) dimethylsilane (2 g, 5.46 mmol), *tert*-butyl *N*-[2-({[3-iodo-1-(oxan-2-yl)-1*H*-pyrazol-4-yl]methyl})(methyl)amino)ethyl]-*N*-methylcarbamate (2.61 g, 5.46 mmol) and potassium carbonate (2.26 g, 16.37 mmol) were suspended in 1,4-dioxane/water (240 ml, 7/1). The solution was degassed with nitrogen for 10 min and Pd(dppf)Cl₂ (0.45 g, 0.55 mmol) was added. The reaction was heated to 100 °C. After overnight, the solvents were evaporated. The residue was purified by Biotage (SNAP HP 100g, eluent heptane/EtOAc (+ 1% NEt₃) 95/5 to 60/40) to afford 2.5 g of the title compound as a yellow oil (62 %; at 80 % purity). ¹H-NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.36 (m, 1H), 6.14 – 5.72 (m, 1H), 5.43 – 5.23 (m, 1H), 4.08 – 3.92 (m, 1H), 3.76 – 3.57 (m, 1H), 3.51 – 3.19 (m, 5H), 2.99 – 2.62 (m, 6H), 2.60 – 2.30 (m, 3H), 2.28 – 2.14 (m, 3H), 2.13 – 1.94 (m, 4H), 1.76 – 1.51 (m, 6H), 1.51 – 1.37 (m, 9H), 1.00 – 0.79 (m, 18H), 0.13 – -0.03 (m, 6H). R_f = 0.29 (EtOAc/heptane 7/3 +1% NEt₃).

Step 7: *tert*-butyl *N*-{2-[(3-[(3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate



[00412] A solution of *tert*-butyl *N*-{2-[(3-[(3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohex-1-en-1-yl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate (80 %, 1 g, 1.35 mmol) in EtOH (10 ml) was cautiously added onto a purged [nitrogen] suspension of Raney-Nickel catalyst (2.5 ml) in EtOH (20 ml). The resulting solution was purged with nitrogen (3 x), hydrogen (2 x) and left under an atmosphere of hydrogen at RT. After overnight, an aliquot was analysed showing only starting material. Additional 7.5ml of catalyst was added and the reaction was left stirring under hydrogen atmosphere for 6 h, after which time LCMS showed complete conversion to the desired product. The solution was filtered through Celite and the pad was washed with EtOAc (150 ml). The filtrate was evaporated under reduced pressure and co-evaporated with toluene to afford 870 mg of the title compound as light yellow oil (92 %). ¹H-NMR (250 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 11.3 Hz, 1H), 5.41 – 5.17 (m, 1H), 4.06 (d, *J* = 8.3 Hz, 1H), 3.67 (t, *J* = 11.2 Hz, 1H), 3.34 (d, *J* = 8.8 Hz, 6H), 2.85 (d, *J* = 12.0 Hz, 5H), 2.68 (s, 1H), 2.47 (s, 2H), 2.20 (d, *J* = 9.2 Hz, 3H), 2.02 (s, 3H), 1.93 – 1.36 (m, 13H), 1.25 (d, *J* = 6.2 Hz, 2H), 1.06 – 0.79 (m, 15H), 0.02 (d, *J* = 7.0 Hz, 6H).

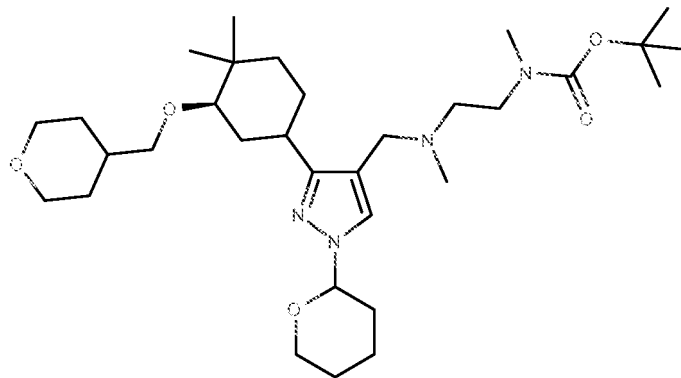
Step 8: *tert*-butyl *N*-{2-[(3-[(3*R*)-3-hydroxy-4,4-dimethylcyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate



[00413] *tert*-Butyl *N*-{2-[(3-[(3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4,4-dimethylcyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate (85 %, 870 mg, 1.25 mmol) was dissolved in 1 M TBAF in THF (12 ml). The reaction was heated to 60 °C and stirred overnight. The reaction was quenched with water (10 ml) and was extracted with EtOAc (3 x 20 ml). The combined organic extracts were dried over Na₂SO₄ and evaporated and to dryness. The residue was purified by Biotage (SNAP 50 g, eluent DCM/MeOH 100/0 to 90/10) to afford 450 mg of title compound as a light yellow oil (60 %). ¹H-NMR (250 MHz, Chloroform-*d*) δ 7.53 – 7.31 (m, 1H), 5.30 – 5.13 (m, 1H), 3.98 (d, *J* = 10.3 Hz, 1H), 3.60 (td, *J* = 11.1, 2.8 Hz, 1H), 3.31 (dd, *J* = 12.4, 6.8

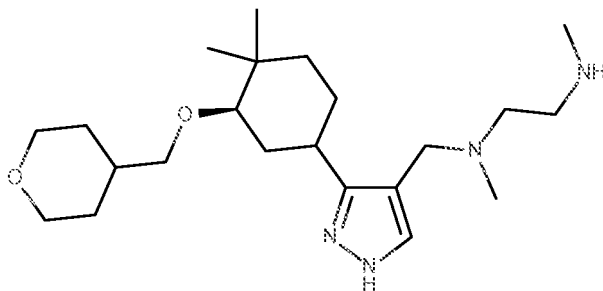
Hz, 9H), 2.89 (dd, $J = 10.3, 6.5$ Hz, 1H), 2.78 (d, $J = 13.1$ Hz, 9H), 2.50 – 2.29 (m, 2H), 2.12 (s, 3H), 1.91 (d, $J = 20.2$ Hz, 4H), 1.77 – 1.47 (m, 8H), 1.37 (d, $J = 7.5$ Hz, 26H), 1.24 – 1.12 (m, 2H), 1.04 – 0.83 (m, 8H). $R_f = 0.14$ (DCM/MeOH 95/5).

Step 9: *tert*-butyl *N*-{2-[(3-[(*3R*)-4,4-dimethyl-3-(oxan-4-ylmethoxy)cyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl](methyl)amino]ethyl}-*N*-methylcarbamate



[00414] Potassium hexamethyldisilazide (3.44 ml, 0.91 M in THF) and 18-crown-6 (17 mg, 0.06 mmol) were added to a solution of *tert*-butyl *N*-{2-[(3-[(*3R*)-3-hydroxy-4,4-dimethylcyclohexyl]-1-(oxan-2-yl)-1*H*-pyrazol-4-yl)methyl] (methyl)amino] ethyl}-*N*-methylcarbamate (300 mg, 0.63 mmol) in dry toluene (10 ml). The reaction was stirred at RT for 1 h, then 4-(bromomethyl)tetrahydro-2*H*-pyran (250 μ l, 1.88 mmol) was added and the solution was heated to 70 °C while monitoring by LCMS. Further aliquots of potassium hexamethyldisilazide (1.5 ml, 0.91 M in THF) and 4-(bromomethyl)tetrahydro-2*H*-pyran (100 μ l, 0.75 mmol) were added after 16 h, 24 h, 48 h and 72 h. The reaction was stopped after 1 week. The solution was washed with water (25 ml) and extracted with EtOAc (3 x 30 ml). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness. The crude residue was purified by low pH prep HPLC in three injections; the product rich fractions were combined (co-evaporated with toluene) to afford 7 mg of desired alkylated (2 %). 60 mg starting material were also recovered. $^1\text{H-NMR}$ (500 MHz, Chloroform- d) δ 7.89 – 7.43 (m, 1H), 5.40 – 5.20 (m, 1H), 4.15 – 3.86 (m, 3H), 3.81 – 3.62 (m, 2H), 3.61 – 3.31 (m, 7H), 3.16 – 3.05 (m, 1H), 2.97 – 2.71 (m, 5H), 2.68 – 2.50 (m, 2H), 2.48 – 2.22 (m, 3H), 2.13 – 1.92 (m, 4H), 1.89 – 1.18 (m, 21H), 1.02 (s, 3H), 0.95 (s, 3H). LC-MS: 1.24 min (2.5 minute LC-MS method), $m/z = 577.35$.

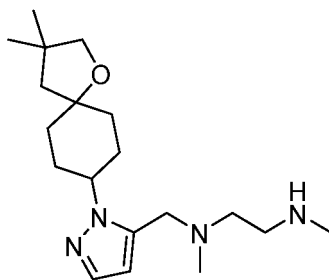
Step 10: ({3-[(3*R*)-4,4-dimethyl-3-(oxan-4-ylmethoxy) cyclohexyl]-1*H*-pyrazol-4-yl)methyl(methyl)(methyl)[2-(methylamino)ethyl]amine (Compound 273)



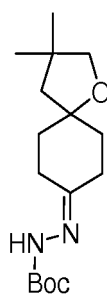
[00415] *tert*-Butyl *N*-{2-[(3-[(3*R*)-4,4-dimethyl-3-(oxan-4-ylmethoxy)cyclohexyl]-1*H*-pyrazol-4-yl)methyl(methyl)amino] ethyl}-*N*-methylcarbamate (7 mg, 0.01 mmol) was dissolved in 1,4-dioxane (2 ml) and HCl (6 N, 1 ml) was added. After 2 h stirring at RT, the solvent was removed under reduced pressure to afford 4 mg the title compound (84 %). ¹H-NMR (500 MHz, Methanol-*d*₄) δ 8.44 (s, 1H), 4.68 – 4.43 (m, 2H), 3.92 (d, *J* = 11.5 Hz, 2H), 3.84 – 3.57 (m, 4H), 3.51 (dd, *J* = 8.8, 6.2 Hz, 1H), 3.46 – 3.37 (m, 2H), 3.28 – 3.16 (m, 2H), 2.93 (d, *J* = 4.3 Hz, 3H), 2.80 (s, 3H), 2.24 – 2.13 (m, 1H), 1.87 – 1.48 (m, 8H), 1.41 – 1.25 (m, 2H), 1.06 (d, *J* = 2.6 Hz, 3H), 1.00 (s, 3H). LC-MS: 2.47 min (7 min method), *m/z* = 393.2.

Compound 274

***N*¹-((4-(4-fluorophenyl)isoxazol-5-yl)methyl)-*N*¹-methylethane-1,2-diamine trifluoroacetate**

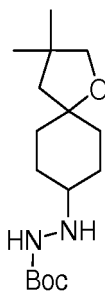


Step 1: 3,3-dimethyl-1-oxaspiro[4.5]decan-8-ylidene](*tert*-butoxy)carbohydrazide



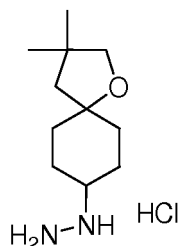
[0001] Into a 50-mL round-bottom flask, was placed hexane (10 mL), (*tert*-butoxy)carbohydrazide (2.64 g, 19.98 mmol, 1.00 equiv), and 3,3-dimethyl-1-oxaspiro[4.5]decan-8-one (3.65 g, 20.03 mmol, 1.00 equiv). The resulting solution was stirred for 15 h at 75°C and then allowed to cool to room temperature. The solids were collected by filtration to give 4 g (67%) of 3,3-dimethyl-1-oxaspiro[4.5]decan-8-ylidene[*tert*-butoxy]carbohydrazide as a white solid. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 9.52 (s, 1H), 3.43 (s, 2H), 2.48-2.09 (m, 4H), 1.86-1.46 (m, 6H), 1.42 (s, 9H), 1.06 (s, 6H) ppm.

Step 2: 3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl[*tert*-butoxy]carbohydrazide



[0002] Into a 250-mL round-bottom flask, was placed 3,3-dimethyl-1-oxaspiro[4.5]decan-8-ylidene[*tert*-butoxy]carbohydrazide (3.5 g, 11.81 mmol, 1.00 equiv), ethanol (60 mL), and 10% palladium/carbon (0.35 g). Hydrogen (3 atm) was then applied to the reaction mixture. The reaction mixture was stirred for 48 h at room temperature. The solids were filtered and the solution was concentrated under vacuum. This resulted in 3.5 g (99%) of 3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl[*tert*-butoxy]carbohydrazide as a white solid. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 8.15 (s, 1H), 4.12 (s, 1H), 3.36 (s, 2H), 2.79-2.56 (m, 1H), 1.80-1.60 (m, 2H), 1.46-1.34 (m, 3H), 1.34-1.20 (m, 14H), 1.02 (s, 6H) ppm.

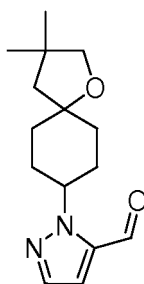
Step 3: [3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]hydrazine hydrochloride salts



[0003] Into a 100-mL round-bottom flask, was placed 3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl[*tert*-butoxy]carbohydrazide (3.5 g, 11.73 mmol, 1.00 equiv) and a solution of saturated hydrogen chloride gas in methanol (35 mL). The resulting solution was stirred for 15 h at room temperature and then concentrated under vacuum. This resulted in 2.7 g (98%) of [3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]hydrazine hydrochloride salts as a white solid. ¹H-NMR

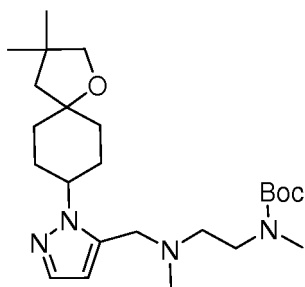
(300 MHz, D₂O): δ 3.43 (s, 2H), 3.18-3.00 (m, 1H), 2.10-1.75 (m, 4H), 1.75-1.25 (m, 6H), 1.00 (s, 6H) ppm.

Step 4: 1-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazole-5-carbaldehyde



[0004] Into a 100-mL round-bottom flask, was placed [3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]hydrazine hydrochloride (1.0 g, 4.26 mmol, 1.00 equiv), [(1*E*)-4,4-dimethoxy-3-oxobut-1-en-1-yl]dimethylamine (740 mg, 4.27 mmol, 1.00 equiv), and methanol (25 mL). The resulting solution was stirred for 15 h at 70°C and then concentrated under vacuum. The residue was diluted with THF (10 mL) and hydrochloric acid (1*N*, 15 mL) and then stirred at room temperature for 2 h. The THF was removed under vacuum and the residue was extracted with 3x30 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (2:3). This resulted in 250 mg (22%) of 1-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazole-5-carbaldehyde as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 9.85 (s, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 5.05-4.90 (m, 1H), 3.51 (s, 2H), 2.45-2.25 (m, 2H), 2.05-1.90 (m, 2H), 1.90-1.75 (m, 2H), 1.65-1.50 (m, 4H), 1.10 (s, 6H) ppm.

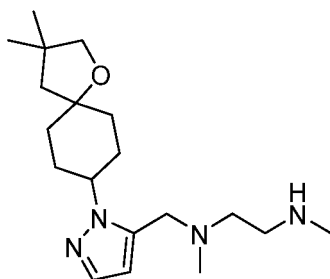
Step 5: *tert*-butyl *N*-(2-[[1-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate



[0005] Into a 250-mL round-bottom flask, was placed 1-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazole-5-carbaldehyde (524 mg, 2.00 mmol, 1.00 equiv), *tert*-butyl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate (590 mg, 3.13 mmol, 1.57 equiv), ClCH₂CH₂Cl (50 mL). Then NaBH(OAc)₃ (3.39 g, 16.00 mmol, 8.01 equiv) was added by batchwise at 0°C. The resulting solution was stirred for 3 h at 0°C. The reaction was then

quenched by the addition of 50 mL of Na₂CO₃ (sat. aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a C18 gel column with CH₃CN/H₂O (4:1). This resulted in 650 mg (75%) of *tert*-butyl *N*-(2-[[1-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl](methylamino)ethyl)-*N*-methylcarbamate as light yellow oil.

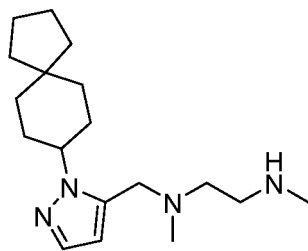
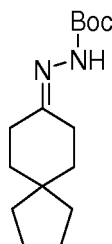
Step 6: *N*¹-((4-(4-fluorophenyl)isoxazol-5-yl)methyl)-*N*¹-methylethane-1,2-diamine trifluoroacetic acid (Compound 274)



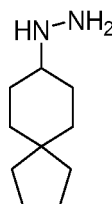
[0006] Into a 50-mL round-bottom flask, was placed *tert*-butyl *N*-(2-[[[(1-[3,3-dimethyl-1-oxaspiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl](methyl)amino]ethyl)-*N*-methylcarbamate (600 mg, 1.38 mmol, 1.00 equiv) and a solution of saturated hydrogen chloride gas in methanol (6 mL). The resulting solution was stirred for 3 h at room temperature and then concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Prep-HPLC-025): Column, XBridge Shield RP18 OBD Column, 5μm, 19*150mm; mobile phase, Water with 10mmol TFA and MeCN (5.0% MeCN up to 21.0% in 6 min, 21.0% 7 min); Detector, UV 254/220nm. This resulted in 550 mg (71%) of *N*¹-((4-(4-fluorophenyl)isoxazol-5-yl)methyl)-*N*¹-methylethane-1,2-diamine trifluoroacetic acid salt as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ7.60 (d, *J* = 1.8 Hz, 1H), 6.53 (d, *J* = 1.8 Hz, 1H), 4.57 (s, 2H), 4.32-4.15 (m, 1H), 3.61-3.41 (m, 2H), 2.81 (s, 3H), 2.70 (s, 3H), 2.15-1.85 (m, 4H), 1.77-1.45 (m, 6H), 0.98 (s, 6H) ppm. LCMS (method A, ESI): RT = 4.73 min, *m/z* = 335 [M+H]⁺.

Compound 275

Methyl[2-(methylamino)ethyl][(1-[spiro[4.5]decan-8-yl]-1H-pyrazol-5-yl)methyl]amine trifluoroacetate

**Step 1: spiro[4.5]decan-8-ylidene (*tert*-butoxy)carbohydrazide**

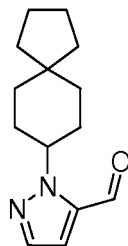
[0001] Into a 100-mL round-bottom flask, was placed spiro[4.5]decan-8-one (1.52 g, 9.98 mmol, 1.00 equiv), (*tert*-butoxy)carbohydrazide (1.32 g, 9.99 mmol, 1.00 equiv), hexane (20 mL). The resulting solution was stirred for 12 h at 75°C then cooled to room temperature and concentrated under vacuum. The residue was triturated with 1 x 5 mL of hexane and the solids were collected by filtration to afford 2.13 g (80%) of spiro[4.5]decan-8-ylidene (*tert*-butoxy)carbohydrazide as a white solid. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 9.49 (s, 1H), 2.29 (d, *J* = 6.3 Hz, 2H), 2.18 (d, *J* = 6.3 Hz, 2H), 1.67-1.32 (m, 21H) ppm.

Step 2: spiro[4.5]decan-8-ylhydrazine hydrochloride

[0002] To a solution of spiro[4.5]decan-8-ylidene (*tert*-butoxy)carbohydrazide (2 g, 7.51 mmol, 1.00 equiv) in tetrahydrofuran (10 mL) at -40°C under dry nitrogen was added a solution of borane (1 M in THF; 8.3 mL, 1.10 equiv) dropwise over approximately 20 min. The resulting solution was stirred for 1 h at room temperature then treated dropwise with hydrochloric acid (6 N, 5 mL) with stirring. The resulting solution was stirred for 12 h at room temperature and then concentrated under vacuum. The residue was triturated with 1 x 50 mL of ether and the solids were collected by filtration to afford 2.5 g (crude) of

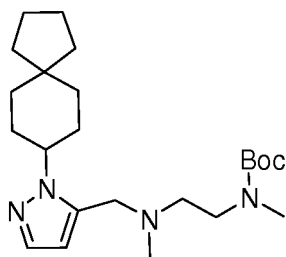
spiro[4.5]decan-8-ylhydrazine hydrochloride as a white solid. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): δ 2.94-2.80 (m, 1H), 1.95-1.80 (m, 2H), 1.45-1.45 (m, 6H), 1.45-1.29 (m, 6H), 1.29-1.15 (m, 2H) ppm.

Step 3: 1-[spiro[4.5]decan-8-yl]-1*H*-pyrazole-5-carbaldehyde



[0003] Into a 100-mL round-bottom flask, was placed spiro[4.5]decan-8-ylhydrazine hydrochloride (1.64 g, 8.01 mmol, 1.00 equiv), [(1*E*)-4,4-dimethoxy-3-oxobut-1-en-1-yl]dimethylamine (2.08 g, 12.01 mmol, 1.50 equiv), methanol (40 mL). The resulting solution was stirred for 12 h at 75°C then cooled to room temperature and concentrated under vacuum. The residue was diluted with 10 mL of hydrochloric acid (6 N) and 30 mL THF and the resulting solution stirred for 2 h at room temperature. The resulting mixture was extracted with 3 x 50 mL of ethyl acetate and the combined organic layers dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate/petroleum ether (1:10) as eluent to afford 160 mg (9%) of 1-[spiro[4.5]decan-8-yl]-1*H*-pyrazole-5-carbaldehyde as a light yellow oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.86 (s, 1H), 7.56 (d, $J = 1.8 \text{ Hz}$, 1H), 6.89 (d, $J = 1.8 \text{ Hz}$, 1H), 5.05-4.90 (m, 1H), 2.16-1.95 (m, 2H), 1.95-1.80 (m, 2H), 1.75-1.35 (m, 12H) ppm.

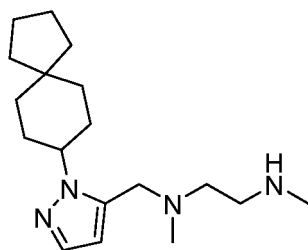
Step 4: *tert*-butyl *N*-methyl-*N*-(2-[methyl[(1-[spiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl]amino]ethyl)carbamate



[0004] To a solution of 1-[spiro[4.5]decan-8-yl]-1*H*-pyrazole-5-carbaldehyde (210 mg, 0.90 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-(2-(methylamino)ethyl)carbamate (340 mg, 1.81 mmol, 2.00 equiv) in DCE (20 mL) was added $\text{NaBH}(\text{OAc})_3$ (1.54 g, 7.26 mmol, 8.04 equiv) portionwise. The resulting solution was stirred for 12 h at room temperature then

quenched with 20 mL of sodium carbonate (sat. aq.). The organic layer was collected and the aqueous layer was extracted with 2 x 20 mL of ethyl acetate and the organic layers combined. The combined organics were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel column using ethyl acetate/petroleum ether (1:1) as eluent to afford 240 mg (66%) of *tert*-butyl *N*-methyl-*N*-(2-[methyl[(1-[spiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl]amino]ethyl)carbamate as a light yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.44 (s, 1H), 6.08 (s, 1H), 4.28-4.11 (m, 1H), 3.50 (s, 2H), 3.42-3.20 (m, 2H), 2.83 (s, 3H), 2.61-2.41 (m, 2H), 2.23 (s, 3H), 2.12-1.98 (m, 2H), 1.85-1.72 (m, 2H), 1.70-1.51 (m, 6H), 1.51-1.32 (m, 15H) ppm.

Step 5: methyl[2-(methylamino)ethyl][(1-[spiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl]amine trifluoroacetate (Compound 275)



[0005] Into a 50-mL round-bottom flask, was placed *tert*-butyl *N*-methyl-*N*-(2-[methyl[(1-[spiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl]amino]ethyl)carbamate (210 mg, 0.52 mmol, 1.00 equiv) which was then dissolved in a solution of saturated hydrogen chloride gas in 1,4-dioxane (10 mL). The reaction mixture was stirred for 12 h at room temperature and the resultant precipitate was collected by filtration. The crude product was purified by Prep-HPLC with the following conditions (Prep-HPLC-025): Column, XBridge Shield RP18 OBD Column, 5 μm, 19 x 150mm.; mobile phase, Water with 10 mmol TFA and MeCN (5.0% MeCN up to 36.0% in 10 min); Detector, UV 254/220nm. This resulted in 200 mg (72%) of methyl[2-(methylamino)ethyl][(1-[spiro[4.5]decan-8-yl]-1*H*-pyrazol-5-yl)methyl]amine trifluoroacetate as a white semi-solid. ¹H-NMR (300 MHz, D₂O): δ 7.58 (d, *J* = 2.1 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 4.54 (s, 2H), 4.22-4.16 (m, 1H), 3.61-3.36 (m, 8H), 2.88 (s, 3H), 2.67 (s, 3H), 1.98-1.75 (m, 2H), 1.74-1.57 (m, 2H), 1.57-1.20 (m, 12H). LCMS (method A, ESI): RT = 1.09 min, *m/z* = 305.4 [M+1]⁺.

*Biological Methods***PRMT1 Biochemical Assay**

[0007] General Materials. S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, 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. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[0008] Substrates. Peptide representative of human histone H4 residues 36-50 was synthesized with an N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was purified by high-performance liquid chromatography (HPLC) to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Biot-Ahx-RLARRGGVKRISGLI-amide (SEQ ID NO.:1).

[0009] Molecular Biology: Full-length human PRMT1 isoform 1 (NM_001536.5) transcript clone was amplified from an HEK 293 cDNA library, incorporating flanking 5' sequence encoding a FLAG tag (DYKDDDDK) (SEQ ID NO.:2) fused directly to Met 1 of PRMT1. The amplified gene was subcloned into pFastBacI (Life Technologies) modified to encode an N-terminal GST tag and a TEV cleavage sequence (MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVCLTQSMARIYIADKHNMLGGCPKERAISMLEGAVLDIRYGVSR IAYSKDFETLKVDFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRIEAI PQIDKYLKSSKYIAWPLQG WQATFGGGDHPPKSDENLYFQGGNS)(SEQ ID NO.:3) fused to Asp of the Flag tag of PRMT1.

[0010] Protein Expression. Recombinant baculovirus were generated according to Bac-to-Bac kit instructions (Life Technologies). Protein over-expression was accomplished by infecting exponentially growing High Five insect cell culture at 1.5X10⁶ cell/ml with 1:100 ratio of virus. Infections were carried out at 27°C for 48 hours, harvested by centrifugation, and stored at -80°C for purification.

[0011] Protein Purification. Expressed full-length human GST-tagged PRMT1 protein was purified from cell paste by glutathione sepharose affinity chromatography after equilibration of the resin with 50 mM phosphate buffer, 200 mM NaCl, 5% glycerol, 5 mM β-mercaptoethanol, pH7.8 (Buffer A). GST-tagged PRMT1 was eluted with 50 mM Tris, 2

mM glutathione, pH 7.8, dialysed in buffer A and concentrated to 1 mg/mL. The purity of recovered protein was 73%. Reference: Wasilko, D.J. and S.E. Lee: "TIPS: titerless infected-cells preservation and scale-up" Bioprocess J., 5 (2006), pp. 29–32.

[0012] Predicted Translations:

GST-tagged PRMT1 (SEQ ID NO.:4)

MSPIILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVKL
TQSMAIIRYIADKHNLGGCPKERAIEISMLEGAVLDIRYGVSRAYS KDFETLKVDFLSKLP EML
KMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRIEAIPIQIDKYLKS
SKYIAWPLQGWAATFGGGDHPPKSDENLYFQGGNSDYKDDDDKMAAAEAANCIMENFVATLANGM
SLQPPLEEVSCGQAESSEKPNADMTSKDYFDSYAHFGIHEEMLKDEVRTLTYRNSMFHNRHLF
KDKVVLDVGSGTGILCMFAAKAGARKVIGIECSSISDYAVKIVKANKLDHVVTIIKGKVEEVELP
VEKVDIIISEWMGYCLFYESMLNTVLYARDKWLAPDGLIFPDRATLYVTAIEDRQYKDYKIHWE
NVYGFDMSCIKDVAIKEPLVDVDPKQLVTNACLIEVDIYTVKVEDLTFTSPFCLQVKRNDYVH
ALVAYFNIEFTRCHKRTGFSTSPESPYTHWKQTVFYMEDYLTVKTGEEIFGTIGMRPNAKNNRDL
DFTIDLDFKGLCELSCSTDYRMR

[0013] General Procedure for PRMT1 Enzyme Assays on Peptide Substrates. The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP, 0.005% BSG, and 0.002% Tween 20, 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 PRMT1, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the PRMT1 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT1 for 30 min at room temperature, then a cocktail (10ul) containing SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: PRMT1 was 0.5 nM, ³H-SAM was 200 nM, non-radiolabeled SAM was 1.5 uM, peptide was 20 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 300 uM, which dilutes the ³H-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 once 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 ³H-

labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{compd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

[0014] Where dpm = disintegrations per minute, compd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{\left(1 + \left(\frac{X}{IC_{50}}\right)^{Hill\ Coefficient}\right)}$$

[0015] 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.

PRMT6 Biochemical Assay

[0016] **General Materials.** S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), sodium butyrate and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[0017] **Substrates.** Peptide representative of human histone H4 residues 36-50 was synthesized with an N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was purified by high-performance liquid chromatography (HPLC) to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Biot-Ahx-RLARRGGV**K**RISGLI-amide and contained a monomethylated lysine at position 44 (SEQ ID NO.:5).

[0018] **Molecular Biology:** Full-length human PRMT6 (NM_018137.2) transcript clone was amplified from an HEK 293 cDNA library, incorporating a flanking 5' sequence encoding a FLAG tag (MDYKDDDDK) (SEQ ID NO.:6) fused directly to Ser 2 of PRMT6 and a 3' sequence encoding a hexa His sequence (HHHHHH) (SEQ ID NO.:17) fused directly to Asp 375. The amplified gene was subcloned into pFastBacMam (Viva Biotech).

[0019] Protein Expression. Recombinant baculovirus were generated according to Bac-to-Bac kit instructions (Life Technologies). Protein over-expression was accomplished by infecting exponentially growing HEK 293F cell culture at 1.3×10^6 cell/ml with virus (MOI = 10) in the presence of 8 mM sodium butyrate. Infections were carried out at 37°C for 48 hours, harvested by centrifugation, and stored at -80°C for purification.

[0020] Protein Purification. Expressed full-length human Flag- and His-tagged PRMT6 protein was purified from cell paste by NiNTA agarose affinity chromatography after equilibration of the resin with buffer containing 50 mM Tris, 300 mM NaCl, 10% glycerol, pH 7.8 (Buffer Ni-A). Column was washed with 20 mM imidazole in the same buffer and Flag-PRMT6-His was eluted with 150 mM imidazole. Pooled fractions were dialysed against buffer Ni-A and further purified by anti-flag M2 affinity chromatography. Flag-PRMT6-His was eluted with 200 ug/ml FLAG peptide in the same buffer. Pooled fractions were dialysed in 20 mM Tris, 150 mM NaCl, 10% glycerol and 5 mM β -mercaptoethanol, pH 7.8. The purity of recovered protein was 95%.

[0021] Predicted Translations:

Flag-PRMT6-His (SEQ ID NO.: 7)

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MDYKDDDDKSQPKKRKLESGGGGEGGEGTEEDGAEREAAALERPRRTKRERDQLYYECYSDVSVH
EEMIADRVRTDAYRLGILRNWAALRGKTVLDVGAGTGILSIFCAQAGARRVYAVEASAIWQQARE
VVRFNGLIEDRVHVLPGPVETVELPEQVDAIVSEWMGYGLLHESMLSSVLHARTKWLKEGGLLLPA
SAELFIAPISDQMLEWRLGFWSQVKQHYGVDMSCLEGFATRCLMGHSEIVVQGLSGEDVLARPQR
FAQLELSRAGLEQELEAGVGGRFCSCYGSAPMHGFATWQVTFPGGESEKPLVLSTSPFHPATH
WKQALLYLNPEVQVEQDQTDVSGEITLLPSRDNPRRLRVLLRYKVGDDQEEKTKDFAMEDHHHHHH
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[0022] General Procedure for PRMT6 Enzyme Assays on Peptide Substrates. The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP, 0.005% BSG, and 0.002% Tween 20, 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 PRMT6, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the PRMT6 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT6 for 30 min at room temperature, then a cocktail (10ul) containing SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: PRMT6 was 1 nM, ^{3} H-SAM was 200 nM, non-radiolabeled SAM was 250 nM, peptide was 75 nM, SAH in the minimum signal control wells was 1 mM,

and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 400 uM, which dilutes the ³H-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 once 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 ³H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

[0023] 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

$$Y = Bottom + \frac{(Top - Bottom)}{(1 + (\frac{X}{IC_{50}})^{Hill\ Coefficient})}$$

[0024] 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.

PRMT8 Biochemical Assay

[0025] **General Materials.** S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), isopropyl-β-D-thiogalactopyranoside (IPTG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[0026] **Substrates.** Peptide representative of human histone H4 residues 31-45 was synthesized with an N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was purified by high-performance liquid chromatography (HPLC) to greater than 95% purity and confirmed by liquid chromatography mass

spectrometry (LC-MS). The sequence was Biot-Ahx-KPAIRRLARRGGVKR-amide (SEQ ID NO.:8).

[0027] Molecular Biology: Full-length human PRMT8 (NM_019854.4) isoform 1 transcript clone was amplified from an HEK 293 cDNA library and subcloned into pGEX-4T-1 (GE Life Sciences). The resulting construct encodes an N-terminal GST tag and a thrombin cleavage sequence (MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVKL TQSMAIIRYIADKHNMLGGCPKERA EISMLEGAVLDIRYGVSR IAYSKDFETLKVD FLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDMFLYDALDVVLYMDPMCLDAFPKLVCFKKRIE AIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLVPRG SPEF) (SEQ ID NO.:9) fused directly to Met 1 of PRMT8.

[0028] Protein Expression. *E. coli* (BL21(DE3) Gold, Stratagene) made competent by the CaCl₂ method were transformed with the PRMT8 construct and ampicillin selection. Protein over-expression was accomplished by growing the PRMT8 expressing *E. coli* clone and inducing expression with 0.3 mM IPTG at 16°C. The culture was grown for 12 hours, harvested by centrifugation, and stored at -80°C for purification.

[0029] Protein Purification. Expressed full-length human GST-tagged PRMT8 protein was purified from cell paste by glutathione sepharose affinity chromatography after the resin was equilibrated with 50 mM phosphate buffer, 200 mM NaCl, 5% glycerol, 5 mM β-mercaptoethanol, pH 7.8 (Buffer A). GST-tagged PRMT8 was eluted with 50 mM Tris, 2 mM glutathione, pH 7.8. Pooled fractions were cleaved by thrombin (10U) and dialysed in buffer A. GST was removed by reloading the cleaved protein sample onto glutathione sepharose column and PRMT8 was collected in the flow-through fractions. PRMT8 was purified further by ceramic hydroxyapatite chromatography. The column was washed with 50 mM phosphate buffer, 100 mM NaCl, 5% glycerol, 5 mM β-mercaptoethanol, pH 7.8 and PRMT8 was eluted by 100 mM phosphate in the same buffer. Protein was concentrated and buffer was exchanged to 50 mM Tris, 300 mM NaCl, 10% glycerol, 5 mM β-mercaptoethanol, pH 7.8 by ultrafiltration. The purity of recovered protein was 89%.

[0030] Predicted Translations:

GST-tagged PRMT8 (SEQ ID NO.:10)

MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVKL
TQSMAIIRYIADKHNMLGGCPKERA EISMLEGAVLDIRYGVSR IAYSKDFETLKVD FLSKLPEML
KMFEDRLCHKTYLNGDHVTHPDMFLYDALDVVLYMDPMCLDAFPKLVCFKKRIE AIPQIDKYLK
SKYIAWPLQGWQATFGGGDHPPKSDLVPRGSPEFMGMKHSSRCLLLRRKMAENAAESTE VN SPPS
QPPQPVPVPAKPVQCVHHVSTQPSCPGRGKMSKLLNPEEMTSRDYYFDSYAHFGIHEEMLKDEVRT

LTyrNSMYHNKHVFKDKVVLdVGSGTGILSMFAAKAGAKKVFGEICSSISDYSEKI I KANHLdNI
 ITIFKGKVEEVELPVEKVDII I SEWMGYCLFYESMLNTVIFARDKWLKPGGLMFPDRAALYVVAI
 EDRQYKDFKIHWVENYGFDMTCIRDVAMKEPLVDIVDPKQVVTNACLIKEVDIYTVKTEELSFT
 SAFCLQIQRNDYVHALVTYFNIEFTKCHKKMGFSTAPDAPYTHWKQTVFYLEDYLTVRRGEEIYG
 TISMKPNAKNVRDLDFTVDLDFKGQLCETSVSNDYKMR

[0031] General Procedure for PRMT8 Enzyme Assays on Peptide Substrates. The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP, 0.005% BSG, and 0.002% Tween 20, 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 PRMT8, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the PRMT8 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT8 for 30 min at room temperature, then a cocktail (10ul) containing ³H-SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: PRMT8 was 1.5 nM, ³H-SAM was 50 nM, non-radiolabeled SAM was 550 nM, peptide was 150 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 400 uM, which dilutes the ³H-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 once 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 ³H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

[0032] 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

$$Y = Bottom + \frac{(Top - Bottom)}{(1 + (\frac{X}{IC_{50}})^{Hill\ Coefficient})}$$

[0033] 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.

PRMT3 Biochemical Assay

[0034] **General Materials.** S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), , isopropyl-β-D-thiogalactopyranoside (IPTG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[0035] **Substrates.** Peptide containing the classic RMT substrate motif was synthesized with an N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was purified by high-performance liquid chromatography (HPLC) to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Biot-Ahx-GGRGGFGGRGGFGGRGGFG-amide (SEQ ID NO.:11).

[0036] **Molecular Biology:** : Full-length human PRMT3 (NM_005788.3) isoform 1 transcript clone was amplified from an HEK 293 cDNA library and subcloned into pGEX-KG (GE Life Sciences). The resulting construct encodes an N-terminal GST tag and a thrombin cleavage sequence
(MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLP
YYIDGDVKLTQSMARIYIADKHNMLGGCPKERAIEISMLEGAVLDIRYGVSR IAYSK
DFETLKVDFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPM
CLDAFPKLVCFKKRIEAI PQIDKYLKSSKYIAWPLQG WQATFGGGDHPPKSDLVPRG
S) (SEQ ID NO.:12) fused directly to Cys 2 of PRMT3.

[0037] **Protein Expression.** *E. coli* (BL21(DE3) Gold, Stratagene) made competent by the CaCl₂ method were transformed with the PRMT3 construct and ampicillin selection. Protein over-expression was accomplished by growing the PRMT3 expressing *E. coli* clone

and inducing expression with 0.3 mM IPTG at 16°C. The culture was grown for 12 hours, harvested by centrifugation, and stored at -80°C for purification.

[0038] Protein Purification. Expressed full-length human GST-tagged PRMT3 protein was purified from cell paste by glutathione sepharose affinity chromatography after equilibration of the resin with 50 mM phosphate buffer, 200 mM NaCl, 5% glycerol, 1 mM EDTA, 5 mM β -mercaptoethanol, pH6.5 (Buffer A). GST-tagged PRMT3 was eluted with 50 mM Tris, 2 mM glutathione, pH 7.1 and 50 mM Tris, 20 mM glutathione, pH 7.1. Pooled fractions were dialysed in 20 mM Tris, 50 mM NaCl, 5% glycerol, 1 mM EDTA, 1 mM DTT, pH7.5 (Buffer B) and applied to a Q Sepharose Fast Flow column. GST-tagged PRMT3 was eluted by 500 mM NaCl in buffer B. Pooled fractions were dialyzed in 25 mM phosphate buffer, 100 mM NaCl, 5% glycerol, 2 mM DTT, pH 6.8 (Buffer C) and loaded on to a ceramic hydroxyapatite column. GST-tagged PRMT3 eluted with 25-400 mM phosphate in buffer C. Protein was concentrated and buffer was exchanged to 20 mM Tris, 150 mM NaCl, 5% glycerol, 5 mM β -mercaptoethanol, pH7.8 by ultrafiltration. The purity of recovered protein was 70%.

[0039] Predicted Translations:

GST-tagged PRMT3 (SEQ ID NO.:13)

MSPILGYWKIKGLVQPTRLLLEYLEEKYEHLIERDEGDKWRNKKFELGLEFPNLPYYIDGDVKL
TQSMAIIRYIADKHNMLGGCPKERAIEISMLEGAVLDIRYGVSR IAYSKDFETLKVDFLSKLPEML
KMFEDRLCHKTYLNGDHVTHPDFMLYDALDVLYMDPMCLDAFPKLVCFKKRIEAIPIQIDKYLKS
SKYIAWPLQGWQATFGGGDHPPKSDLVPRGSCSLASGATGGRGAVENEEDLPELSDSGDEAAWED
EDDADLPHGKQQT PCLFCNRLFTSAEETFSHCKSEHQFNIDSMVHKHGLEFYGYIKLINFIRLKN
PTVEYMNSIYNPVPWEKEEYLKPVLEDDLLLQFDVEDLYEPVSVPF SYPNGLSENTSVVEKLKHM
EARALSAEAAALARAREDLQMKQFAQDFVMHTDVRTCSSSTS VIADLQEDEDGVYFSSYGHYGIH
EEMLKDKIRTESYRDFIYQNPHIFKDKVVL DVGCGTGILSMFAAKAGAKKVLGVDQSEILYQAMD
IIRLNKLED TITLIKGKIEEVHLPVEKVDV IISEWMGYFLLFESMLDSVLYAKNKYLAKGGSVYP
DICTISLVAVSDVNKHADRIAFWDDVYGFKMSCMKKAVIPEAVVEVLDPKTLISEPCGIKHIDCH
TTSISDLEFSSDFTLKITRTSMCTAIAGYFDIYFEKNCHNRVVFSTGPQSTKTHWKQTVFLLLEKP
FSVKAGEALKGKVT VHKNKKDPRSLT VTLTLNNSTQTYGLQ

[0040] General Procedure for PRMT3 Enzyme Assays on Peptide Substrates. The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP, 0.005% BSG, and 0.002% Tween 20, 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 PRMT3, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the PRMT3 enzyme was added by

Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT3 for 30 min at room temperature, then a cocktail (10ul) containing SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: PRMT3 was 0.5 nM, ³H-SAM was 100 nM, non-radiolabeled SAM was 1.8 uM, peptide was 330 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of potassium chloride (10ul) to a final concentration of 100 mM. 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 once 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 ³H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{compd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

[0041] Where dpm = disintegrations per minute, compd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{(1 + (\frac{X}{IC_{50}})^{Hill\ Coefficient})}$$

[0042] 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.

CARM1 Biochemical Assay

[0043] **General Materials.** S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), sodium butyrate and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[0044] Substrates. Peptide representative of human histone H3 residues 16-30 was synthesized with an N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was purified by high-performance liquid chromatography (HPLC) to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Biot-Ahx-PRKQLATKAARKSAP-amide and contained a monomethylated arginine at position 26 (SEQ ID NO.:14).

[0045] Molecular Biology: Human CARM1 (PRMT4) (NM_199141.1) transcript clone was amplified from an HEK 293 cDNA library, incorporating a flanking 5' sequence encoding a FLAG tag (MDYKDDDDDK) (SEQ ID NO.:6) fused directly to Ala 2 of CARM1 and 3' sequence encoding a hexa His sequence (EGHHHHHH) (SEQ ID NO.:15) fused directly to Ser 608. The gene sequence encoding isoform1 containing a deletion of amino acids 539-561 was amplified subsequently and subcloned into pFastBacMam (Viva Biotech).

[0046] Protein Expression. Recombinant baculovirus were generated according to Bac-to-Bac kit instructions (Life Technologies). Protein over-expression was accomplished by infecting exponentially growing HEK 293F cell culture at 1.3×10^6 cell/ml with virus (MOI = 10) in the presence of 8 mM sodium butyrate. Infections were carried out at 37°C for 48 hours, harvested by centrifugation, and stored at -80°C for purification.

[0047] Protein Purification. Expressed full-length human Flag- and His-tagged CARM1 protein was purified from cell paste by anti-flag M2 affinity chromatography with resin equilibrated with buffer containing 20 mM Tris, 150 mM NaCl, 5% glycerol, pH 7.8. Column was washed with 500 mM NaCl in buffer A and Flag-CARM1-His was eluted with 200 ug/ml FLAG peptide in buffer A. Pooled fractions were dialyzed in 20 mM Tris, 150 mM NaCl, 5% glycerol and 1 mM DTT, pH 7.8. The purity of recovered protein was 94.

[0048] Predicted Translations:

Flag-CARM1-His (SEQ ID NO.:16)

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MDYKDDDDKAAAAA AVGPGAGGAGSAVPGGAGPCATVSVFPGARLLTIGDANGEIQRHAEQQALR
LEVRAGPDSAGIALYSHEDVCVFKCSVSRETECSRVGKQSFIIITLGCNSVLIQFATPNDFCSFYN
ILKTCRGHTLERSVFSERTEESSAVQYFQFYGYLSQQQNMMDYVRTGTYQRAILQNHTDFKDKI
VLDVGC GSGILSFFAAQAGARKIYAVEASTMAQHA EVLVKSNLTDRIVVIPGKVEEVSLPEQVD
II ISEPMGYMLFNERMLESYLHAKKYLKPSGNMFPTIGDVHLAPFTDEQLYMEQFTKANFWYQPS
FHGVDLSALRGAAVDEYFRQPVDTFDIRILMAKSVKYTVNFLEAKEGDLHRIEIPFKFHMLHSG
LVHGLAFWFDVAFIGSIMTVWLSTAPTEPLTHWYQVRCLFQSPLFAKAGDTLSGTCLLIANKRQS
YDISIVAQVDQTGSKSSNLLDLKNPFFRYTGTTSPPPGSHYTSPSENMMWNTGSTYNLSSGMAVA
GMPTAYDLSSVIASGSSVGHNNLIPLGSSGAQGSGGGSTSAHYAVNSQFTMGGAISMASPMSIP
TNTMHYGSEGGHHHHH
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[0049] General Procedure for CARM1 Enzyme Assays on Peptide Substrates. The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP,

0.005% BSG, and 0.002% Tween 20, 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 CARM1, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the CARM1 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with CARM1 for 30 min at room temperature, then a cocktail (10ul) containing ^3H -SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: CARM1 was 0.25 nM, ^3H -SAM was 30 nM, peptide was 250 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 300 uM, which dilutes the ^3H -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 once 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 ^3H -labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{\text{compd}} - dpm_{\text{min}}}{dpm_{\text{max}} - dpm_{\text{min}}} \right) \times 100$$

[0050] Where dpm = disintegrations per minute, compd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{\left(1 + \left(\frac{X}{IC_{50}}\right)^{Hill\ Coefficient}\right)}$$

[0051] 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.

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
1	A	A	B	D	B
2	A	A	B	C	B
3	-	A	B	D	C
4	A	A	B	E	B
5	A	A	B	C	B
6	A	A	B	D	B
7	A	A	B	D	A
8	A	A	B	D	B
9	A	A	B	D	C
10	B	B	C	E	E
11	A	A	B	C	A
12	C	C	E	E	E
13	A	A	B	D	B
14	A	B	B	D	B
15	A	A	B	C	B
16	A	B	B	D	B
17	A	A	B	C	A
18	A	A	A	C	A
19	B	B	C	D	D
20	A	A	B	C	B
21	C	B	D	E	E
22	A	A	B	D	D
23	A	A	B	D	C
24	A	B	B	E	-
25	B	B	C	-	-
26	-	B	D	-	-
27	-	C	E	-	-
28	B	A	C	-	-
29	B	B	C	-	-
30	-	B	D	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
31	-	D	E	-	-
32	B	A	C	-	-
33	A	A	B	-	-
34	A	A	B	-	-
35	A	A	B	-	-
36	A	A	B	-	-
37	A	A	B	-	-
38	A	A	B	-	-
39	-	A	B	-	-
40	-	A	B	-	-
41	A	A	D	-	-
42	A	A	B	-	-
43	-	A	-	-	-
44	C	B	-	-	-
45	A	A	-	-	-
46	A	A	-	-	-
47	A	A	-	-	-
48	A	A	-	-	-
49	A	A	-	-	-
50	A	A	-	-	-
51	A	A	-	-	-
52	A	A	-	-	-
53	A	A	-	-	-
54	A	A	-	-	-
55	A	A	-	-	-
56	A	A	-	-	-
57	A	A	-	-	-
58	A	A	-	-	-
59	A	B	-	-	-
60	A	B	-	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
61	A	A	-	-	-
62	A	A	A	-	-
63	A	A	A	-	-
64	-	-	-	-	-
65	A	A	A	-	-
66	-	-	-	-	-
67	A	A	A	-	-
68	-	-	-	-	-
69	-	-	-	-	-
70	A	A	A	-	-
71	-	-	-	-	-
72	-	-	-	-	-
73	-	-	-	-	-
74	-	-	-	-	-
75	-	-	-	-	-
76	-	-	-	-	-
77	-	-	-	-	-
78	-	-	-	-	-
79	-	-	-	-	-
80	-	-	-	-	-
81	-	-	-	-	-
82	-	-	-	-	-
83	-	-	-	-	-
84	-	-	-	-	-
85	-	-	-	-	-
86	C	D	D	-	-
87	B	D	C	-	-
88	-	-	-	-	-
89	-	-	-	-	-
90	A	B	B	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
91	A	A	A	-	-
92	A	A	A	-	-
93	A	A	A	-	-
94	-	-	-	-	-
95	A	A	A	-	-
96	-	-	-	-	-
97	-	-	-	-	-
98	-	-	-	-	-
99	-	-	-	-	-
100	-	-	-	-	-
101	-	-	-	-	-
102	-	-	-	-	-
103	-	-	-	-	-
104	A	A	A	-	-
105	-	-	-	-	-
106	A	A	A	-	-
107	A	B	A	-	-
108	A	B	B	-	-
109	A	B	A	-	-
110	A	A	A	-	-
111	A	A	A	-	-
112	A	A	A	-	-
113	A	A	B	-	-
114	B	A	B	-	-
115	A	A	B	-	-
116	A	A	A	-	-
117	A	A	B	-	-
118	C	E	E	-	-
119	B	C	B	-	-
120	A	A	A	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
121	A	A	A	-	-
122	B	E	D	-	-
123	A	A	A	-	-
124	A	A	A	-	-
125	A	A	A	-	-
126	A	A	A	-	-
127	A	A	A	-	-
128	A	A	A	-	-
129	A	A	A	-	-
130	A	A	A	-	-
131	B	E	C	-	-
132	B	D	D	-	-
133	A	A	A	-	-
134	A	A	A	-	-
135	A	A	A	-	-
136	A	A	A	-	-
137	A	A	A	-	-
138	B	C	C	-	-
139	A	A	B	-	-
140	A	A	A	-	-
141	A	A	A	-	-
142	A	A	A	-	-
143	A	A	A	-	-
144	A	A	A	-	-
145	A	A	-	-	-
146	A	A	-	-	-
147	A	A	-	-	-
148	A	A	-	-	-
149	A	A	-	-	-
150	A	A	-	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
151	A	A	-	-	-
152	A	A	-	-	-
153	A	A	-	-	-
154	A	A	-	-	-
155	A	A	-	-	-
156	A	A	-	-	-
157	A	A	-	-	-
158	A	A	-	-	-
159	A	A	-	-	-
160	A	B	-	-	-
161	A	A	A	-	-
162	A	A	A	-	-
163	A	A	A	-	-
164	A	A	A	-	-
165	A	B	A	-	-
166	A	A	A	-	-
167	A	A	A	-	-
168	A	A	A	-	-
169	A	A	A	-	-
170	A	A	A	-	-
171	A	A	-	-	-
172	A	A	-	-	-
173	A	A	-	-	-
174	A	A	-	-	-
175	A	A	A	-	-
176	A	A	A	-	-
177	A	B	B	-	-
178	A	A	A	-	-
179	A	A	A	-	-
180	A	A	-	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
181	A	A	-	-	-
182	A	A	A	-	-
183	A	A	A	-	-
184	A	B	A	-	-
185	A	A	A	-	-
186	B	B	A	-	-
187	B	B	B	-	-
188	B	C	C	-	-
189	B	C	B	-	-
190	B	B	B	-	-
191	A	B	B	-	-
192	B	B	B	-	-
193	A	A	A	-	-
194	A	A	A	-	-
195	A	A	A	-	-
196	B	B	B	-	-
197	A	A	A	-	-
198	D	D	D	-	-
199	A	A	A	-	-
200	A	A	A	-	-
201	A	B	A	-	-
202	A	A	A	-	-
203	A	A	A	-	-
204	A	A	A	-	-
205	A	A	A	-	-
206	A	B	A	-	-
207	A	A	A	-	-
208	A	A	A	-	-
209	A	A	A	-	-
210	A	A	A	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
211	A	A	A	-	-
212	A	A	A	-	-
213	A	A	B	-	-
214	A	A	A	-	-
215	A	A	A	-	-
216	A	A	A	-	-
217	A	A	A	-	-
218	A	A	A	-	-
219	A	A	A	-	-
220	A	A	A	-	-
221	A	A	A	-	-
222	A	A	A	-	-
223	A	A	A	-	-
224	A	A	A	-	-
225	A	A	A	-	-
226	A	A	A	-	-
227	A	A	A	-	-
228	A	A	A	-	-
229	A	A	A	-	-
230	A	A	A	-	-
231	A	A	A	-	-
232	A	A	A	-	-
233	A	A	A	-	-
234	A	A	A	-	-
235	A	A	A	-	-
236	A	A	A	-	-
237	A	A	A	-	-
238	A	A	A	-	-
239	A	A	A	-	-
240	A	A	A	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
241	A	A	A	-	-
242	A	A	A	-	-
243	A	A	A	-	-
244	A	A	B	-	-
245	A	A	A	-	-
246	A	A	A	-	-
247	A	A	A	-	-
248	A	A	A	-	-
249	A	A	A	-	-
250	A	A	A	-	-
251	A	A	A	-	-
252	A	A	A	-	-
253	A	A	A	-	-
254	A	A	A	-	-
255	A	A	A	-	-
256	A	A	A	-	-
257	A	B	A	-	-
258	A	A	A	-	-
259	A	A	A	-	-
260	A	A	A	-	-
261	A	A	A	-	-
262	A	A	A	-	-
263	A	A	A	-	-
264	A	B	B	-	-
265	A	B	B	-	-
266	A	A	A	-	-
267	D	D	D	-	-
268	A	B	B	-	-
269	A	B	B	-	-
270	A	B	B	-	-

Table 2. Biochemical IC ₅₀					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
271	A	B	A	-	-
272	A	A	A	-	-
273	A	A	A	-	-
274	A	B	A	-	-
275	A	A	A	-	-

“-” indicates no data provided.

For Table 2, “A” indicates an IC₅₀ ≤ 0.100 μM, “B” indicates an IC₅₀ of 0.101 – 1.00 μM, “C” indicates an IC₅₀ of 1.01 – 3.00 μM, “D” indicates an IC₅₀ of 3.01 – 10 μM, and IC₅₀ ≥ 10.01 μM.

Table 2a. Biochemical IC ₅₀ (Numerical, μM)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
1	0.01	0.07	0.39	6.83	0.26
2	0.01	0.04	0.17	3.00	0.11
3	-	0.02	0.95	9.40	1.23
4	0.02	0.02	0.59	>10	0.50
5	0.01	0.00	0.42	1.45	0.31
6	0.04	0.03	0.24	3.94	0.57
7	0.01	0.02	0.52	5.91	0.09
8	0.02	0.04	0.36	5.81	0.37
9	0.01	0.01	0.76	8.93	3.00
10	0.39	0.31	1.92	>10	>10
11	0.01	0.05	0.25	1.58	0.05
12	1.58	1.08	>10	>10	>10
13	0.01	0.01	0.30	3.62	0.20
14	0.09	0.93	0.66	6.77	0.51
15	0.05	0.04	0.70	2.34	0.31
16	0.02	0.15	0.69	5.79	0.11
17	0.01	0.05	0.41	2.36	0.09
18	0.00	0.01	0.04	1.75	0.10
19	0.19	0.17	2.30	7.74	3.78
20	0.02	0.02	0.47	2.34	0.25

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
21	1.49	0.67	9.56	>10	>10
22	0.01	0.02	0.30	6.46	3.77
23	0.01	0.01	0.28	9.65	2.78
24	0.02	0.18	0.30	>10	-
25	0.25	0.29	2.86	-	-
26	-	0.51	5.63	-	-
27	-	2.41	>10	-	-
28	0.18	0.08	1.68	-	-
29	-	0.29	3.81	-	-
30	-	6.59	>10	-	-
31	0.11	0.03	1.15	-	-
32	0.02	0.02	0.77	-	-
33	0.02	0.02	0.50	-	-
34	0.02	0.03	0.44	-	-
35	0.00	0.01	0.14	-	-
36	0.00	0.01	0.28	-	-
37	0.01	0.01	0.13	-	-
38	0.00	0.01	0.26	-	-
39	-	0.01	0.36	-	-
40	0.02	0.02	7.01	-	-
41	0.01	0.00	0.35	-	-
42	-	0.02	0.0300	-	-
43	-	0.00	0.0116	-	-
44	-	0.02	0.0624	-	-
45	0.0028	0.0056	0.0053	-	-
46	0.0079	0.0122	0.0062	-	-
47	0.0043	0.0173	0.0125	-	-
48	0.0074	0.0178	0.0083	-	-
49	0.0043	0.0199	0.0073	-	-
50	0.0086	0.0206	0.0112	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
51	0.0094	0.0239	0.0214	-	-
52	0.0047	0.0243	0.0104	-	-
53	0.0105	0.0380	0.0128	-	-
54	0.0080	0.0382	0.0247	-	-
55	0.0128	0.0404	0.0247	-	-
56	0.0138	0.0618	0.0320	-	-
57	0.0186	0.0694	0.0301	-	-
58	0.0265	0.1077	0.0721	-	-
59	0.0196	0.1277	0.0484	-	-
60	0.0275	0.1549	0.1286	-	-
61	0.0205	0.0491	-	-	-
62	0.01187	0.02902	0.02	-	-
63	0.0090	0.0121	0.0120	-	-
64	-	-	-	-	-
65	0.00965	0.04193	0.01355	-	-
66	-	-	-	-	-
67	0.0078	0.0180	0.0119	-	-
68	-	-	-	-	-
69	-	-	-	-	-
70	0.0092	0.0440	0.0242	-	-
71	-	-	-	-	-
72	-	-	-	-	-
73	-	-	-	-	-
74	-	-	-	-	-
75	-	-	-	-	-
76	-	-	-	-	-
77	-	-	-	-	-
78	-	-	-	-	-
79	-	-	-	-	-
80	-	-	-	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
81	-	-	-	-	-
82	-	-	-	-	-
83	-	-	-	-	-
84	-	-	-	-	-
85	-	-	-	-	-
86	1.94296	3.40906	3.96737	-	-
87	0.56419	3.72633	1.01384	-	-
88	-	-	-	-	-
89	-	-	-	-	-
90	0.0344	0.12244	0.11687	-	-
91	0.01668	0.06307	0.02896	-	-
92	0.0209	0.04904	0.04206	-	-
93	0.03128	0.07193	0.08812	-	-
94	-	-	-	-	-
95	0.00935	0.0692	0.01887	-	-
96	-	-	-	-	-
97	-	-	-	-	-
98	-	-	-	-	-
99	-	-	-	-	-
100	-	-	-	-	-
101	-	-	-	-	-
102	-	-	-	-	-
103	-	-	-	-	-
104	0.00804	0.04046	0.01158	-	-
105	-	-	-	-	-
106	0.0095	0.01348	0.0145	-	-
107	0.0212	0.1296	0.0554	-	-
108	0.0610	0.3255	0.2521	-	-
109	0.0267	0.1243	0.0560	-	-
110	0.0131	0.0294	0.0429	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
111	0.0224	0.0455	0.0599	-	-
112	0.0189	0.0574	0.0692	-	-
113	0.0572	0.0669	0.1193	-	-
114	0.1009	0.0926	0.3400	-	-
115	0.0887	0.0627	0.1964	-	-
116	0.0098	0.0187	0.0118	-	-
117	0.0386	0.0962	0.1428	-	-
118	2.1552	> 10.0	> 10.0	-	-
119	0.1239	2.7522	0.7278	-	-
120	0.0101	0.0428	0.0251	-	-
121	0.0152	0.0977	0.0326	-	-
122	0.4207	> 10.0	8.3743	-	-
123	0.0088	0.0180	0.0247	-	-
124	0.0064	0.0262	0.0108	-	-
125	0.0053	0.0131	0.0090	-	-
126	0.0040	0.0094	0.0065	-	-
127	0.0165	0.0223	0.0478	-	-
128	0.0052	0.0131	0.0082	-	-
129	0.0236	0.0297	0.0837	-	-
130	0.0034	0.0042	0.0045	-	-
131	0.2699	> 10.0	1.9689	-	-
132	0.6264	5.4954	4.3316	-	-
133	0.0059	0.0124	0.0091	-	-
134	0.0139	0.0351	0.0248	-	-
135	0.0121	0.0349	0.0317	-	-
136	0.0029	0.0072	0.0068	-	-
137	0.0073	0.0233	0.0162	-	-
138	0.3486	1.2075	1.4305	-	-
139	0.0305	0.0226	0.1157	-	-
140	0.0156	0.0240	0.0339	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
141	0.0107	0.0230	0.0297	-	-
142	0.0072	0.0199	0.0159	-	-
143	0.0106	0.0220	0.0330	-	-
144	0.0216	0.0356	0.0784	-	-
145	0.0262	0.0380	-	-	-
146	0.0140	0.0217	-	-	-
147	0.0183	0.0327	-	-	-
148	0.0048	0.0081	-	-	-
149	0.0045	0.0072	-	-	-
150	0.0440	0.0556	-	-	-
151	0.0369	0.0477	-	-	-
152	0.0142	0.0352	-	-	-
153	0.0232	0.0284	-	-	-
154	0.0177	0.0443	-	-	-
155	0.0315	0.0608	-	-	-
156	0.0172	0.0578	-	-	-
157	0.0185	0.0479	-	-	-
158	0.0202	0.0910	-	-	-
159	0.0197	0.0538	-	-	-
160	0.0218	0.1121	-	-	-
161	0.0256	0.0729	0.0374	-	-
162	0.0389	0.0610	0.0927	-	-
163	0.0173	0.0657	0.0158	-	-
164	0.0197	0.0708	0.0191	-	-
165	0.0176	0.1204	0.0181	-	-
166	0.0180	0.0486	0.0230	-	-
167	0.0110	0.0315	0.0130	-	-
168	0.0198	0.0451	0.0281	-	-
169	0.0065	0.0178	0.0102	-	-
170	0.0210	0.0578	0.0237	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
171	0.0147	0.0411	-	-	-
172	0.0230	0.0458	-	-	-
173	0.0232	0.0899	-	-	-
174	0.0155	0.0844	-	-	-
175	0.0133	0.0376	0.0296	-	-
176	0.0102	0.0364	0.0286	-	-
177	0.0276	0.1129	0.1499	-	-
178	0.0058	0.0157	0.0205	-	-
179	0.0159	0.0629	0.0573	-	-
180	0.0049	0.0147	-	-	-
181	0.0047	0.0279	-	-	-
182	0.01161	0.0735	0.03227	-	-
183	0.01348	0.08768	0.03943	-	-
184	0.01977	0.10057	0.04732	-	-
185	0.01421	0.03518	0.02442	-	-
186	0.11047	0.10652	0.08958	-	-
187	0.19316	0.26079	0.18533	-	-
188	0.27493	1.23016	1.53507	-	-
189	0.10809	1.47313	0.47825	-	-
190	0.12394	0.15596	0.35151	-	-
191	0.0504	0.10664	0.15195	-	-
192	0.21645	0.17268	0.45873	-	-
193	0.0284	0.09512	0.06882	-	-
194	0.01446	0.02273	0.03525	-	-
195	0.01444	0.05169	0.0356	-	-
196	0.14877	0.11139	0.41502	-	-
197	0.00827	0.01065	0.01563	-	-
198	10	8.53693	10	-	-
199	0.01683	0.03653	0.03833	-	-
200	0.01152	0.04163	0.01623	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
201	0.02286	0.13436	0.03183	-	-
202	0.01266	0.06637	0.02686	-	-
203	0.02837	0.03683	0.08436	-	-
204	0.01837	0.06361	0.05164	-	-
205	0.01283	0.07151	0.01537	-	-
206	0.01946	0.2066	0.02894	-	-
207	0.00568	0.01846	0.00913	-	-
208	0.00694	0.04527	0.01276	-	-
209	0.02776	0.05208	0.04385	-	-
210	0.01313	0.03166	0.02286	-	-
211	0.00828	0.01138	0.01002	-	-
212	0.00557	0.01357	0.00828	-	-
213	0.05388	0.09132	0.16503	-	-
214	0.01978	0.05049	0.02743	-	-
215	0.01406	0.0306	0.02297	-	-
216	0.01208	0.0205	0.01779	-	-
217	0.03018	0.03404	0.05952	-	-
218	0.0417	0.03035	0.06702	-	-
219	0.00896	0.03189	0.01499	-	-
220	0.00929	0.01841	0.01294	-	-
221	0.00644	0.01915	0.01545	-	-
222	0.04299	0.02131	0.09002	-	-
223	0.00665	0.01575	0.00865	-	-
224	0.00927	0.01805	0.01018	-	-
225	0.00762	0.01164	0.01389	-	-
226	0.03311	0.04149	0.05758	-	-
227	0.0168	0.01782	0.03576	-	-
228	0.069	0.01848	0.10005	-	-
229	0.01084	0.02912	0.01595	-	-
230	0.01346	0.02307	0.02574	-	-

Table 2a. Biochemical IC ₅₀ (Numerical, μ M)*					
Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
231	0.00649	0.01474	0.00932	-	-
232	0.00911	0.01937	0.02101	-	-
233	0.02075	0.04787	0.04267	-	-
234	0.01611	0.08411	0.04276	-	-
235	0.02571	0.03408	0.04404	-	-
236	0.02903	0.06239	0.05783	-	-
237	0.04219	0.04098	0.08329	-	-
238	0.0296	0.05387	0.08009	-	-
239	0.00655	0.00775	0.01319	-	-
240	0.0061	0.00672	0.01091	-	-
241	0.0224	0.03276	0.04894	-	-
242	0.02834	0.04166	0.08368	-	-
243	0.03244	0.01514	0.07082	-	-
244	0.03978	0.05482	0.11313	-	-
245	0.01854	0.06216	0.01834	-	-
246	0.01258	0.0283	0.02378	-	-
247	0.01107	0.02018	0.01644	-	-
248	0.01319	0.03262	0.02818	-	-
249	0.02419	0.08278	0.08453	-	-
250	0.02396	0.01435	0.04241	-	-
251	0.01305	0.01711	0.02073	-	-
252	0.03086	0.04826	0.05152	-	-
253	0.00715	0.01335	0.01168	-	-
254	0.01728	0.01764	0.044	-	-
255	0.01016	0.02765	0.02448	-	-
256	0.02367	0.03851	0.04405	-	-
257	0.02982	0.15318	0.03096	-	-
258	0.00759	0.01798	0.01083	-	-
259	0.01579	0.0331	0.01706	-	-
260	0.02021	0.08314	0.03733	-	-

Table 2a. Biochemical IC₅₀ (Numerical, μ M)*

Cmpd No.	PRMT1	PRMT6	PRMT8	PRMT3	CARM1
261	0.013	0.03165	0.01668	-	-
262	0.03373	0.0812	0.07236	-	-
263	0.01915	0.0638	0.03513	-	-
264	0.07798	0.1327	0.18082	-	-
265	0.05883	0.17447	0.17058	-	-
266	0.0193	0.07899	0.0631	-	-
267	3.4983	10	5.91407	-	-
268	0.06863	0.14146	0.20985	-	-
269	0.05127	0.10664	0.15456	-	-
270	0.06247	0.14863	0.20383	-	-
271	0.03706	0.1208	0.10019	-	-
272	0.01236	0.07387	0.02578	-	-
273	0.01145	0.04045	0.02257	-	-
274	0.00819	0.10255	0.01193	-	-
275	0.00462	0.01859	0.01038	-	-

* For Table 2a, numerical values represent data from a single experiment or an average of multiple experiments.

RKO methylation assay

[0052] RKO adherent cells were purchased from ATCC (American Type Culture Collection), Manassas, VA, USA. DMEM/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum, 0.05% trypsin 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. Mono-methyl arginine antibody was purchased from Cell Signaling Technology, Danvers, MA, USA. Methanol was purchased from VWR, Franklin, MA, USA. 10% Tween 20 was purchased from KPL, Inc., Gaithersburg, Maryland, USA. DRAQ5 was purchased from Biostatus Limited, Leicestershire, UK.

[0053] RKO adherent cells were maintained in growth medium (DMEM/Glutamax medium supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37 °C under 5% CO₂.

[0054] Cell treatment, In Cell Western (ICW) for detection of mono-methyl arginine and DNA content. RKO cells were seeded in assay medium at a concentration of 20,000 cells per mL to a poly-D-lysine coated 384 well culture plate (BD Biosciences 356697) with 50 μ L per well. Compound (100 nL) from a 96-well source plate was added directly to 384 well cell plate. Plates were incubated at 37°C, 5% CO₂ for 72 hours. After three days of incubation, plates were brought to room temperature outside of the incubator for ten minutes and blotted on paper towels to remove cell media. 50 μ L of ice cold 100% methanol was added directly to each well and incubated for 30 min at room temperature. After 30 min, plates were transferred to a Biotek EL406 plate washer and washed 2 times with 100 μ L per well of wash buffer (1X PBS). Next 60 μ L per well of Odyssey blocking buffer (Odyssey Buffer with 0.1% Tween 20 (v/v)) were added to each plate and incubated 1 hour at room temperature. Blocking buffer was removed and 20 μ L per well of primary antibody was added (mono-methyl arginine diluted 1:200 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 μ L per well of wash buffer. Next 20 μ L 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 μ L per well wash buffer then 2 times with 100 μ L 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.

[0055] Calculations: First, the ratio for each well was determined by:

$$\left(\frac{\text{monomethyl Arginine 800nm value}}{\text{DRAQ5 700nm value}} \right)$$

[0056] Each plate included fourteen control wells of DMSO only treatment (minimum activation) as well as fourteen control wells for maximum activation treated with 20 μ M of a reference compound. The average of the ratio values for each control type was calculated and used to determine the percent activation 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 20 μ M. Percent activation was determined and EC₃₀ curves were generated using triplicate wells per concentration of compound.

$$\text{Percent Activation} = 100 - \left(\left(\frac{(\text{Individual Test Sample Ratio}) - (\text{Minimum Activation Ratio})}{(\text{Maximum Activation Ratio}) - (\text{Minimum Activation Ratio})} \right) * 100 \right)$$

Table 3. In Cell Western

Cmpd No.	EC ₃₀	Cmpd No.	EC ₃₀	Cmpd No.	EC ₃₀
9	B	106	A	193	A
10	C	107	-	194	A
21	C	108	B	195	B
22	A	109	A	196	B
23	A	110	A	197	A
24	A	111	A	198	A
25	B	112	-	199	A
26	C	113	B	200	A
27	C	114	-	201	A
28	B	115	A	202	A
29	C	116	B	203	A
30	C	117	-	204	A
31	C	118	B	205	A
32	A	119	A	206	A
33	B	120	A	207	A
34	A	121	-	208	A
35	A	122	-	209	A
36	A	123	A	210	A
37	A	124	A	211	A
38	A	125	A	212	A
39	A	126	A	213	A
40	A	127	A	214	A
41	C	128	A	215	A
42	C	129	A	216	A
43	A	130	-	217	A
44	B	131	-	218	
45	A	132	-	219	A
46	A	133	A	220	A
47	-	134	A	221	A
48	A	135	A	222	A

Table 3. In Cell Western							
Cmpd No.	EC ₃₀		Cmpd No.	EC ₃₀		Cmpd No.	EC ₃₀
49	-		136	A		223	A
50	A		137	A		224	A
51	A		138	-		225	A
52	-		139	A		226	A
53	A		140	A		227	A
54	A		141	A		228	-
55	A		142	A		229	A
56	-		143	A		230	A
57	A		144	A		231	A
58	-		145	A		232	A
59	-		146	A		233	A
60	A		147	B		234	A
61	A		148	A		235	A
62	A		149	A		236	A
63	A		150	A		237	A
64	-		151	A		238	A
65	A		152	A		239	A
66	-		153	A		240	A
67	A		154	A		241	A
68	-		155	B		242	-
69	-		156	A		243	-
70	A		157	A		244	A
71	-		158	A		245	-
72	-		159	A		246	A
73	-		160	A		247	A
74	-		161	B		248	A
75	-		162	B		249	A
76	-		163	A		250	-
77	-		164	A		251	A
78	-		165	A		252	A

Table 3. In Cell Western					
Cmpd No.	EC ₃₀		Cmpd No.	EC ₃₀	
79	-		166	A	
80	-		167	A	
81	-		168	A	
82	-		169	A	
83	-		170	-	
84	-		171	A	
85	-		172	B	
86	A		173	A	
87	A		174	A	
88	-		175	C	
89	-		176	A	
90	A		177	A	
91	A		178	A	
92	A		179	A	
93	-		180	A	
94	-		181	A	
95	A		182	A	
96	-		183	A	
97	-		184	A	
98	-		185	A	
99	-		186	-	
100	-		187	B	
101	-		188	-	
102	-		189	B	
103	-		190	B	
104	A		191	B	
105	-		192	B	
		</			

“-” indicates no data provided.

For Table 3, “A” indicates an EC₃₀ ≤ 3.00 μM, “B” indicates an EC₃₀ of 3.01 – 12.00 μM, and “C” indicates an EC₃₀ > 12.01 μM.

Table 3a. In Cell Western (Numerical, μ M)*

Cmpd No.	EC ₃₀	Cmpd No.	EC ₃₀	Cmpd No.	EC ₃₀
9	5.61	106	0.0227	193	1.43822
10	>20	107	-	194	1.1848
21	>20	108	8.5466	195	4.88623
22	1.24	109	2.4785	196	4.8862
23	1.61	110	2.5472	197	0.40624
24	2.40	111	0.9130	198	0.4062
25	11.83	112	-	199	0.80245
26	>20	113	7.3455	200	0.02034
27	>20	114	-	201	0.15455
28	11.10	115	0.0189	202	0.32701
29	>20	116	8.8958	203	0.3270
30	>20	117	-	204	1.55419
31	>20	118	9.5749	205	0.01445
32	2.35	119	0.0773	206	0.07648
33	3.33	120	0.0098	207	0.01212
34	1.15	121	-	208	0.06719
35	0.73	122	0.3455	209	0.91597
36	0.63	123	0.0440	210	0.27952
37	0.26	124	0.0214	211	0.15488
38	0.13	125	0.0876	212	0.43283
39	0.50	126	0.6376	213	0.4328
40	0.87	127	0.0292	214	0.09582
41	>20	128	1.0750	215	0.16359
42	>20	129	0.0045	216	0.11104
43	2.60	130	-	217	0.1110
44	4.57	131	-	218	-
45	0.0540	132	0.0038	219	0.29433
46	0.0080	133	0.0438	220	0.2188
47	0.0520	134	0.0332	221	0.4903

Table 3a. In Cell Western (Numerical, μ M)*							
Cmpd No.	EC ₃₀		Cmpd No.	EC ₃₀		Cmpd No.	EC ₃₀
48	0.0140		135	1.0140		222	2.60878
49	0.0500		136	0.0350		223	0.27538
50	0.0270		137	0.0150		224	0.08472
51	0.0520		138	-		225	0.64935
52	0.0410		139	0.6270		226	1.53074
53	0.0170		140	0.1640		227	1.5307
54	0.0870		141	0.1320		228	-
55	0.0630		142	0.0520		229	0.68908
56	0.0960		143	0.0590		230	1.31527
57	0.0250		144	0.0630		231	0.09668
58	0.9780		145	2.3000		232	0.95704
59	0.3570		146	0.1600		233	1.05613
60	2.8410		147	8.6000		234	1.0561
61	0.1490		148	0.0160		235	0.81272
62	0.16924		149	0.1060		236	0.8127
63	1.0852		150	0.2560		237	1.43678
64	-		151	0.7050		238	2.15067
65	0.07752		152	0.1190		239	2.1507
66	-		153	0.1290		240	1.17758
67	0.0810		154	1.7890		241	1.1776
68	-		155	4.0850		242	-
69	-		156	1.3570		243	-
70	0.0500		157	2.4890		244	2.52536
71	-		158	0.0080		245	-
72	-		159	0.0630		246	0.0799
73	-		160	0.1660		247	0.6979
74	-		161	5.0200		248	1.3093
75	-		162	6.6800		249	0.6585
76	-		163	0.0660		250	-
77	-		164	0.0780		251	1.4511

Table 3a. In Cell Western (Numerical, μ M)*					
Cmpd No.	EC ₃₀		Cmpd No.	EC ₃₀	
78	-		165	0.5100	
79	-		166	0.0830	
80	-		167	0.0180	
81	-		168	0.0850	
82	-		169	0.0160	
83	-		170	-	
84	-		171	0.1920	
85	-		172	4.4570	
86	0.0168		173	0.4080	
87	2.5254		174	0.0850	
88	-		175	>20	
89	-		176	2.1420	
90	0.3158		177	0.5710	
91	2.05655		178	0.0760	
92	2.17333		179	0.4760	
93	-		180	0.0190	
94	-		181	0.1070	
95	0.12166		182	0.41111	
96	-		183	0.31865	
97	-		184	0.45829	
98	-		185	0.45302	
99	-		186	-	
100	-		187	3.1603	
101	-		188	-	
102	-		189	6.62284	
103	-		190	6.6228	
104	0.01166		191	9.24747	
105	-		192	9.2475	
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* For Table 3a, numerical values represent data from a single experiment or an average of multiple experiments.

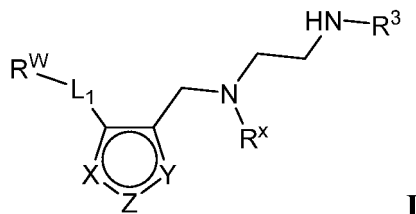
Other Embodiments

[0057] 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.

Claims

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

X is N, Z is NR⁴, and Y is CR⁵; or

X is NR⁴, Z is N, and Y is CR⁵; or

X is CR⁵, Z is NR⁴, and Y is N; or

X is CR⁵, Z is N, and Y is NR⁴;

R^x is optionally substituted C₁₋₄ alkyl or optionally substituted C₃₋₄ cycloalkyl;

L₁ is a bond, -O-, -N(R^B)-, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O)N(R^B)-, -C(O)N(R^B)N(R^B)-, -OC(O)-, -OC(O)N(R^B)-, -NR^BC(O)-, -NR^BC(O)N(R^B)-, -NR^BC(O)N(R^B)N(R^B)-, -NR^BC(O)O-, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B)N(R^B)-, -NR^BC(=NR^B)-, -C(S)-, -C(S)N(R^B)-, -NR^BC(S)-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, -N(R^B)SO₂-, -SO₂N(R^B)-, or an optionally substituted C₁₋₆ saturated or unsaturated hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain is optionally and independently replaced with -O-, -N(R^B)-, -S-, -C(O)-, -C(O)O-, -C(O)S-, -C(O)N(R^B)-, -C(O)N(R^B)N(R^B)-, -OC(O)-, -OC(O)N(R^B)-, -NR^BC(O)-, -NR^BC(O)N(R^B)-, -NR^BC(O)N(R^B)N(R^B)-, -NR^BC(O)O-, -SC(O)-, -C(=NR^B)-, -C(=NNR^B)-, -C(=NOR^A)-, -C(=NR^B)N(R^B)-, -NR^BC(=NR^B)-, -C(S)-, -C(S)N(R^B)-, -NR^BC(S)-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -SO₂-, -N(R^B)SO₂-, or -SO₂N(R^B)-;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally

substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or an R^B and R^W on the same nitrogen atom may be taken together with the intervening nitrogen to form an optionally substituted heterocyclic ring;

R^W is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; provided that when L_1 is a bond, R^W is not hydrogen, optionally substituted aryl, or optionally substituted heteroaryl;

R^3 is hydrogen, C_{1-4} alkyl, or C_{3-4} cycloalkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl; or optionally substituted C_{1-4} alkyl-Cy;

Cy is optionally substituted C_{3-7} cycloalkyl, optionally substituted 4- to 7-membered heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

R^5 is hydrogen, halo, -CN, optionally substituted C_{1-4} alkyl, or optionally substituted C_{3-4} cycloalkyl;

wherein, and unless otherwise specified,

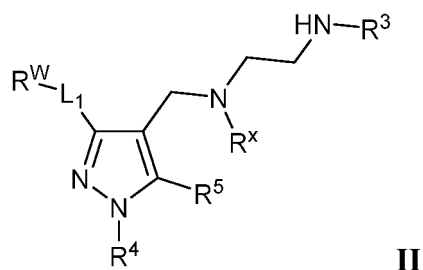
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

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

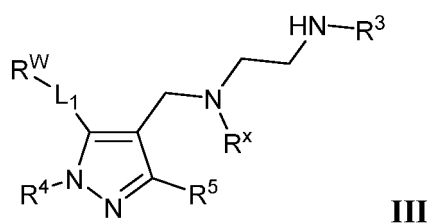
heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic $4n+2$ aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

2. The compound of claim 1, wherein the compound is of Formula (II):



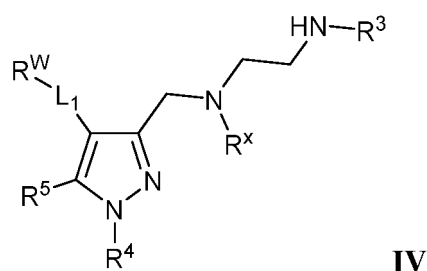
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is of Formula (III):



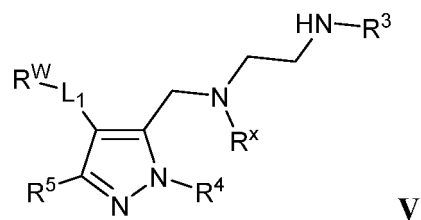
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is of Formula (IV):



or a pharmaceutically acceptable salt thereof.

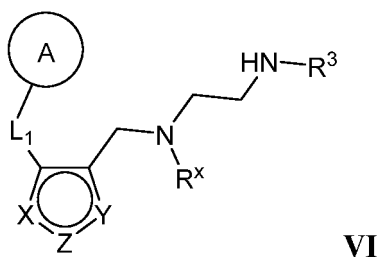
5. The compound of claim 1, wherein the compound is of Formula (V):



or a pharmaceutically acceptable salt thereof.

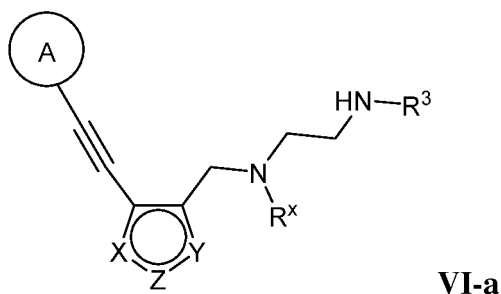
6. The compound of any one of claims 1-5, wherein $-L_1-R^W$ is optionally substituted carbocyclyl.

7. The compound of claim 6, wherein $-L_1-R^W$ is optionally substituted cyclohexyl.
8. The compound of any one of claims 1-5, wherein $-L_1-R^W$ is optionally substituted heterocyclyl.
9. The compound of claim 8, wherein $-L_1-R^W$ is optionally substituted piperidine.
10. The compound of any one of claims 1-5, wherein $-L_1-R^W$ is optionally substituted alkyl.
11. The compound of claim 10, wherein L_1 is C_{1-4} alkylene and R^W is optionally substituted aryl or optionally substituted heteroaryl.
12. The compound of claim 1, wherein the compound is of Formula (VI):



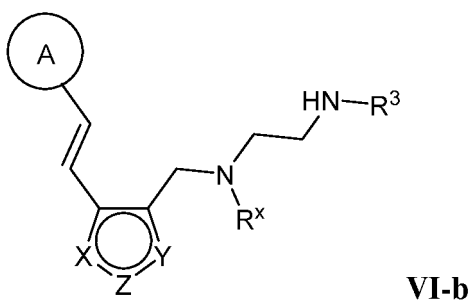
or a pharmaceutically acceptable salt thereof, wherein Ring A is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

13. The compound of claim 12, wherein the compound is of Formula (VI-a):



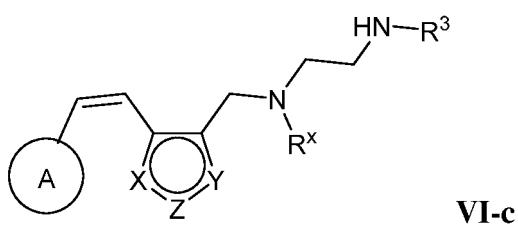
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 12, wherein the compound is of Formula (VI-b):



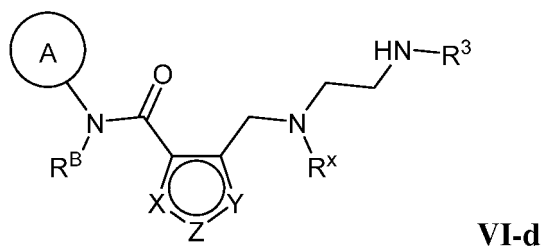
or a pharmaceutically acceptable salt thereof.

15. The compound of claim 12, wherein the compound is of Formula (VI-c):



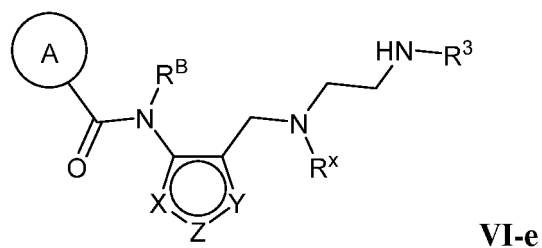
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 12, wherein the compound is of Formula (VI-d):



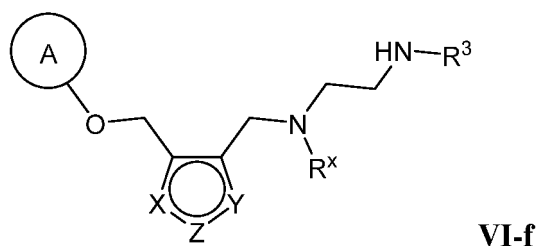
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 12, wherein the compound is of Formula (VI-e):



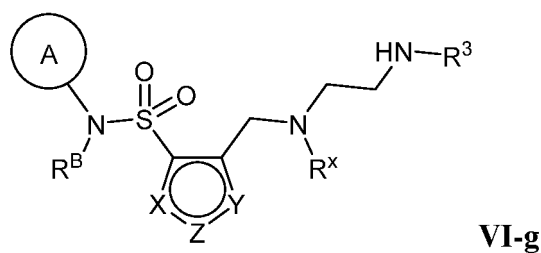
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 12, wherein the compound is of Formula (VI-f):



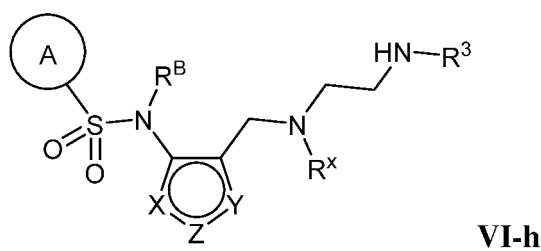
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 12, wherein the compound is of Formula (VI-g):



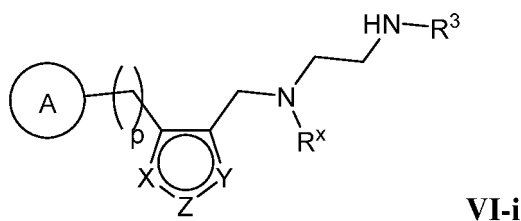
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 12, wherein the compound is of Formula (VI-h):



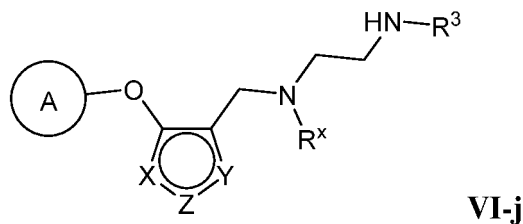
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 12, wherein the compound is of Formula (VI-i):



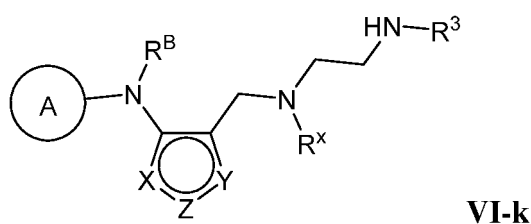
or a pharmaceutically acceptable salt thereof, wherein p is 1, 2, 3, 4, 5, or 6.

22. The compound of claim 12, wherein the compound is of Formula (VI-j):



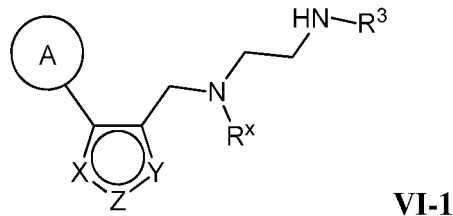
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 12, wherein the compound is of Formula (VI-k):



or a pharmaceutically acceptable salt thereof.

24. The compound of claim 12, wherein the compound is of Formula (VI-l):



or a pharmaceutically acceptable salt thereof.

25. The compound of any one of claims 12-24, wherein Ring A is optionally substituted phenyl.

26. The compound of any one of claims 12-24, wherein Ring A is optionally substituted heteroaryl.

27. The compound of any one of claims 12-24, wherein Ring A is optionally substituted carbocyclyl.

28. The compound of any one of claims 12-24, wherein Ring A is optionally substituted heterocyclyl.
29. The compound of any one of claims 12-24, wherein Ring A is optionally substituted bicyclic carbocyclyl.
30. The compound of any one of claims 12-24, wherein Ring A is optionally substituted bicyclic heterocyclyl.
31. The compound of any one of claims 1-30, wherein R^3 is hydrogen.
32. The compound of any one of claims 1-30, wherein R^3 is C_{1-4} alkyl.
33. The compound of claim 32, wherein R^3 is methyl.
34. The compound of any one of claims 1-30, wherein R^3 is cyclopropyl or cyclobutyl.
35. The compound of any one of claims 1-34, wherein R^4 is hydrogen.
36. The compound of any one of claims 1-34, wherein R^4 is optionally substituted C_{1-6} alkyl.
37. The compound of claim 36, wherein R^4 is unsubstituted C_{1-6} alkyl.
38. The compound of claim 37, wherein R^4 is methyl.
39. The compound of any one of claims 1-38, wherein R^5 is hydrogen.
40. The compound of any one of claims 1-38, wherein R^5 is optionally substituted C_{1-4} alkyl.
41. The compound of claim 40, wherein R^5 is unsubstituted C_{1-4} alkyl.
42. The compound of claim 41, wherein R^5 is methyl.

43. The compound of any one of claims 1-42, wherein R^x is optionally substituted C₁₋₄ alkyl.
44. The compound of claim 37, wherein R^x is unsubstituted C₁₋₄ alkyl.
45. The compound of claim 44, wherein R^x is methyl.
46. The compound of claim 44, wherein R^x is ethyl.
47. The compound of claim 44, wherein R^x is isopropyl.
48. The compound of claim 43, wherein R^x is substituted C₁₋₄ alkyl.
49. The compound of claim 48, wherein R^x is hydroxyethyl or methoxyethyl.
50. The compound of any one of claims 1-42, wherein R^x is optionally substituted C₃₋₄ cycloalkyl.
51. The compound of claim 50, wherein R^x is cyclopropyl.
52. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds depicted in Table 1A, and pharmaceutically acceptable salts thereof.
53. A pharmaceutical composition comprising a compound of any one of claims 1-52 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
54. A kit or packaged pharmaceutical comprising a compound of any one of claims 1-52 or a pharmaceutically acceptable salt thereof, and instructions for use thereof.
55. A method of inhibiting an arginine methyl transferase (RMT) comprising contacting a cell with an effective amount of a compound of any one of claims 1-52 or a pharmaceutically acceptable salt thereof.

56. The method of claim 55, wherein the arginine methyl transferase is PRMT1.
57. The method of claims 55, wherein the arginine methyl transferase is PRMT6.
58. The method of claims 55, wherein the arginine methyl transferase is PRMT3.
59. The method of claims 55, wherein the arginine methyl transferase is PRMT8.
60. The method of claims 55, wherein the arginine methyl transferase is CARM1.
61. A method of modulating gene expression comprising contacting a cell with an effective amount of a compound of any one of claims 1-52 or a pharmaceutically acceptable salt thereof.
62. A method of modulating transcription comprising contacting a cell with an effective amount of a compound of any one of claims 1-52 or a pharmaceutically acceptable salt thereof.
63. The method of any one of claims 55-62, wherein the cell is in vitro.
64. The method of any one of claims 55-62, wherein the cell is in a subject.
65. A method of treating a RMT-mediated disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 53.
66. The method of claims 65, wherein the RMT-mediated disorder is a PRMT1-mediated disorder.
67. The method of claim 65, wherein the RMT-mediated disorder is a PRMT6-mediated disorder.

68. The method of claims 65, wherein the RMT-mediated disorder is a PRMT3-mediated disorder.
69. The method of claim 65, wherein the RMT-mediated disorder is a PRMT8-mediated disorder.
70. The method of claims 65, wherein the RMT-mediated disorder is a CARM1-mediated disorder.
71. The method of claim 65, wherein the disorder is a proliferative disorder.
72. The method of claim 71, wherein the disorder is cancer.
73. The method of claim 65, wherein the disorder is a neurological disorder.
74. The method of claim 73, wherein the disorder is amyotrophic lateral sclerosis.
75. The method of claim 65, wherein the disorder is a muscular dystrophy.
76. The method of claim 65, wherein the disorder is an autoimmune disorder.
77. The method of claim 65, wherein the disorder is a vascular disorder.
78. The method of claim 65, wherein the disorder is a metabolic disorder.