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(71) Applicant: **SKYHAWK THERAPEUTICS, INC.** [US/US]; 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US).

(72) Inventors: **LUZZIO, Michael**; 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **WANG, Tiansheng**; 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US).

(74) Agent: **KUZNETSOV, Alexey, G.**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304 (US).

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(54) Title: PROCESS FOR THE PREPARATION OF INTERMEDIATES USEFUL IN THE PREPARATION OF COMPOUNDS THAT MODULATE SPLICING

(57) Abstract: Described herein are processes for preparing compounds useful in the preparation of small molecule splicing modulator compounds that modulate splicing of mRNA, such as pre-mRNA, encoded by genes, and compounds used in such processes.

PROCESS FOR THE PREPARATION OF INTERMEDIATES USEFUL IN THE PREPARATION OF COMPOUNDS THAT MODULATE SPLICING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/061,760 filed on August 5, 2020, and U.S. Provisional Application No. 63/161,231 filed on March 15, 2021, the disclosures of which is hereby incorporated by reference in their entirety.

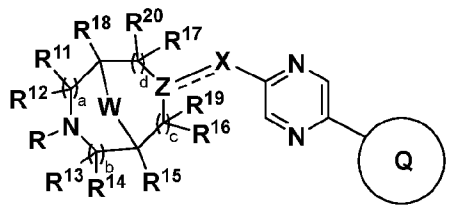
BACKGROUND

[0002] Compounds that modulate splicing of pre-mRNA, sometimes referred to as small molecule splicing modulators (SMSMs), are useful in treating many diseases which are caused by aberrant pre-mRNA splicing. These SMSMs are also useful in treating diseases in which modulation of pre-mRNA splicing affects the level of a protein, which in turn can be used to treat the diseases by either increasing, or decreasing the level of the particular protein. SMSMs useful in these types of methods are disclosed by, for example, in PCT publications WO 2019/028440 and WO 2020/163541.

[0003] There, exists, therefore, a need to develop new processes and intermediates for the synthesis of these SMSMs.

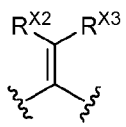
SUMMARY

[0004] In one aspect, described herein is a process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

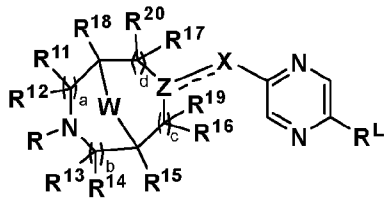


Formula (I)

wherein,

Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}-$, $-CR^{X2}R^{X3}-$,  , or $=CR^{X1}-$; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted

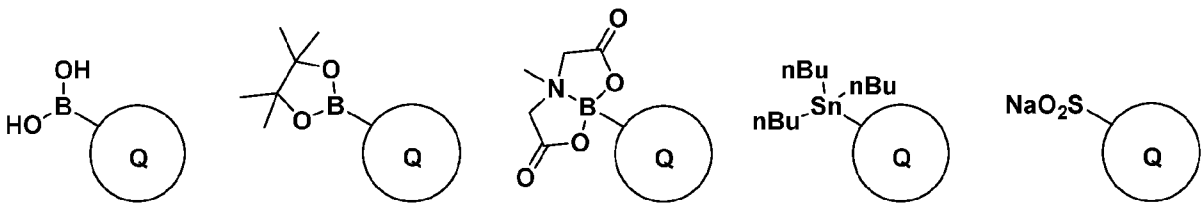
C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, -O(C=O)R^{L1}, -SR^{L1}, -S(=O)R^{L1}, -S(=O)$_2R^{L1}$, or -S(=O)(=NR^{L1})R^{L1}; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)

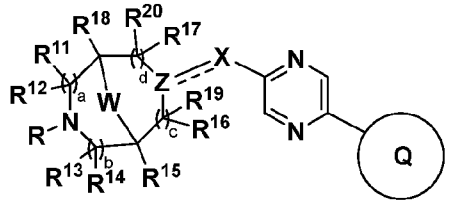


Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

to produce a compound of Formula (I);

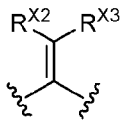
wherein each variable within Formula (III), Formula (IV), Formula (IVa), Formula (V), and Formula (VI) is as described above for Formula (I).

[0005] In one aspect, described herein is a process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

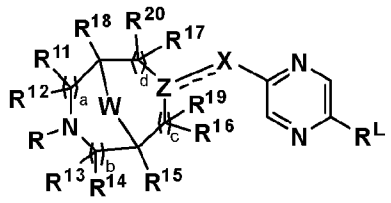


Formula (I)

wherein,

Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}-$, $-CR^{X2}R^{X3}-$,  , or $=CR^{X1}-$; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a

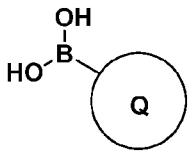
substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a compound of Formula (III)

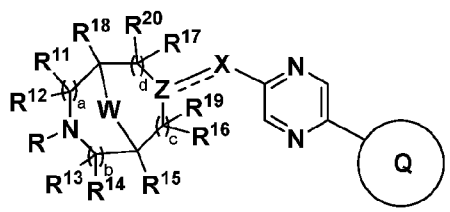


Formula (III)

wherein each variable within Formula (III) is as described above for Formula (I).

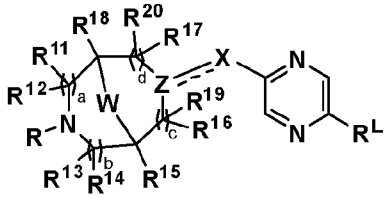
In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (III) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0006] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

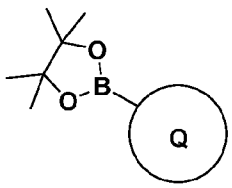
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

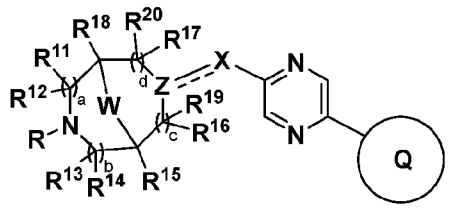
with a compound of Formula (IV)



Formula (IV)

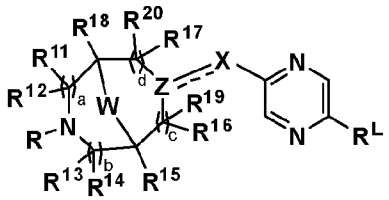
wherein each variable within Formula (I) and Formula (IV) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (IV) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0007] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

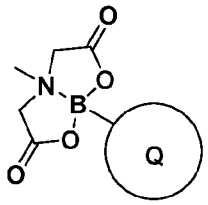
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

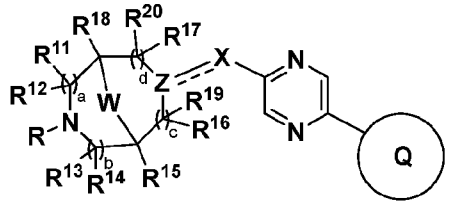
with a compound of Formula (IVa)



Formula (IVa)

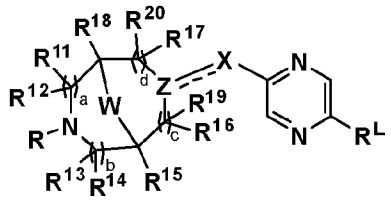
wherein each variable within Formula (I) and Formula (IVa) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (IVa) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0008] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

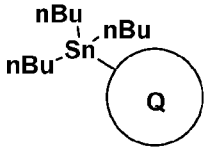
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

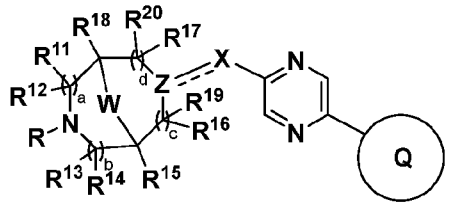
with a compound of Formula (V)



Formula (V)

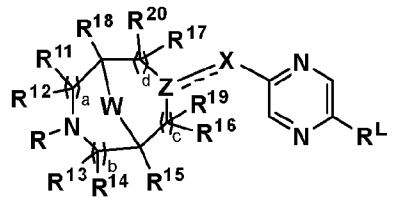
wherein each variable within Formula (I), and Formula (V) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (V) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0009] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

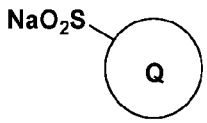
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a compound of Formula (VI)

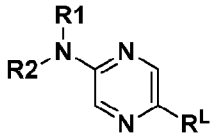


Formula (VI)

wherein each variable within Formula (I) and Formula (VI) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (VI) in the presence of a palladium catalyst,

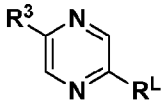
tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0010] In another aspect described herein, is a process for preparing a compound of Formula (VII)



Formula (VII)

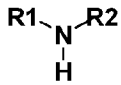
comprising reacting a compound of Formula (VIII)



Formula (VIII)

wherein R^3 is a halogen, such as Cl, Br, or I; or O-CH_2CF_3; R^L is halogen, -O(C=O)R^{L1}, -SR^{L1}, -S(=O)R^{L1}, or -S(=O)$_2R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

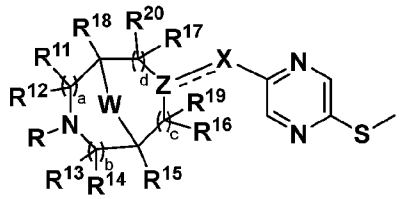
with a compound of Formula (IX)



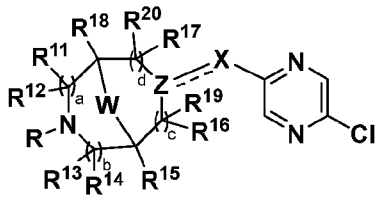
Formula (IX)

to produce a compound of Formula (VII), wherein each R1 and R2 is independently hydrogen, halogen, -OH, –OR^{31}, –CN,–SR^{31}, -S(=O)R^{31}, -SO_2R^{31}, -N$R^{31}R^{32}$, -NR^{31}S(=O)(=NR^{31})R^{32}, -NR^{31}S(=O)$_2R^{31}R^{32}$, -SO_2N$R^{31}R^{32}$, -C(=O)R^{31}, -OC(=O)R^{31}, -C(=O)OR^{31}, -OC(=O)OR^{31}, -C(=O)N$R^{31}R^{32}$, -OC(=O)N$R^{31}R^{32}$, -NR^{31}C(=O)R^{32}, -P(=O)$R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0011] In some embodiments, a compound of Formula (II) has a structure of Formula (IIa) or Formula (IIb):

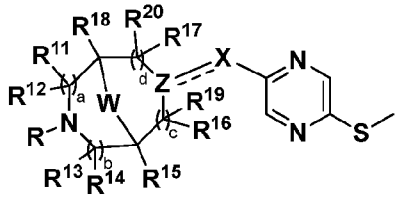


Formula (IIa)



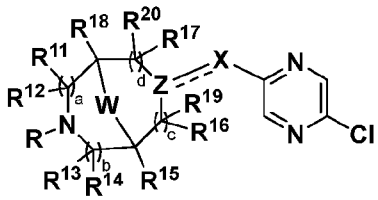
Formula (IIb).

[0012] In some embodiments, a compound of Formula (II) has a structure of Formula (IIa):



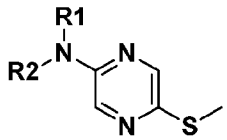
Formula (IIa).

[0013] In some embodiments, a compound of Formula (II) has a structure of Formula (IIb):



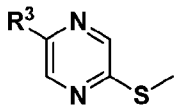
Formula (IIb).

[0014] In some embodiments, a compound of Formula (VII) has a structure of Formula (VIIa):



Formula (VIIa);

and a compound of Formula (VIII) has a structure of Formula (VIIIa):



Formula (VIIIa).

[0015] Also provided herein are uses of a compound disclosed herein, in the manufacture of a SMSM for the treatment of a condition or disease.

INCORPORATION BY REFERENCE

[0016] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

[0017] Certain specific details of this description are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the present disclosure may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments.

[0018] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below.

Definitions

[0019] The terms "small molecule splicing modulator" or "SMSM" denote a small molecule compound that binds to a cell component (*e.g.*, DNA, RNA, pre-mRNA, protein, RNP, snRNA, carbohydrates, lipids, co-factors, nutrients and/or metabolites) and modulates splicing of a target polynucleotide, e.g., a pre-mRNA. For example, an SMSM can bind directly or indirectly to a target polynucleotide, *e.g.*, RNA (*e.g.*, a pre-mRNA) with a mutated, non-mutated, bulged and/or aberrant splice site, resulting in modulation of splicing of the target polynucleotide. For example, an SMSM can bind directly or indirectly to a protein, *e.g.*, a spliceosome protein or a ribonuclear protein, resulting in steric modulation of the protein and modulation of splicing of a target RNA. For example, an SMSM can bind directly or indirectly to a spliceosome component, *e.g.*, a spliceosome protein or snRNA resulting in steric modulation of the spliceosome protein or snRNA and modulation of splicing of target polynucleotide. These terms specifically exclude compounds consisting of oligonucleotides. These terms include small molecule compounds that may bind to one or more secondary or tertiary structure elements of a target RNA. These sites include RNA triplexes, 3WJs, 4WJs, parallel-Y junctions, hairpins, bulge loops, pseudoknots, internal loops, and other higher-order RNA structural motifs.

[0020] "Steric alteration", "steric modification" or "steric modulation" herein refers to changes in the spatial orientation of chemical moieties with respect to each other. A person of ordinary skill in the art would recognize steric mechanisms include, but are not limited to, steric hindrance, steric

shielding, steric attraction, chain crossing, steric repulsions, steric inhibition of resonance, and steric inhibition of protonation.

[0021] Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of hydrogen, unless indicated otherwise.

[0022] The definitions described herein apply irrespective of whether the terms in question appear alone or in combination. It is contemplated that the definitions described herein can be appended to form chemically-relevant combinations, such as *e.g.* "heterocycloalkylaryl", "haloalkylheteroaryl", "arylalkylheterocycloalkyl", or "alkoxyalkyl". The last member of the combination is the radical which is binding to the rest of the molecule. The other members of the combination are attached to the binding radical in reversed order in respect of the literal sequence, *e.g.* the combination arylalkylheterocycloalkyl refers to a heterocycloalkyl-radical which is substituted by an alkyl which is substituted by an aryl.

[0023] When indicating the number of substituents, the term "one or more" refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0024] The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

[0025] The term "substituted" denotes that a specified group bears one or more substituents. Where any group can carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents.

[0026] The following abbreviations are used throughout the specification: acetic acid (AcOH); ethyl acetate (EtOAc); butyl alcohol (n-BuOH); 1,2-dichloroethane (DCE); dichloromethane (CH_2Cl_2, DCM); diisopropylethylamine (Diipea); dimethylformamide (DMF); hydrogen chloride (HCl); methanol (MeOH); methoxymethyl bromide (MOMBr); N-methyl-2-pyrrolidone (NMP); methyl Iodide (MeI); n-propanol (n-PrOH); p-methoxybenzyl (PMB); triethylamine (Et_3N); [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II); ($Pd(dppf)Cl_2$); sodium ethane thiolate (EtSNa); sodium acetate (NaOAc); sodium hydride (NaH); sodium hydroxide (NaOH); tetrahydropyran (THP); tetrahydrofuran (THF).

[0027] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3... C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of

example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[0028] The term "oxo" refers to the =O substituent.

[0029] The term "thioxo" refers to the =S substituent.

[0030] The term "halo", "halogen", and "halide" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

[0031] The term "alkyl" refers to a straight or branched hydrocarbon chain radical, having from one to twenty carbon atoms, and which is attached to the rest of the molecule by a single bond. An alkyl comprising up to 10 carbon atoms is referred to as a C_1-C_{10} alkyl, likewise, for example, an alkyl comprising up to 6 carbon atoms is a C_1-C_6 alkyl. Alkyls (and other moieties defined herein) comprising other numbers of carbon atoms are represented similarly. Alkyl groups include, but are not limited to, C_1-C_{10} alkyl, C_1-C_9 alkyl, C_1-C_8 alkyl, C_1-C_7 alkyl, C_1-C_6 alkyl, C_1-C_5 alkyl, C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl, C_2-C_8 alkyl, C_3-C_8 alkyl and C_4-C_8 alkyl. Representative alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*i*-propyl), *n*-butyl, *i*-butyl, *s*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, 1-ethyl-propyl, and the like. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, the alkyl is -$CH(CH_3)_2$ or -$C(CH_3)_3$. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below. "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group. In some embodiments, the alkylene is -CH_2-, -CH_2CH_2-, or -$CH_2CH_2CH_2$-. In some embodiments, the alkylene is -CH_2-. In some embodiments, the alkylene is -CH_2CH_2-. In some embodiments, the alkylene is -$CH_2CH_2CH_2$-.

[0032] The term "alkoxy" refers to a radical of the formula -OR^a where R^a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below. Representative alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy. In some embodiments, the alkoxy is methoxy. In some embodiments, the alkoxy is ethoxy.

[0033] The term "alkylamino" refers to a radical of the formula -NHR^a or -NR^aR^a where each R^a is, independently, an alkyl radical as defined above. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted as described below.

[0034] The term "alkenyl" refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula -$C(R^a)$=CR^a_2, wherein R^a refers to the remaining portions of the alkenyl group, which may be the same or different. In some

embodiments, R^a is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $-C(CH_3)=CHCH_3$, and $-CH_2CH=CH_2$.

[0035] The term "alkynyl" refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula $-C\equiv C-R^a$, wherein R^a refers to the remaining portions of the alkynyl group. In some embodiments, R^a is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non-limiting examples of an alkynyl group include $-C\equiv CH$, $-C\equiv CCH_3$ $-C\equiv CCH_2CH_3$, $-CH_2C\equiv CH$.

[0036] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing $4n+2$ π electrons, where n is an integer. Aromatics can be optionally substituted. The term "aromatic" includes both aryl groups (*e.g.*, phenyl, naphthalenyl) and heteroaryl groups (*e.g.*, pyridinyl, quinolinyl).

[0037] The term "aryl" refers to a radical comprising at least one aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthyl. In some embodiments, the aryl is phenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-"(such as in "aralkyl") is meant to include aryl radicals that are optionally substituted. In some embodiments, an aryl group comprises a partially reduced cycloalkyl group defined herein (e.g., 1,2-dihydronaphthalene). In some embodiments, an aryl group comprises a fully reduced cycloalkyl group defined herein (e.g., 1,2,3,4-tetrahydronaphthalene). When aryl comprises a cycloalkyl group, the aryl is bonded to the rest of the molecule through an aromatic ring carbon atom. An aryl radical can be a monocyclic or polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) ring system, which may include fused, spiro or bridged ring systems.

[0038] The term "haloalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro-or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. The term "perhaloalkyl" denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms.

[0039] The term "haloalkoxy" denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkoxyl include monofluoro-, difluoro-or trifluoro-methoxy, -ethoxy or -propoxy, for example 3,3,3-trifluoropropoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, fluoromethoxy, or trifluoromethoxy. The term "perhaloalkoxy" denotes an alkoxy group where all hydrogen atoms of the alkoxy group have been replaced by the same or different halogen atoms.

[0040] The term "bicyclic ring system" denotes two rings which are fused to each other via a common single or double bond (annelated bicyclic ring system), via a sequence of three or more common atoms (bridged bicyclic ring system) or via a common single atom (spiro bicyclic ring system). Bicyclic ring systems can be saturated, partially unsaturated, unsaturated or aromatic. Bicyclic ring systems can comprise heteroatoms selected from N, O and S.

[0041] The terms "carbocyclic" or "carbocycle" refer to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycle includes cycloalkyl and aryl.

[0042] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are saturated or partially unsaturated. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, or from three to five carbon atoms. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, the monocyclic cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl or cyclohexenyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl. Polycyclic radicals include, for example, adamantyl, 1,2-dihydronaphthalenyl, 1,4-dihydronaphthalenyl, tetrainyl, decalinyl, 3,4-dihydronaphthalenyl-1(2H)-one, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

[0043] The term "bridged" refers to any ring structure with two or more rings that contains a bridge connecting two bridgehead atoms. The bridgehead atoms are defined as atoms that are the part of the

skeletal framework of the molecule and which are bonded to three or more other skeletal atoms. In some embodiments, the bridgehead atoms are C, N, or P. In some embodiments, the bridge is a single atom or a chain of atoms that connects two bridgehead atoms. In some embodiments, the bridge is a valence bond that connects two bridgehead atoms. In some embodiments, the bridged ring system is cycloalkyl. In some embodiments, the bridged ring system is heterocycloalkyl.

[0044] The term "fused" refers to any ring structure described herein which is fused to an existing ring structure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with one or more N, S, and O atoms. The non-limiting examples of fused heterocyclyl or heteroaryl ring structures include 6-5 fused heterocycle, 6-6 fused heterocycle, 5-6 fused heterocycle, 5-5 fused heterocycle, 7-5 fused heterocycle, and 5-7 fused heterocycle.

[0045] The term "haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

[0046] The term "haloalkoxy" refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, fluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1,2-difluoroethoxy, 3-bromo-2-fluoropropoxy, 1,2-dibromoethoxy, and the like. Unless stated otherwise specifically in the specification, a haloalkoxy group may be optionally substituted.

[0047] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C_1-C_6 fluoroalkyl. In some embodiments, a fluoroalkyl is selected from trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[0048] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* -NH-, -N(alkyl)-, or -N(aryl)-), sulfur (*e.g.* -S-, -S(=O)-, or -$S(=O)_2$-), or combinations thereof. In some embodiments, a heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In some embodiments, a heteroalkyl is attached to the rest of the molecule at a heteroatom of the heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_6 heteroalkyl. Representative heteroalkyl groups include, but are not limited to -OCH_2OMe, -OCH_2CH_2OH, -OCH_2CH_2OMe, or -$OCH_2CH_2OCH_2CH_2NH_2$.

[0049] The term "heteroalkylene" refers to an alkyl radical as described above where one or more carbon atoms of the alkyl is replaced with a O, N or S atom. "Heteroalkylene" or "heteroalkylene chain" refers to a straight or branched divalent heteroalkyl chain linking the rest of the molecule to a radical group. Unless stated otherwise specifically in the specification, the heteroalkyl or heteroalkylene group may be optionally substituted as described below. Representative heteroalkylene groups include, but are not limited to $-OCH_2CH_2O-$, $-OCH_2CH_2OCH_2CH_2O-$, or $-OCH_2CH_2OCH_2CH_2OCH_2CH_2O-$.

[0050] The term "heterocycloalkyl" refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, or bicyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. The nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized. The nitrogen atom may be optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides and oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 12 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 1 or 2 N atoms. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 3 or 4 N atoms. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 0-2 N atoms, 0-2 O atoms, 0-2 P atoms, and 0-1 S atoms in the ring. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 1-3 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted.

[0051] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) that includes at least one heteroatom selected from nitrogen, oxygen and sulfur, wherein each heterocyclic group has from 3 to 12 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. In some embodiments, heterocycles are monocyclic, bicyclic, polycyclic, spirocyclic or bridged compounds. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 12 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 12 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, $_3$ h-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

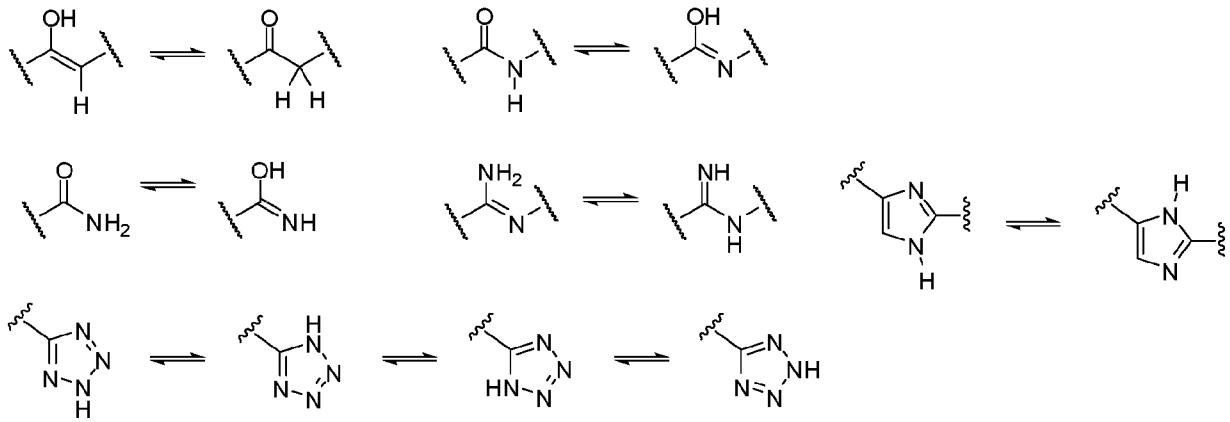
[0052] The term "heteroaryl" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. In some embodiments, heteroaryl is monocyclic or bicyclic. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl,

pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, furazanyl, indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Illustrative examples of bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0-6 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 4-6 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, 0-1 P atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C_1-C_9 heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5 heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, a bicyclic heteroaryl is a C_6-C_9 heteroaryl. In some embodiments, a heteroaryl group comprises a partially reduced cycloalkyl or heterocycloalkyl group defined herein (e.g., 7,8-dihydroquinoline). In some embodiments, a heteroaryl group comprises a fully reduced cycloalkyl or heterocycloalkyl group defined herein (e.g., 5,6,7,8-tetrahydroquinoline). When heteroaryl comprises a cycloalkyl or heterocycloalkyl group, the heteroaryl is bonded to the rest of the molecule through a heteroaromatic ring carbon or hetero atom. A heteroaryl radical can be a monocyclic or polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) ring system, which may include fused, spiro or bridged ring systems. The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0053] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from D, halogen, -CN, -NH_2, -NH(alkyl), -N(alkyl)$_2$, -OH, -CO_2H, -CO_2alkyl, -C(=O)NH_2, -C(=O)NH(alkyl), -C(=O)N(alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$NH(alkyl), -S(=O)$_2$N(alkyl)$_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH_2, -NH(CH_3), -N(CH_3)$_2$, -OH, -CO_2H, -CO_2(C_1-C_4 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4 alkyl), -

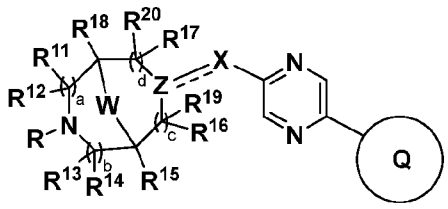
$C(=O)N(C_1\text{-}C_4$ alkyl)$_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1\text{-}C_4$ alkyl), $-S(=O)_2N(C_1\text{-}C_4$ alkyl)$_2$, $C_1\text{-}C_4$ alkyl, $C_3\text{-}C_6$ cycloalkyl, $C_1\text{-}C_4$ fluoroalkyl, $C_1\text{-}C_4$ heteroalkyl, $C_1\text{-}C_4$ alkoxy, $C_1\text{-}C_4$ fluoroalkoxy, $-SC_1\text{-}C_4$ alkyl, $-S(=O)C_1\text{-}C_4$ alkyl, and $-S(=O)_2(C_1\text{-}C_4$ alkyl). In some embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, - NH(cyclopropyl), $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent includes oxo (=O). In some embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, -OH, =O, $-NH(CH_3)$, $-N(CH_3)_2$, - NH(cyclopropyl), $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$.

[0054] The term "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The compounds presented herein may exist as tautomers. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric interconversions include:



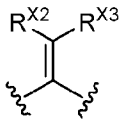
[0055] As used herein, a "small molecular weight compound" can be used interchangeably with "small molecule" or "small organic molecule". Small molecules refer to compounds other than peptides or oligonucleotides; and typically have molecular weights of less than about 2000 Daltons, *e.g.*, less than about 900 Daltons.

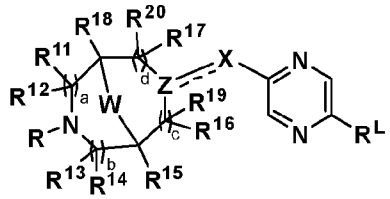
[0056] In one aspect, described herein is a process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (I)

wherein,

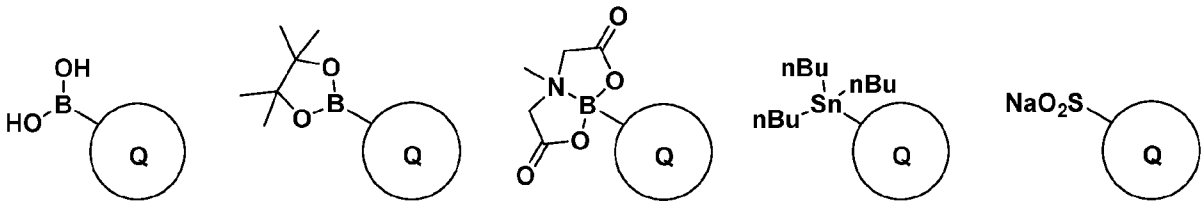
Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}-$, $-CR^{X2}R^{X3}-$,  , or $=CR^{X1}-$; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a coupling reagent, such as a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)

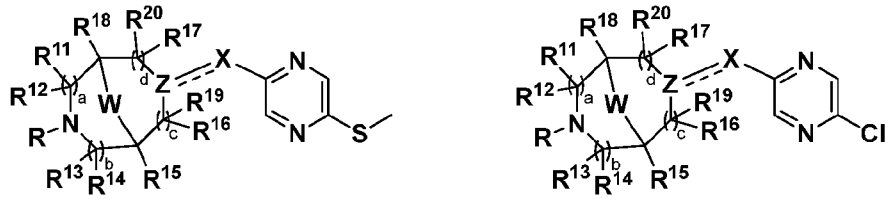


Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

to produce a compound of Formula (I);

wherein each variable within Formula (III), Formula (IV), Formula (IVa), Formula (V), and Formula (VI) is as described above for Formula (I).

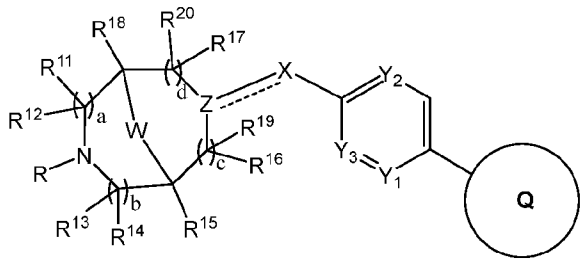
[0057] In some embodiments, a compound of Formula (II) has a structure of Formula (IIa) or Formula (IIb):



Formula (IIa) Formula (IIb).

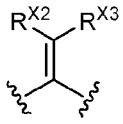
[0058] In some embodiments, a coupling reagent is a boronic acid or a boronic acid derivative such as boronic ester (e.g., pinacolyl or MIDA (N-methyliminodiacetate) ester). In some embodiments, the boronic acid derivative is potassium trifluoroborate. In some embodiments, the boronic acid derivative is sodium trihydroxyborate.

[0059] In one aspect, described herein is a process for preparing a compound of Formula (I'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

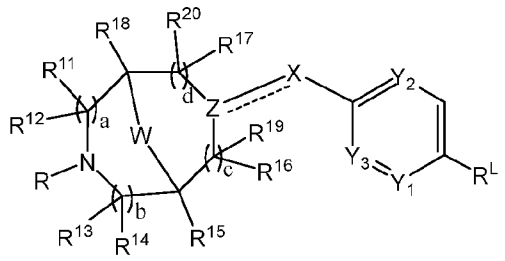


Formula (I')

wherein,

Y_1, Y_2, and Y_3 are each independently N or CH; Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, -NR^{X1}-, -$CR^{X2}R^{X3}$-,  , or =CR^{X1}-; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ==== is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–

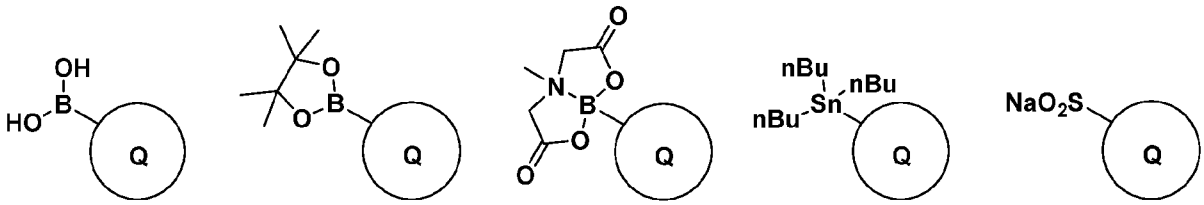
C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II')



Formula (II')

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II') is as described above for Formula (I');

with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)



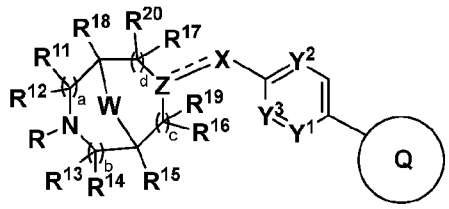
Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

to produce a compound of Formula (I);

wherein each variable within Formula (III), Formula (IV), Formula (IVa), Formula (V), and Formula (VI) is as described above for Formula (I').

[0060] In some embodiments of a compound of Formula (I'), two or more of Y_1, Y_2, and Y_3 are N.

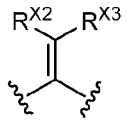
[0061] In one aspect, described herein is a process for preparing a compound of Formula (I'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

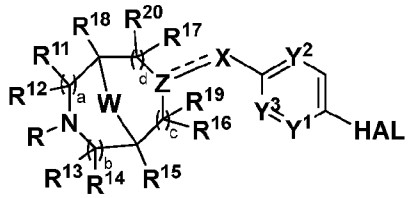


Formula (I')

wherein,

Y_1, Y_2, and Y_3 are each independently N or CH; Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or

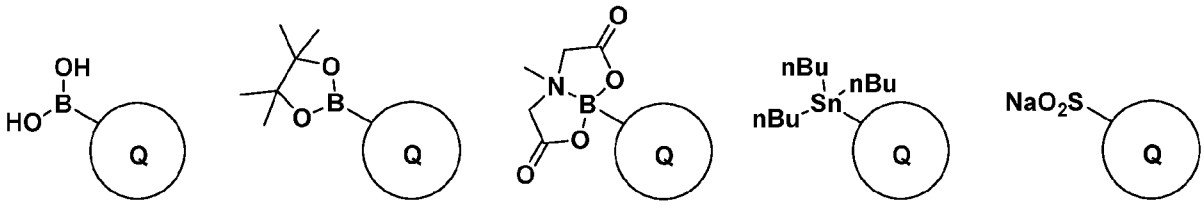
unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, -NR^{X1}-, -$CR^{X2}R^{X3}$-,  , or =CR^{X1}-; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II*)



Formula (II*)

wherein HAL represents a halogen;

with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)

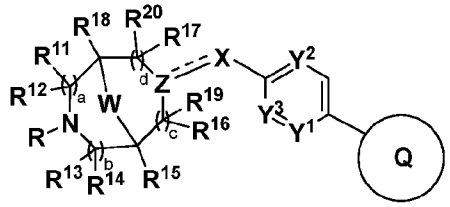


Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

to produce a compound of Formula (I').

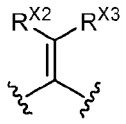
[0062] In some embodimetns, HAL is Cl. In some embodimetns, HAL is F. In some embodimetns, HAL is Br. In some embodimetns, HAL is I.

[0063] In one aspect, described herein is a process for preparing a compound of Formula (I'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

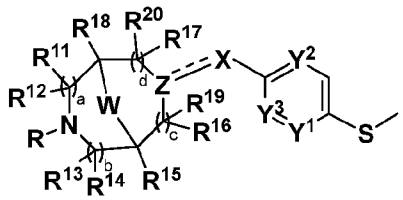


Formula (I')

wherein,

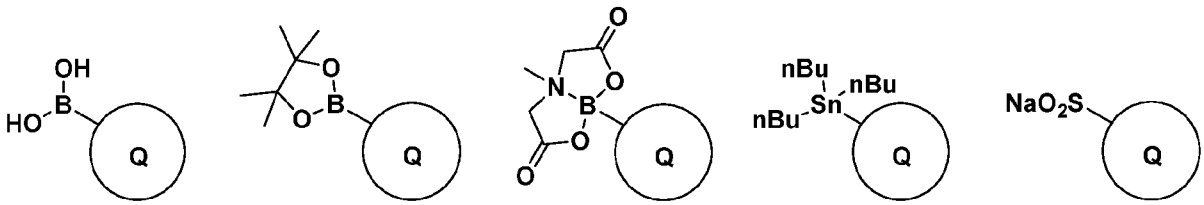
Y_1, Y_2, and Y_3 are each independently N or CH; Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, -NR^{X1}-, -$CR^{X2}R^{X3}$-,  , or =CR^{X1}-; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ==== is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen,

halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $-OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or a protecting group (e.g. Boc); a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (IIa')



Formula (IIa')

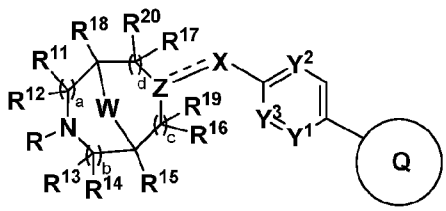
with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)



Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

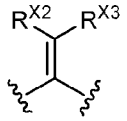
to produce a compound of Formula (I').

[0064] In one aspect, described herein is a process for preparing a compound of Formula (I'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

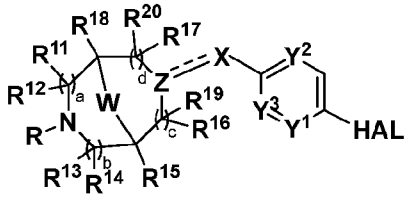


Formula (I')

wherein,

Y_1, Y_2, and Y_3 are each independently N or CH; Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}$-, $-CR^{X2}R^{X3}$-,  , or

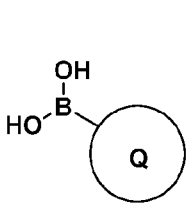
$=CR^{X1}$-; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ==== is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, –OR^{31}, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or a protecting group (e.g. Boc); a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II*)



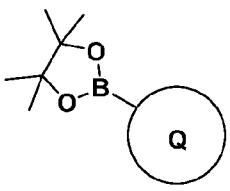
Formula (II*)

wherein HAL represents a halogen;

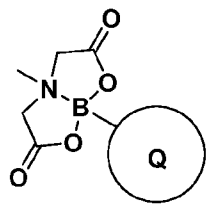
with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)



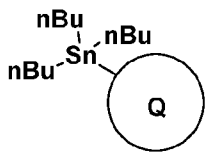
Formula (III)



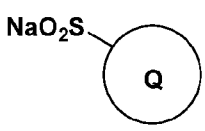
Formula (IV)



Formula (IVa)



Formula (V)

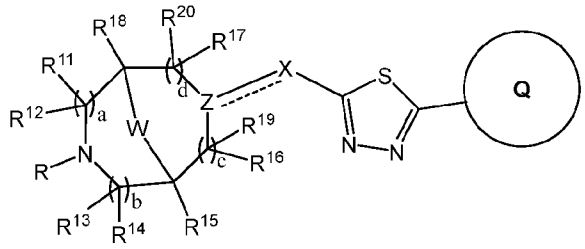


Formula (VI)

to produce a compound of Formula (I').

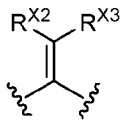
[0065] In some embodiments, R is a protecting group, e.g. *tert*-butyloxycarbonyl (Boc).

[0066] In one aspect, described herein is a process for preparing a compound of Formula (I''), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

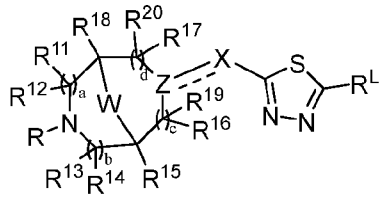


Formula (I'')

wherein,

Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}-$, $-CR^{X2}R^{X3}-$,  , or $=CR^{X1}-$; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ==== is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or

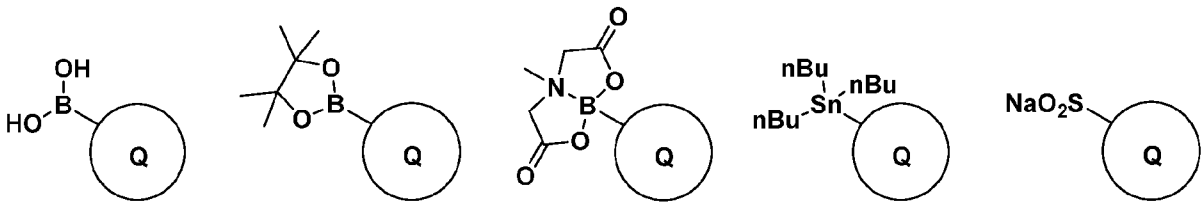
substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II'')



Formula (II'')

wherein R^L is halogen, -O(C=O)R^{L1}, -SR^{L1}, -S(=O)R^{L1}, -S(=O)$_2R^{L1}$, or -S(=O)(=NR^{L1})R^{L1}; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II'') is as described above for Formula (I'');

with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)



Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

to produce a compound of Formula (I);

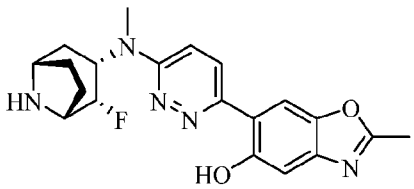
[0067] wherein each variable within Formula (III), Formula (IV), Formula (IVa), Formula (V), and Formula (VI) is as described above for Formula (I'').

[0068] In some embodiments, a compound of Formula (II), Formula (II') or Formula (II'') is reacted with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), in the presence of a transition metal catalyst such as palladium catalyst. In some embodiments, a compound of Formula (II) or Formula (II') is reacted with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), in the presence of a solvent such as 1, 4 dioxane, tetrahydrofuran or dimethylformamide. In some embodiments, a compound of Formula (II), Formula (II') or Formula (II'') is reacted with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), in the presence of a copper salt such as copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid.

[0069] In some embodiments, the compound of Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa') is used in a process to produce a compound of Formula (I) comprising a step of stereoselectivity. In some embodiments, the step of stereoselectivity comprises asymmetric synthesis. In some embodiments, the step of stereoselectivity comprises asymmetric synthesis and

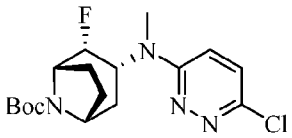
chiral resolution. In some embodiments, the step of stereoselectivity comprises the use of one or more chiral centers in a compound of Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'). In some embodiments, the one or more chiral centers is a chiral auxiliary. In some embodiments, the chiral auxiliary is $-S(=O)(=NR^{L1})R^{L1}$.

[0070] In some embodiments the compound of Formula (I'), is a compound of Formula (I'a):



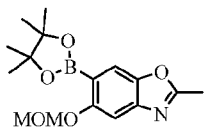
Formula (I'a).

[0071] In some embodiments, a compound of Formula (II') is a compound of Formula (II'a):



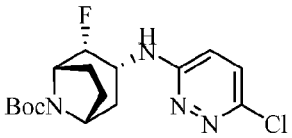
Formula (II'a).

[0072] In some embodiments, a compound of Formula (IV) is a compound of Formula (IVaa):



Formula (IVaa).

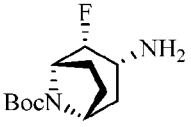
[0073] In some embodiments, a process of preparing a compound of Formula (II'a) comprises the step of reacting a compound of Formula (X):



Formula (X)

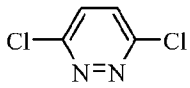
with a base, such as potassium t-butoxide in a solvent, such as dimethylformamide and a methylation agent, such as methyl iodide.

[0074] In some embodiments of a process for preparing a compound of Formula (X), the process comprises the step of reacting a compound of Formula (XI):



Formula (XI)

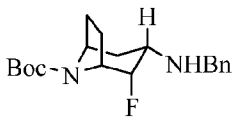
with a compound of Formula (XII):



Formula (XII)

in the presence of a base such as *N,N*-Diisopropylethylamine and a solvent such as dimethyl sulfoxide.

[0075] In some embodiments of a process for preparing a compound of Formula (XI), the process comprises the step of reacting a compound of Formula (XIII):

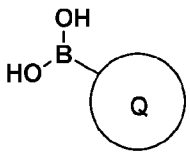


Formula (XIII)

in a solvent, such as ethanol in the presence of a palladium catalyst under a hydrogen atmosphere.

[0076] In some embodiments of a process for preparing a chirally pure compound of Formula (XIII), the process comprises the step of reacting a racemic mixture of a compound of Formula (XIII) with a chiral resolving agent, such as *(R)-(-)*-mandelic acid in the presence of a solvent, such as methyl ethyl ketone. In some embodiments of a process for preparing a chirally pure compound of Formula (XIII), the process comprises further steps of neutralizing a precipitated salt with sodium bicarbonate and extraction with ethyl acetate. In some embodiments of a process for preparing a chirally pure compound of Formula (XIII), the process comprises repeating steps until the desired chiral purity is achieved. In some embodiments, the chiral purity of a compound of Formula (XIII) is 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or 100%.

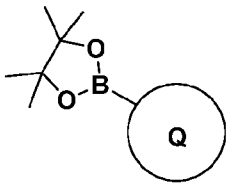
[0077] In some embodiments of a process for preparing a compound of Formula (I), the process comprises the step of reacting the compound of Formula (II) with a compound of Formula (III)



Formula (III)

to produce a compound of Formula (I).

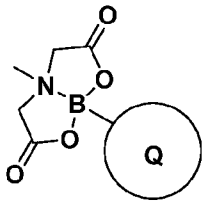
[0078] In some embodiments of a process for preparing a compound of Formula (I), the process comprising the step of reacting the compound of Formula (II) with the compound of Formula (IV)



Formula (IV)

to produce a compound of Formula (I).

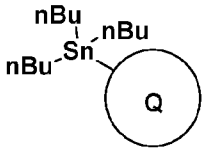
[0079] In some embodiments of a process for preparing a compound of Formula (I), the process comprising the step of reacting the compound of Formula (II) with the compound of Formula (IVa)



Formula (IVa)

to produce a compound of Formula (I).

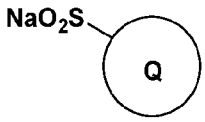
[0080] In some embodiments of a process for preparing a compound of Formula (I), the process comprising the step of reacting the compound of Formula (II) with the compound of Formula (V)



Formula (V)

to produce a compound of Formula (I).

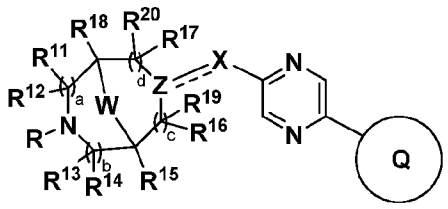
[0081] In some embodiments of a process for preparing a compound of Formula (I), the process comprising the step of reacting a compound of Formula (II) with a compound of Formula (VI)



Formula (VI)

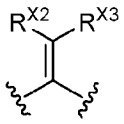
to produce a compound of Formula (I).

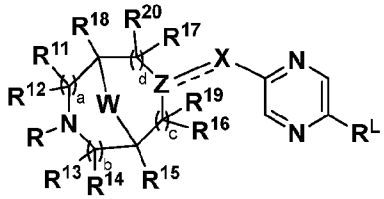
[0082] In one aspect, described herein is a process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (I)

wherein,

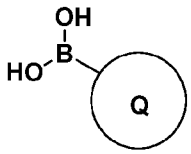
Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}-$, $-CR^{X2}R^{X3}-$,  , or $=CR^{X1}-$; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a compound of Formula (III)

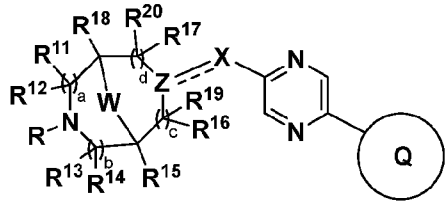


Formula (III)

wherein each variable within Formula (III) is as described above for Formula (I).

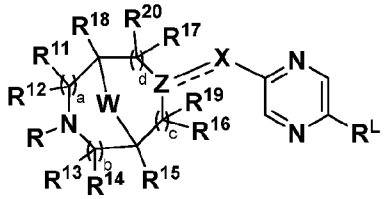
In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (III) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0083] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

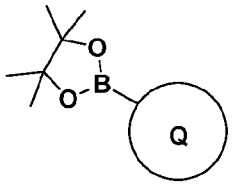
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

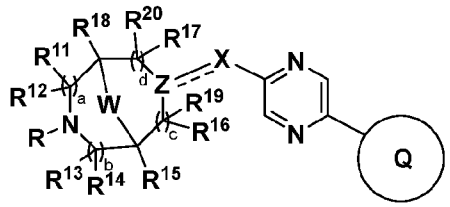
with a compound of Formula (IV)



Formula (IV)

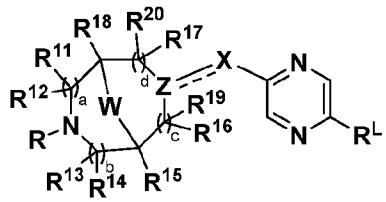
wherein each variable within Formula (I), Formula (II), and Formula (IV) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (IV) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0084] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

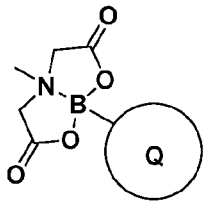
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

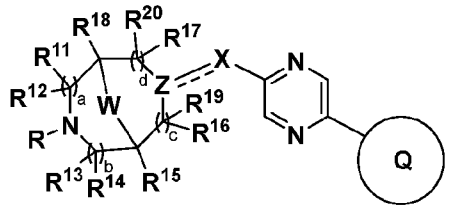
with a compound of Formula (IV)



Formula (IVa)

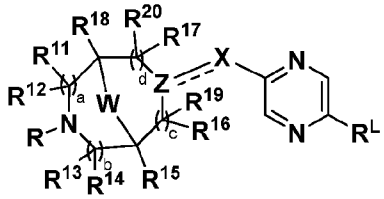
wherein each variable within Formula (I), Formula (II), and Formula (IVa) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (IVa) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0085] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

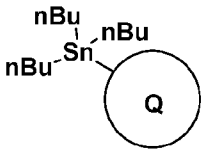
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

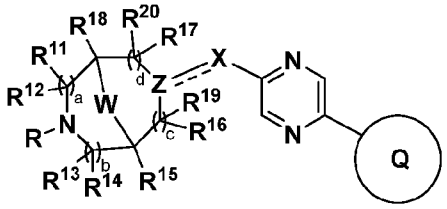
with a compound of Formula (V)



Formula (V)

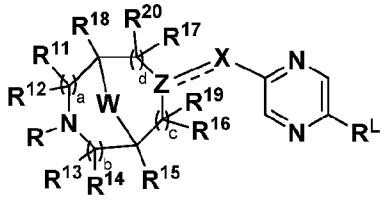
wherein each variable within Formula (I), Formula (II), and Formula (V) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (V) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0086] In another aspect described herein, is a process for preparing a compound of Formula (I)



Formula (I)

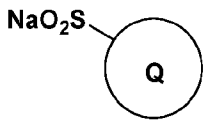
comprising reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a compound of Formula (VI)



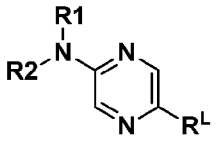
Formula (VI)

wherein each variable within Formula (I), Formula (II), and Formula (VI) is as described above for Formula (I). In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with a compound of Formula (VI) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid to produce a compound of Formula (I).

[0087] In some embodiments of a process for preparing a compound of Formula (I), a compound of Formula (II) is reacting with the compound of Formula (III), Formula (IV), Formula (IVa), Formula

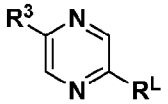
(V), or Formula (VI) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-thienyl carboxylic acid.

[0088] In another aspect described herein, is a process for preparing a compound of Formula (VII)



Formula (VII)

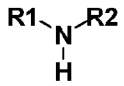
comprising reacting a compound of Formula (VIII)



Formula (VIII)

wherein R^3 is a halogen, such as Cl, Br, or I; or O-CH_2CF_3

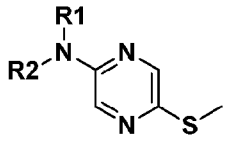
with a compound of Formula (IX)



Formula (IX)

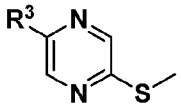
to produce a compound of Formula (VII), wherein each R1 and R2 is independently hydrogen, halogen, -OH, $-OR^{31}$, –CN,$–SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, $-NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-P(=O)R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0089] In some embodiments, a compound of Formula (VII) has a structure of Formula (VIIa):



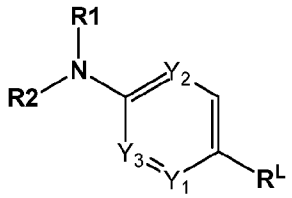
Formula (VIIa);

and a compound of Formula (VIII) has a structure of Formula (VIIIa):



Formula (VIIIa).

[0090] In another aspect described herein, is a process for preparing a compound of Formula (VII')

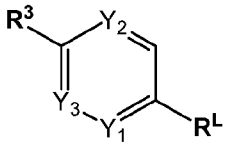


Formula (VII')

wherein,

Y_1, Y_2, and Y_3 are each independently N or CH

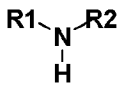
comprising reacting a compound of Formula (VIII')



Formula (VIII')

wherein R^3 is a halogen, such as Cl, Br, or I; or O-CH_2CF_3

with a compound of Formula (IX)

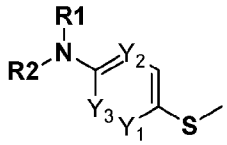


Formula (IX)

to produce a compound of Formula (VII'), wherein each R1 and R2 is independently hydrogen, halogen, -OH, $-OR^{31}$, –CN,$–SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, $-NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-P(=O)R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted

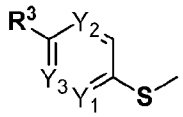
polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0091] In some embodiments, a compound of Formula (VII') has a structure of Formula (VIIa'):



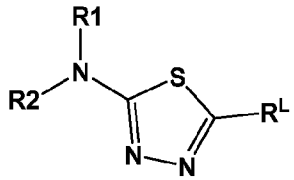
Formula (VIIa');

and a compound of Formula (VIII') has a structure of Formula (VIIIa'):



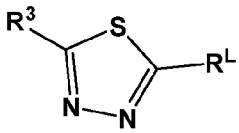
Formula (VIIIa').

[0092] In another aspect described herein, is a process for preparing a compound of Formula (VII'')



Formula (VII'')

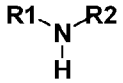
comprising reacting a compound of Formula (VIII'')



Formula (VIII'')

wherein R^3 is a halogen, such as Cl, Br, or I; or O-CH_2CF_3

with a compound of Formula (IX)

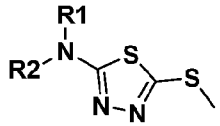


Formula (IX)

to produce a compound of Formula (VII''), wherein each R1 and R2 is independently hydrogen, halogen, -OH, $-OR^{31}$, –CN,$-SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, -

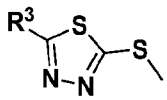
$NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-P(=O)R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0093] In some embodiments, a compound of Formula (VII'') has a structure of Formula (VIIa''):



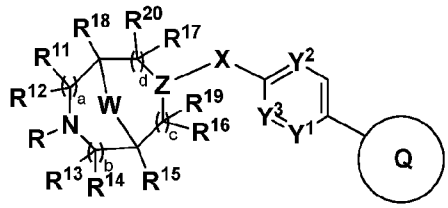
Formula (VIIa'');

and a compound of Formula (VIII'') has a structure of Formula (VIIIa''):



Formula (VIIIa'').

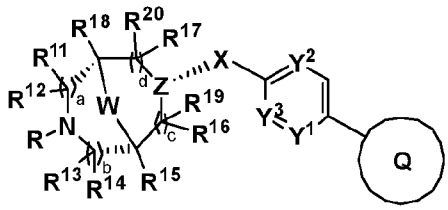
[0094] In some embodiments, a compound of Formula (I) is a compound of Formula (Ia)



Formula (Ia).

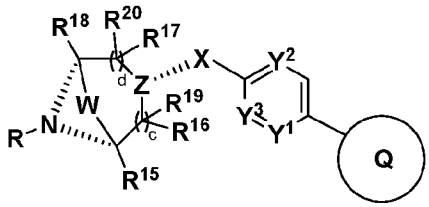
[0095] In some embodiments, the nitrogen atom bearing R group and the X group are on the same side of a plane. In some embodiments, the nitrogen atom bearing R group and the X group are on the opposite side of a plane.

[0096] In some embodiments, a compound of Formula (I) is a compound of Formula (Ib)



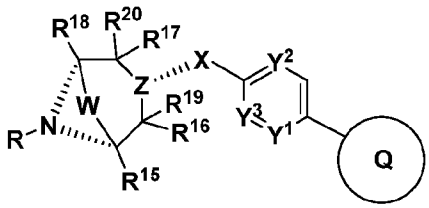
Formula (Ib).

[0097] In some embodiments, a compound of Formula (I) is a compound of Formula (Ic)



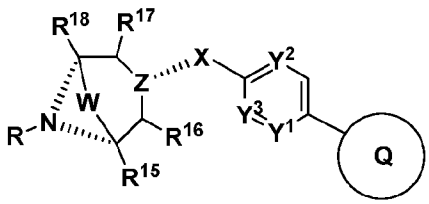
Formula (Ic).

[0098] In some embodiments, a compound of Formula (I) is a compound of Formula (Id)



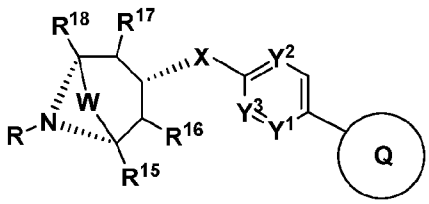
Formula (Id).

[0099] In some embodiments, a compound of Formula (I) is a compound of Formula (Ie)



Formula (Ie).

[0100] In some embodiments, a compound of Formula (I) is a compound of Formula (If)



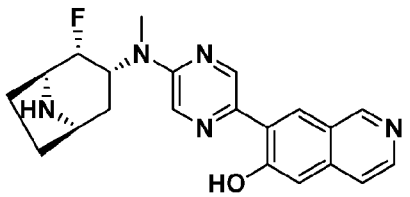
Formula (If).

[0101] In some embodiments, Y^1 is N, Y^2 is N, and Y^3 is CH. In some embodiments, Y^1 is N, Y^2 is CH, and Y^3 is N. In some embodiments, Y^1 is N, Y^2 is N, and Y^3 is N. In some embodiments, R is hydrogen or substituted or unsubstituted C_1–C_4 alkyl. In some embodiments, R is hydrogen, -CH_3, -

CH_2CH_3, or $-CH_2CH_2CH_3$. In some embodiments, R is hydrogen. In some embodiments, R is $-CH_3$. In some embodiments, R is $-CH_2CH_3$. In some embodiments, R is $-CH_2CH_2CH_3$. In some embodiments, each R^{15} and R^{18} is independently hydrogen or substituted or unsubstituted C_1–C_4 alkyl. In some embodiments, each R^{15} and R^{18} is independently hydrogen, $-CH_3$, or $-CH_2CH_3$. In some embodiments, each R^{15} and R^{18} is hydrogen. In some embodiments, each R^{15} and R^{18} is $-CH_3$. In some embodiments, R^{15} is hydrogen and R^{18} is $-CH_3$. In some embodiments, R^{15} is $-CH_3$ and R^{18} is hydrogen. In some embodiments, each R^{16} and R^{17} is independently hydrogen, F, –or substituted or unsubstituted C_1–C_4 alkyl. In some embodiments, each R^{16} and R^{17} is independently hydrogen, F, $-CH_3$, or $-CH_2CH_3$. In some embodiments, each R^{16} and R^{17} is independently hydrogen or F. In some embodiments, R^{16} is hydrogen and R^{17} is F. In some embodiments, R^{16} is F and R^{17} is hydrogen. In some embodiments, W is substituted or unsubstituted C_1-C_3 alkylene. In some embodiments, W is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. In some embodiments, W is $-CH_2CH_2-$. In some embodiments, W is $-CH_2CH_2CH_2-$. In some embodiments, X is $-NR^{X1}-$. In some embodiments, R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, or substituted or unsubstituted C_3–C_6 cycloalkyl. In some embodiments, R^{X1} is hydrogen, –CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, cyclopropyl, or cyclobutyl. In some embodiments, R^{X1} is hydrogen. In some embodiments, R^{X1} is –CN. In some embodiments, R^{X1} is $-CH_3$. In some embodiments, R^{X1} is $-CH_2CH_3$. In some embodiments, R^{X1} is $-CH_2CH_2CH_3$. In some embodiments, R^{X1} is $-OCH_3$. In some embodiments, R^{X1} is $-OCH_2CH_3$. In some embodiments, R^{X1} is $-OCH_2CH_2CH_3$. In some embodiments, R^{X1} is cyclopropyl. In some embodiments, R^{X1} is cyclobutyl. In some embodiments, ring Q is substituted or unsubstituted aryl. In some embodiments, ring Q is substituted aryl. In some embodiments, ring Q is aryl substituted with -OH and substituted or unsubstituted heteroaryl. In some embodiments, ring Q is 2-hydroxyphenyl substituted with substituted or unsubstituted heteroaryl. In some embodiments, ring Q is 2-hydroxyphenyl substituted with substituted or unsubstituted monocyclic heteroaryl. In some embodiments, ring Q is 2-hydroxyphenyl substituted with substituted or unsubstituted 5-membered heteroaryl. In some embodiments, the 5-membered heteroaryl comprises 0-1 O, 0-1 S, and 0-4 N heteroatoms. In some embodiments, the 5-membered heteroaryl is optionally substituted by one or more substituents each independently selected from oxo, C_1-C_3 alkyl, and halogen. In some embodiments, ring Q is 2-hydroxyphenyl substituted with substituted or unsubstituted pyrazole or substituted or unsubstituted oxadiazole. In some embodiments, ring Q is 2-hydroxyphenyl substituted with pyrazole substituted with $-CH_3$. In some embodiments, ring Q is 2-hydroxyphenyl substituted with oxadiazole substituted with $-CH_3$. In some embodiments, ring Q is 2-hydroxyphenyl substituted with substituted or unsubstituted 6-membered heteroaryl. In some embodiments, the 6-membered heteroaryl comprises 1-4 N heteroatoms. In some

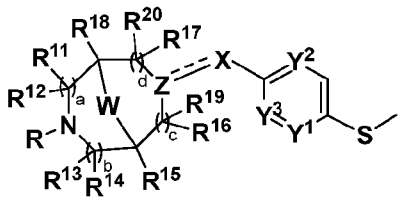
embodiments, the 6-membered heteroaryl is optionally substituted by one or more substituents each independently selected from oxo, C_1-C_3 alkyl, and halogen. In some embodiments, the 6-membered heteroaryl is 1-methylpyridin-2(1H)-one. In some embodiments, ring Q is substituted or unsubstituted 6/6 fused heteroaryl. In some embodiments, the 6/6 fused heteroaryl comprises 1-4 N heteroatoms. In some embodiments, the 6/6 fused heteroaryl comprises 1-2 N heteroatoms. In some embodiments, the 6/6 fused heteroaryl is optionally substituted by one or more substituents each independently selected from oxo, C_1-C_3 alkyl, and halogen. In some embodiments, the 6/6 fused heteroaryl is optionally substituted by one or more substituents each independently selected from oxo and C_1-C_3 alkyl. In some embodiments, the 6/6 fused heteroaryl is selected from 7-hydroxy-2-methylphthalazin-1-one, 6-hydroxy-3-methylquinazolin-4-one, and 7-hydroxy-2-methylisoquinolin-1-one. In some embodiments, the 6/6 fused heteroaryl is 7-hydroxy-N-methylquinoline-2-carboxamide. In some embodiments, ring Q is substituted or unsubstituted 6/5 fused heteroaryl. In some embodiments, the 6/5 fused heteroaryl comprises 0-1 O, 0-1 S and 0-3 N heteroatoms. In some embodiments, the 6/6 fused heteroaryl comprises 0-1 O and 1-2 N heteroatoms. In some embodiments, the 6/5 fused heteroaryl is optionally substituted by one or more substituents each independently selected from oxo, C_1-C_3 alkyl, and halogen. In some embodiments, the 6/5 fused heteroaryl is optionally substituted by one or more substituents each independently selected from oxo and C_1-C_3 alkyl. In some embodiments, the 6/5 fused heteroaryl is selected from 2-methylbenzo[d]oxazol-5-ol and 3-methylbenzo[d]oxazol-2(3H)-one.

[0102] In some embodiments, a compound of Formula (I) is a compound of Formula (Ia)

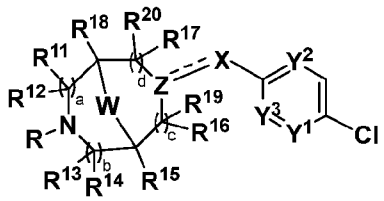


Formula (Ia).

[0103] In some embodiments, a compound of Formula (II) is a compound of Formula (IIa) or Formula (IIb)

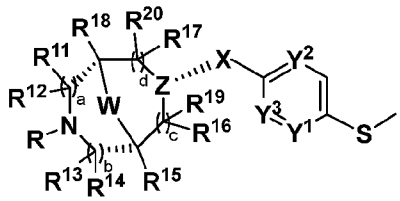


Formula (IIa)

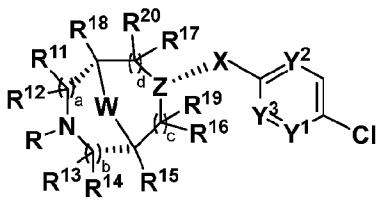


Formula (IIb).

[0104] In some embodiments, a compound of Formula (II) is a compound of Formula (IIc) or Formula (IId):

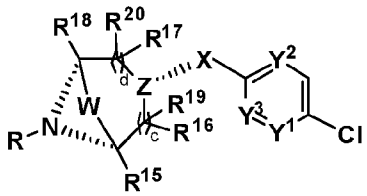


Formula (IIc)



Formula (IId).

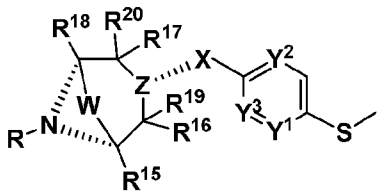
[0105] In some embodiments, a compound of Formula (II) is a compound of Formula (IIe) or Formula (IIf):



Formula (IIe)

Formula (IIf).

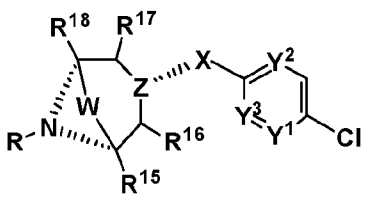
[0106] In some embodiments, a compound of Formula (II) is a compound of Formula (IIg) or Formula (IIh):



Formula (IIg)

Formula (IIh).

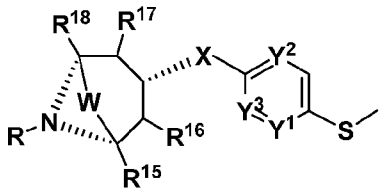
[0107] In some embodiments, a compound of Formula (II) is a compound of Formula (IIi) or Formula (IIj):



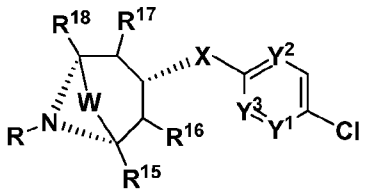
Formula (IIi)

Formula (IIj).

[0108] In some embodiments, a compound of Formula (II) is a compound of Formula (IIk) or Formula (III):



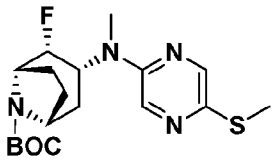
Formula (IIk)



Formula (III).

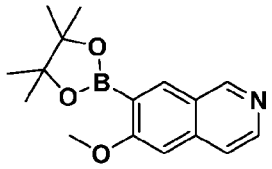
[0109] In some embodiments, Y^1 is N, Y^2 is N, and Y^3 is CH. In some embodiments, Y^1 is N, Y^2 is CH, and Y^3 is N. In some embodiments, Y^1 is N, Y^2 is N, and Y^3 is N. In some embodiments, R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4heteroalkyl. In some embodiments, R is substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4heteroalkyl. In some embodiments, R is substituted or unsubstituted C_1–C_4 alkyl. In some embodiments, R is substituted or unsubstituted C_1–C_4heteroalkyl. In some embodiments, R is C_1–C_4heteroalkyl substituted with oxo and $-CH_3$. In some embodiments, R is *tert*-butyloxycarbonyl. In some embodiments, each R^{15} and R^{18} is independently hydrogen or substituted or unsubstituted C_1–C_4 alkyl. In some embodiments, each R^{15} and R^{18} is independently hydrogen, $-CH_3$, or $-CH_2CH_3$. In some embodiments, each R^{15} and R^{18} is hydrogen. In some embodiments, each R^{15} and R^{18} is $-CH_3$. In some embodiments, R^{15} is hydrogen and R^{18} is $-CH_3$. In some embodiments, R^{15} is $-CH_3$ and R^{18} is hydrogen. In some embodiments, each R^{16} and R^{17} is independently hydrogen, F, –or substituted or unsubstituted C_1–C_4 alkyl. In some embodiments, each R^{16} and R^{17} is independently hydrogen, F, $-CH_3$, or $-CH_2CH_3$. In some embodiments, each R^{16} and R^{17} is independently hydrogen or F. In some embodiments, R^{16} is hydrogen and R^{17} is F. In some embodiments, R^{16} is F and R^{17} is hydrogen. In some embodiments, W is substituted or unsubstituted C_1-C_3 alkylene. In some embodiments, W is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. In some embodiments, W is $-CH_2CH_2-$. In some embodiments, W is $-CH_2CH_2CH_2-$. In some embodiments, X is $-NR^{X1}-$. In some embodiments, R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, or substituted or unsubstituted C_3–C_6 cycloalkyl. In some embodiments, R^{X1} is hydrogen, –CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, cyclopropyl, or cyclobutyl. In some embodiments, R^{X1} is hydrogen. In some embodiments, R^{X1} is –CN. In some embodiments, R^{X1} is $-CH_3$. In some embodiments, R^{X1} is $-CH_2CH_3$. In some embodiments, R^{X1} is $-CH_2CH_2CH_3$. In some embodiments, R^{X1} is $-OCH_3$. In some embodiments, R^{X1} is $-OCH_2CH_3$. In some embodiments, R^{X1} is $-OCH_2CH_2CH_3$. In some embodiments, R^{X1} is cyclopropyl. In some embodiments, R^{X1} is cyclobutyl.

[0110] In some embodiments, a compound of Formula (II) is a compound of Formula (IIaaa)



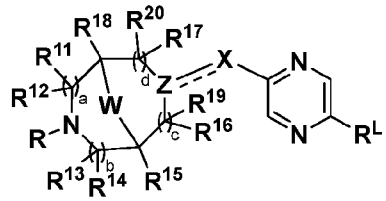
Formula (IIaaa).

[0111] In some embodiments, a compound of Formula (IV) is a compound of Formula (IVaaa)



Formula (IVaaa).

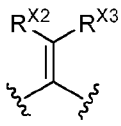
[0112] In one aspect, described herein is a compound of Formula (II),



Formula (II)

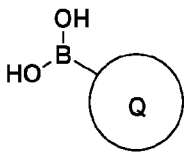
wherein,

R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, or $-S(=O)_2R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}$-, $-CR^{X2}R^{X3}$-,  , or $=CR^{X1}$-; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or

unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $-OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3.

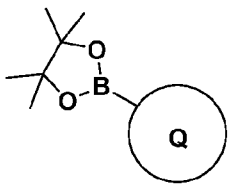
[0113] In one aspect, described herein is a compound of Formula (III),



Formula (III)

wherein ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

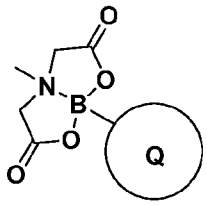
[0114] In one aspect, described herein is a compound of Formula (IV),



Formula (IV)

wherein ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

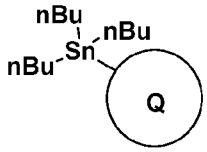
[0115] In one aspect, described herein is a compound of Formula (IVa),



Formula (IVa)

wherein ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

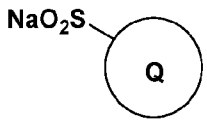
[0116] In one aspect, described herein is a compound of Formula (V),



Formula (V)

wherein ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

[0117] In one aspect, described herein is a compound of Formula (VI)



Formula (VI)

wherein ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

[0118] In one aspect, described herein is a compound of Formula (VII),

Formula (VII)

wherein each R1 and R2 is independently hydrogen, halogen, -OH, $-OR^{31}$, –CN,$–SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, $-NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-P(=O)R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted

monocyclic heteroaryl, substituted or unsubstituted polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0119] In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is substituted or unsubstituted aryl. In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is substituted or unsubstituted cycloalkyl. In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is substituted or unsubstituted heterocycloalkyl. In some embodiments, ring Q is a fused ring. In some embodiments, ring Q is monocyclic. In some embodiments, ring Q is polycyclic. In some embodiments, ring Q is bicyclic. In some embodiments, ring Q is unsubstituted. In some embodiments, ring Q is substituted.

[0120] In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is substituted or unsubstituted phenyl.

[0121] In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is 2–hydroxy–phenyl substituted with 1, 2, or 3 substituents independently selected from: deuterium, halogen, -OH, -NO_2, -CN, -SR^{31}, -$S(=O)R^{31}$, -$S(=O)_2R^{31}$, -$N(R^{31})_2$, -$C(=O)R^{31}$, -$OC(=O)R^{31}$, -$C(=O)OR^{31}$, -$C(=O)N(R^{31})_2$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0122] In some embodiments, each R^{31} is independently hydrogen, deuterium, substituted or unsubstituted C_1–C_4 alkyl, -CD_3, substituted or unsubstituted C_1–C_4 haloalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_5 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

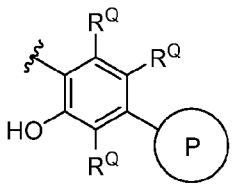
[0123] In some embodiments, ring Q is 2–hydroxy–phenyl substituted with substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0124] In some embodiments, ring Q is 2–hydroxy–phenyl substituted with substituted or unsubstituted aryl. In some embodiments, if aryl is substituted then it is substituted with 1 or 2 substituents independently selected from: deuterium, halogen, -OH, -NO_2, -CN, $–SR^{31}$, $–S(=O)R^{31}$, $–S(=O)_2R^{31}$, $–N(R^{31})_2$, $–C(=O)R^{31}$, $–OC(=O)R^{31}$, $–C(=O)OR^{31}$, $–C(=O)N(R^{31})_2$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_3-C_7 cycloalkyl, and substituted or unsubstituted C_2-C_7 heterocycloalkyl.

[0125] In some embodiments, each R^{31} is independently hydrogen, deuterium, substituted or unsubstituted C_1–C_4 alkyl, -CD_3, substituted or unsubstituted C_1–C_4 haloalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_5 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0126] In some embodiments, ring Q is 2–hydroxy–phenyl substituted with substituted or unsubstituted heteroaryl. In some embodiments, if heteroaryl is substituted then it is substituted with 1 or 2 substituents independently selected from: deuterium, halogen, -OH, -NO_2, -CN, $–SR^{31}$, $–S(=O)R^{31}$, $–S(=O)_2R^{31}$, $–N(R^{31})_2$, $–C(=O)R^{31}$, $–OC(=O)R^{31}$, $–C(=O)OR^{31}$, $–C(=O)N(R^{31})_2$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_3-C_7 cycloalkyl, and substituted or unsubstituted C_2-C_7 heterocycloalkyl.

[0127] In some embodiments, each R^{31} is independently hydrogen, deuterium, substituted or unsubstituted C_1–C_4 alkyl, -CD_3, substituted or unsubstituted C_1–C_4 haloalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_5 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0128] In some embodiments, ring Q is 

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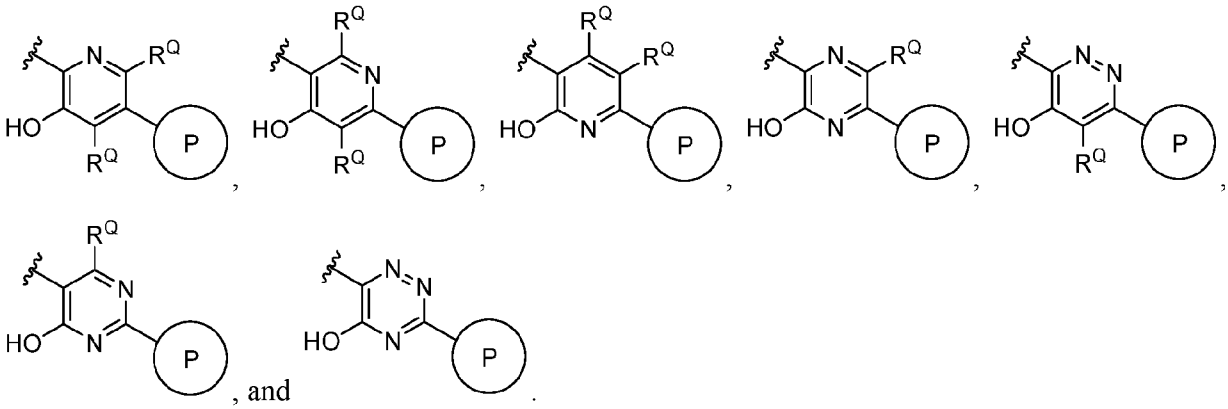
[0129] In some embodiments, each R^Q is independently selected from hydrogen, deuterium, –F, –Cl, -CN, –OH, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, $–CF_3$, $–OCH_3$, -OCH_2CH_3, -CH_2OCH_3, -$OCH_2CH_2CH_3$, and -$OCH(CH_3)_2$. In some embodiments, ring P is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0130] In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is substituted or unsubstituted heteroaryl.

[0131] In some embodiments, ring Q is substituted or unsubstituted 5- or 6-membered monocyclic heteroaryl.

[0132] In some embodiments, ring Q is substituted or unsubstituted 6-membered monocyclic heteroaryl.

[0133] In some embodiments, ring Q is 6-membered monocyclic heteroaryl selected from:



, and .

[0134] In some embodiments, each R^Q is independently selected from hydrogen, deuterium, –F, –Cl, -CN, –OH, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $–CF_3$, $–OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_3$, $-OCH_2CH_2CH_3$, and $-OCH(CH_3)_2$. In some embodiments, ring P is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

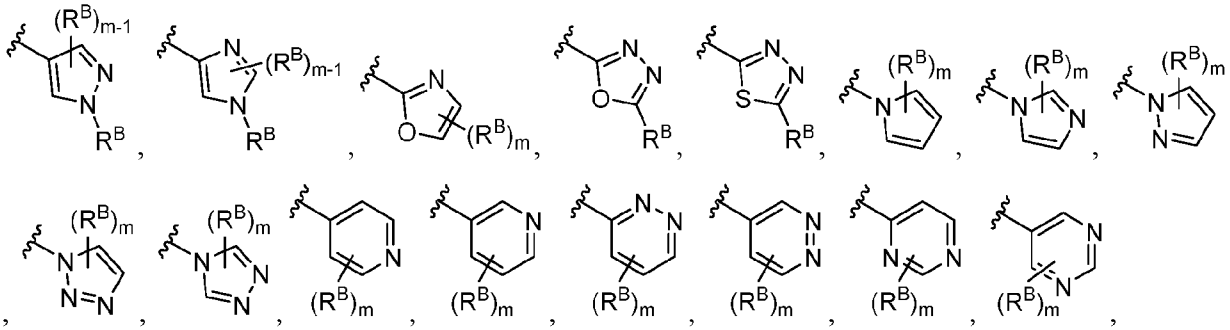
[0135] In some embodiments, each R^Q is independently hydrogen,–F, –Cl, -CN, –OH, $-CH_3$,$–CF_3$, or $–OCH_3$.

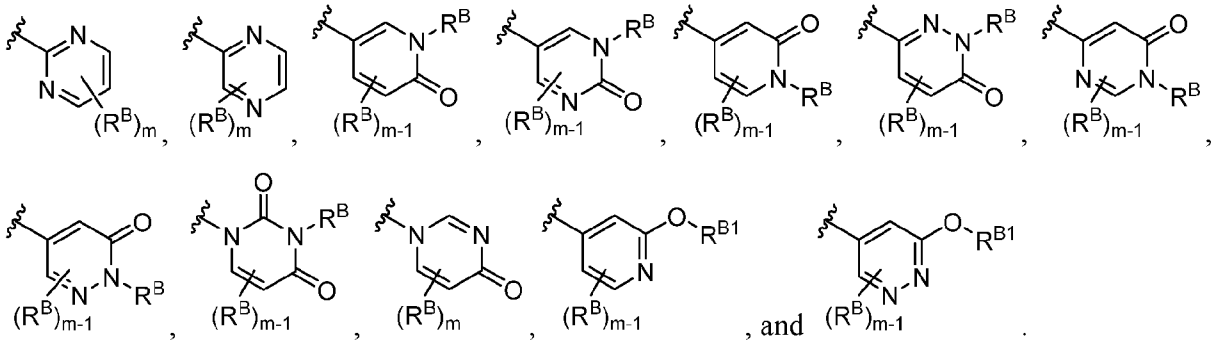
[0136] In some embodiments, each R^Q is independently hydrogen or –F.

[0137] In some embodiments, each R^Q is hydrogen.

[0138] In some embodiments, ring P is substituted or unsubstituted heteroaryl.

[0139] In some embodiments, ring P is heteroaryl selected from the group consisting of:

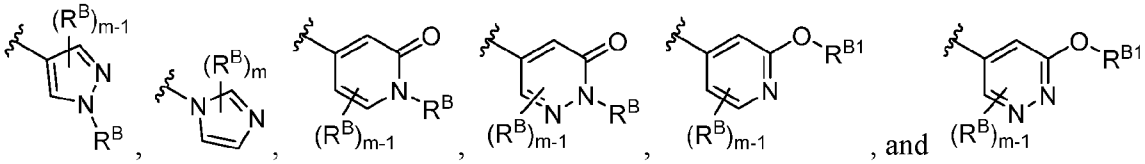




[0140] In some embodiments, each R^B is independently selected from H, deuterium, halogen, hydroxy, cyano, substituted or unsubstituted C_1-C_6 alkyl, -CD_3, substituted or unsubstituted C_1–C_6 fluoroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 alkoxy, deuterium substituted C_1-C_6 alkoxy, -OCD_3, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_2–C_7 heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0141] In some embodiments, R^{B1} is selected from hydrogen, deuterium, substituted or unsubstituted C_1-C_6 alkyl, -CD_3, substituted or unsubstituted C_1–C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_{3-7} cycloalkyl, and substituted or unsubstituted C_2–C_7 heterocycloalkyl. In some embodiments, m is 0, 1, 2, or 3.

[0142] In some embodiments, ring P is heteroaryl selected from the group consisting of:



[0143] In some embodiments, each R^B is independently selected from H, deuterium, halogen, hydroxy, cyano, substituted or unsubstituted C_1-C_6 alkyl, -CD_3, substituted or unsubstituted C_1–C_6 fluoroalkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 alkoxy, deuterium substituted C_1-C_6 alkoxy, -OCD_3, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_2–C_7 heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0144] In some embodiments, R^{B1} is selected from hydrogen, deuterium, substituted or unsubstituted C_1-C_6 alkyl, -CD_3, substituted or unsubstituted C_1–C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_{3-7} cycloalkyl, and substituted or unsubstituted C_2–C_7 heterocycloalkyl. In some embodiments, m is 0, 1, 2, or 3

[0145] In some embodiments, each R^B is independently H, deuterium, –F, –Cl, –CN, –CH_3, –CF_3, –OH, or –OCH_3.

[0146] In some embodiments, each R^B is independently –F or $–OCH_3$.

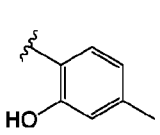
[0147] In some embodiments, R^{B1} is hydrogen, deuterium, $–CH_3$, $–CF_3$, or $–CD_3$.

[0148] In some embodiments, m is 0 or 1.

[0149] In some embodiments, ring Q is 2–naphthyl substituted at the 3 position with 0, 1, and 2 substituents independently selected from: deuterium, halogen, -OH, $-NO_2$, -CN, $–SR^{31}$, $–S(=O)R^{31}$, $–S(=O)_2R^{31}$, $–N(R^{31})_2$, $–C(=O)R^{31}$, $–OC(=O)R^{31}$, $–C(=O)OR^{31}$, $–C(=O)N(R^{31})_2$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0150] In some embodiments, each R^{31} is independently hydrogen, deuterium, substituted or unsubstituted C_1–C_4 alkyl, $-CD_3$, substituted or unsubstituted C_1–C_4 haloalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_5 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0151] In some embodiments, ring Q is selected from the group consisting of: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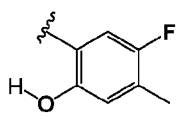
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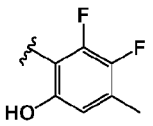
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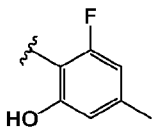
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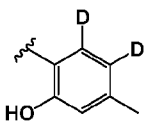
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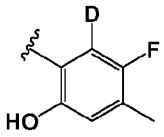
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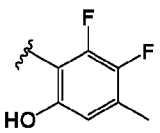
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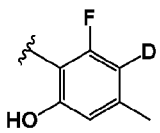
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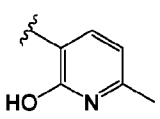
[0152] In some embodiments, ring Q is selected from the group consisting of: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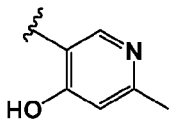
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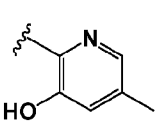
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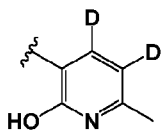
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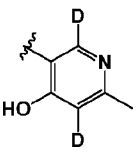
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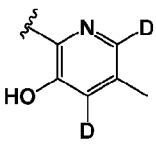
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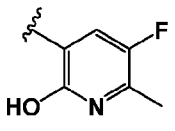
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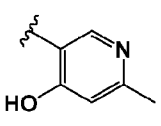
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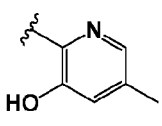
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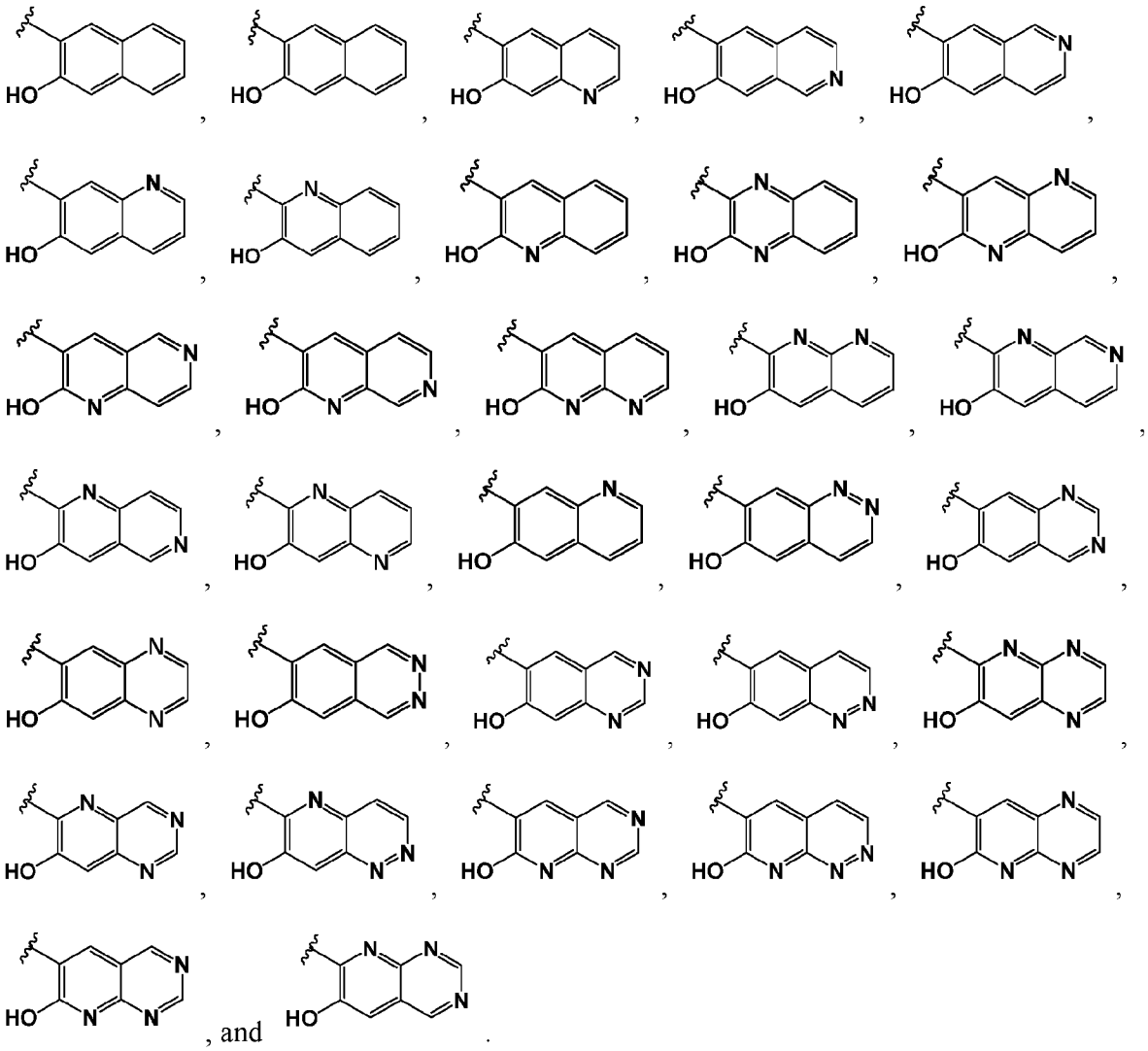
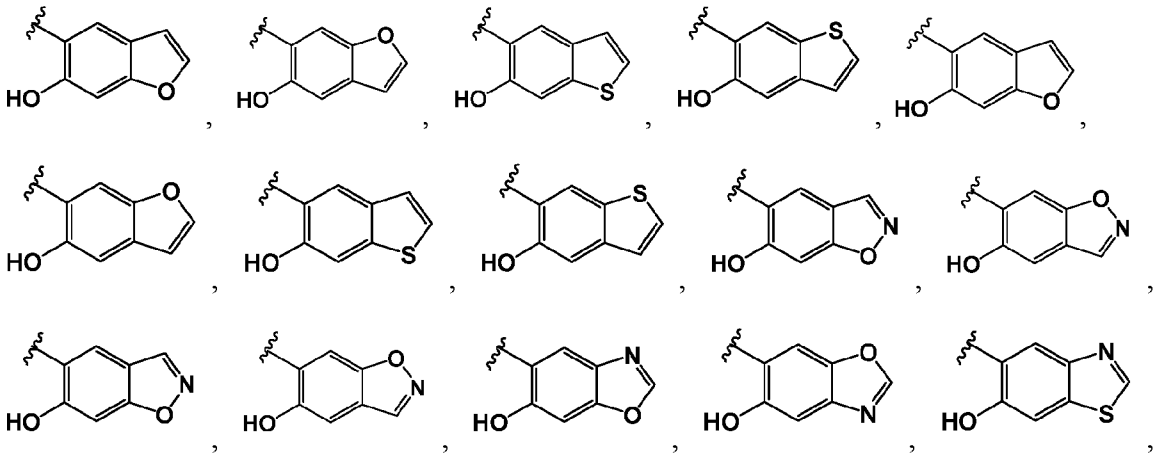
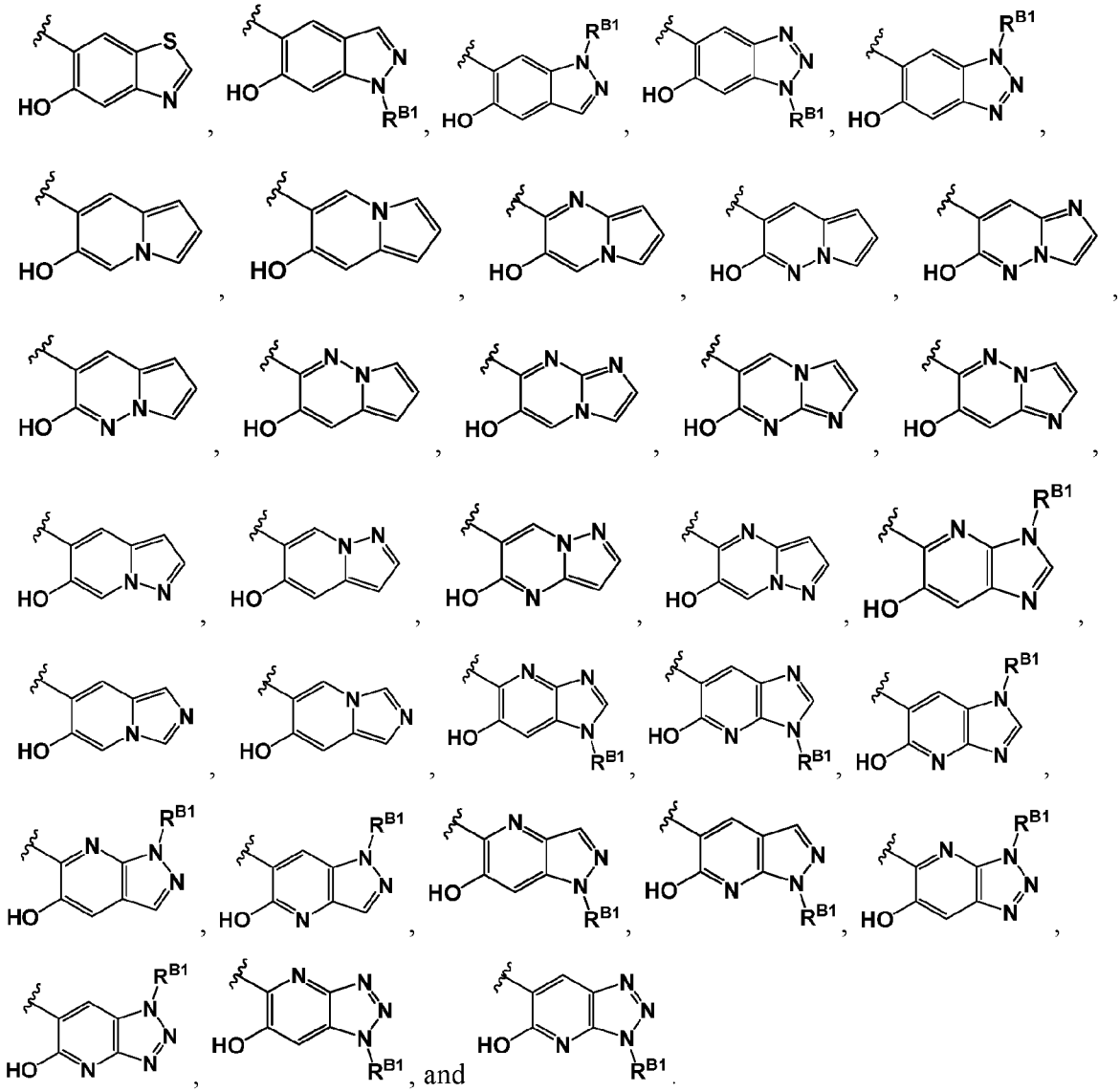
[0153] In some embodiments, ring Q is selected from the group consisting of:



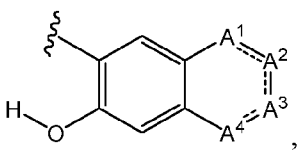
[0154] In some embodiments, ring Q is selected from the group consisting of:



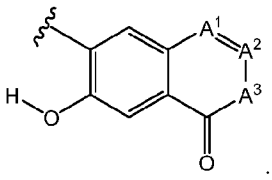
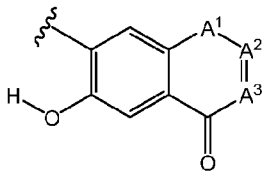
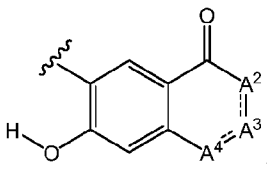
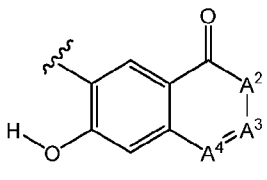
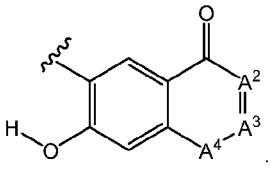
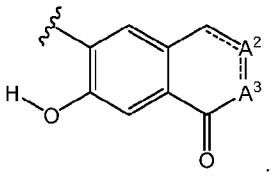
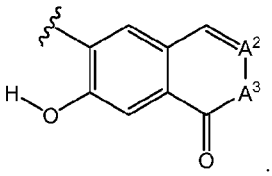
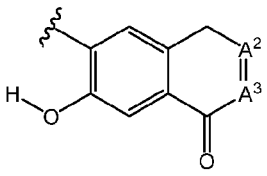
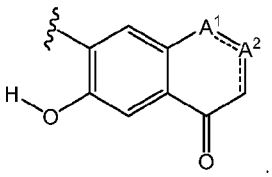
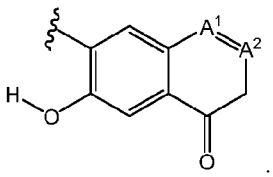
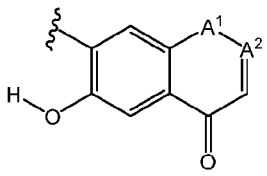
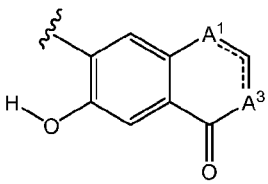
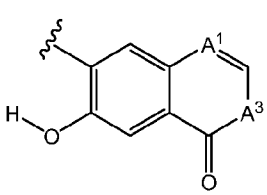
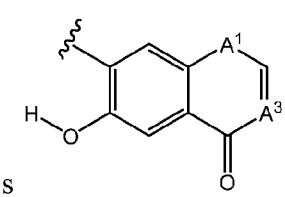
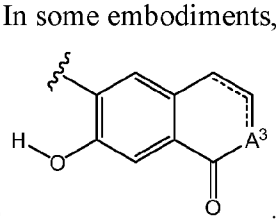
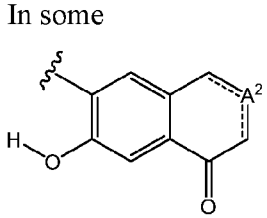


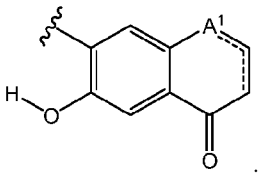
[0155] In some embodiments, R^{B1} is selected from hydrogen, deuterium, substituted or unsubstituted C_1-C_6 alkyl, -CD_3, substituted or unsubstituted C_1–C_6 fluoroalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_{3-7} cycloalkyl, and substituted or unsubstituted C_2–C_7 heterocycloalkyl.

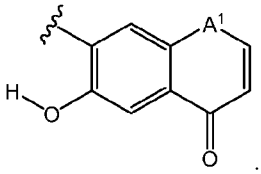
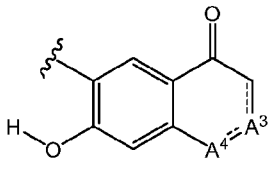
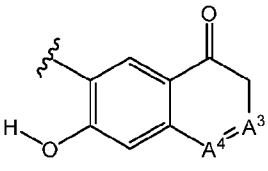
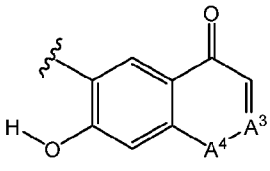
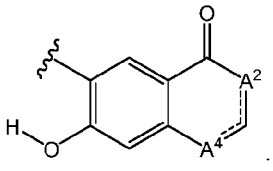
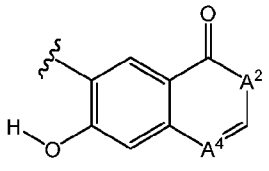
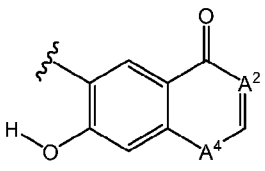
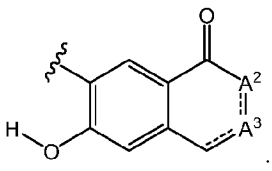
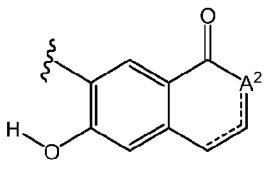
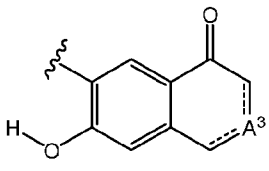
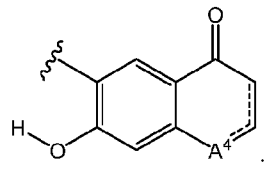
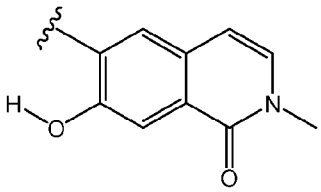
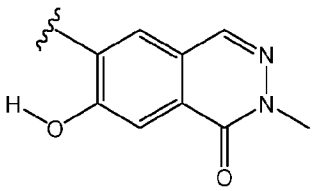
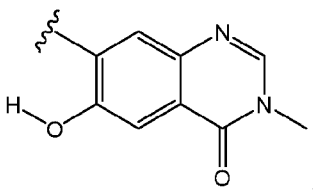
[0156] In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is:



, wherein each A^1, A^2, A^3, and A^4 is independently N, -NR^{Y1}-, -O-, -S-, or CR^{A1}; each R^{A1} is independently hydrogen, halogen =O, or substituted or unsubstituted C_1-C_6 alkyl; and each R^{Y1} is independently hydrogen or substituted or unsubstituted C_1–C_6 alkyl. In some

embodiments, each R^{A1} is H. In some embodiments, each R^{Y1} is H. In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  .



. In some embodiments, ring Q is . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  . In some embodiments, ring Q is  .

[0157] In some embodiments, A^1 is CH, CH_2, CF, CF_2, $C(CH_3)$, N, $N(CH_3)$, O, or C(=O). In some embodiments, A^1 is CH, CF, $C(CH_3)$, N, $N(CH_3)$, O, or C(=O). In some embodiments, A^1 is CH, CF, C(CH3), N, O, or C(=O). In some embodiments, A^1 is CH. In some embodiments, A^1 is CF. In some embodiments, A^1 is $C(CH_3)$. In some embodiments, A^1 is N. In some embodiments, A^1 is O. In some embodiments, A^1 is C(=O). In some embodiments, A^2 is CH, CH_2, $C(CH_3)$, N, $N(CH_3)$, or $C(CH_3)$. In some embodiments, A^2 is CH, $C(CH_3)$, N, $N(CH_3)$, or $C(CH_3)$. In some embodiments, A^2 is CH, $C(CH_3)$, N, or $C(CH_3)$. In some embodiments, A^2 is CH. In some embodiments, A^2 is $C(CH_3)$. In some embodiments, A^2 is N. In some embodiments, A^2 is $C(CH_3)$. In some embodiments, A^3 is CH, CH_2, $C(CH_3)$, N, $N(CH_3)$, or $C(CH_3)$. In some embodiments, A^3 is CH, $C(CH_3)$, N, $N(CH_3)$, or $C(CH_3)$. In some embodiments, A^3 is CH, $C(CH_3)$, N, or $C(CH_3)$. In some embodiments, A^3 is CH. In some embodiments, A^3 is $C(CH_3)$. In some embodiments, A^3 is N. In some embodiments, A^3 is $C(CH_3)$. In some embodiments, A^4 is CH, CH_2, $C(CH_3)$, N, $N(CH_3)$, O, or C(=O). In some embodiments, A^4 is CH, $C(CH_3)$, N, $N(CH_3)$, O, or C(=O). In some embodiments, A^4 is CH, $C(CH_3)$, N, O, or C(=O). In some embodiments, A^4 is CH. In some embodiments, A^4 is $C(CH_3)$. In some embodiments, A^4 is N. In some embodiments, A^4 is O. In some embodiments, A^4 is C(=O). In some embodiments, one of A^1 , A^2, A^3, and A^4 is C(=O).

[0158] In some embodiments, R is substituted or unsubstituted C_1–C_4 heteroalkyl. In some embodiments, R is C_1–C_4 heteroalkyl substituted by a t-butyl group. In some embodiments, R is *tert*-butyloxycarbonyl (BOC).

[0159] In some embodiments, ring Q is optionally substituted phenyl. In some embodiments, ring Q is optionally substituted naphthyl.

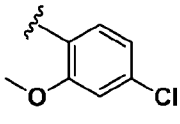
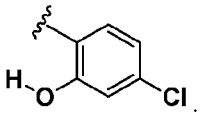
[0160] In some embodiments, ring Q is substituted or unsubstituted fused heteroaryl. In some embodiments, ring Q is substituted or unsubstituted 6-6 fused heteroaryl. In some embodiments, ring Q is substituted or unsubstituted 6-5 fused heteroaryl. In some embodiments, ring Q is substituted or unsubstituted 5-6 fused heteroaryl. In some embodiments, ring Q is substituted or unsubstituted 7-5 fused heteroaryl. In some embodiments, ring Q is substituted or unsubstituted 5-7 fused heteroaryl.

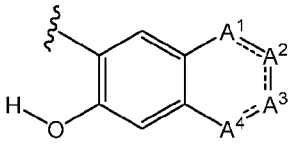
[0161] In some embodiments, ring Q is fully aromatic. In some embodiments, ring Q is partially unsaturated.

[0162] In some embodiments, ring Q is 2-OH phenyl substituted by a halogen, such as Cl.

[0163] In some embodiments, ring Q is optionally substituted heteroaryl. In some embodiments, ring Q is optionally substituted monocyclic heteroaryl. In some embodiments, ring Q is optionally substituted bicyclic heteroaryl. In some embodiments, ring Q is optionally substituted, fused 5-7, 5-6,

6-6, 6-5 or 7-5 heteroaryl. In some embodiments, ring Q is optionally substituted, fused 6-6 heteroaryl.

[0164] In some embodiments, ring Q is  . In some embodiments, ring Q is  .

[0165] In some embodiments of a compound of Formula (I), Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI), ring Q is:  , wherein each A^1, A^2, A^3, and A^4 is independently N, -NR^{Y1}-, -O-, -S-, -$S(=O)_2$-, $C(R^{A1})_2$ or CR^{A1}; each R^{A1} is independently hydrogen, halogen =O, or substituted or unsubstituted C_1-C_6 alkyl; and each R^{Y1} is independently hydrogen or substituted or unsubstituted C_1–C_6 alkyl.

[0166] In some embodiments, A^1 is CH, CH_2, CF, $C(CH_3)$, N, O, or C(=O). In some embodiments, A^1 is CH. In some embodiments, A^1 is CH_2. In some embodiments, A^1 is -$S(=O)_2$-. In some embodiments, A^1 is CF. In some embodiments, A^1 is $C(CH_3)$. In some embodiments, A^1 is N. In some embodiments, A^1 is O. In some embodiments, A^1 is C(=O). In some embodiments, A^1 is S. In some embodiments, A^1 is CR^{A1}. In some embodiments, A^1 is CR^{A1} and R^{A1} is H. In some embodiments, A^1 is CR^{A1} and R^{A1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{A1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{A1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{A1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{A1} are replaced by deuterium. In some embodiments, R^{A1} is H. In some embodiments, R^{A1} is methyl. In some embodiments, R^{A1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{A1} is CD_3 or CD_2CD_3. In some embodiments, R^{A1} is halogen. In some embodiments, R^{A1} is F. In some embodiments, A^1 is NR^{Y1}. In some embodiments, A^1 is NR^{Y1} and R^{Y1} is H. In some embodiments, A^1 is NR^{Y1} and R^{Y1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{Y1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{Y1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{Y1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{Y1} are replaced by deuterium. In some embodiments, R^{Y1} is H. In some embodiments, R^{Y1} is

methyl. In some embodiments, R^{Y1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{Y1} is CD_3 or CD_2CD_3.

[0167] In some embodiments, A^2 is CH, CH_2, $C(CH_3)$, N, or $C(CH_3)$. In some embodiments, A^2 is CH. In some embodiments, A^2 is CH_2. In some embodiments, A^2 is $C(CH_3)$. In some embodiments, A^2 is $-S(=O)_2-$. In some embodiments, A^2 is N. In some embodiments, A^2 is $C(CH_3)$. In some embodiments, A^2 is S. In some embodiments, A^2 is CR^{A1}. In some embodiments, A^2 is CR^{A1} and R^{A1} is H. In some embodiments, A^2 is CR^{A1} and R^{A1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{A1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{A1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{A1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{A1} are replaced by deuterium. In some embodiments, R^{A1} is H. In some embodiments, R^{A1} is methyl. In some embodiments, R^{A1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{A1} is CD_3 or CD_2CD_3. In some embodiments, R^{A1} is halogen. In some embodiments, R^{A1} is F. In some embodiments, A^2 is NR^{Y1}. In some embodiments, A^2 is NR^{Y1} and R^{Y1} is H. In some embodiments, A^2 is NR^{Y1} and R^{Y1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{Y1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{Y1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{Y1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{Y1} are replaced by deuterium. In some embodiments, R^{Y1} is H. In some embodiments, R^{Y1} is methyl. In some embodiments, R^{Y1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{Y1} is CD_3 or CD_2CD_3.

[0168] In some embodiments, A^3 is CH, CH_2, $C(CH_3)$, N, or $C(CH_3)$. In some embodiments, A^3 is CH. In some embodiments, A^3 is CH_2. In some embodiments, A^3 is $C(CH_3)$. In some embodiments, A^3 is $-S(=O)_2-$. In some embodiments, A^3 is N. In some embodiments, A^3 is $C(CH_3)$. In some embodiments, A^3 is S. In some embodiments, A^3 is CR^{A1}. In some embodiments, A^3 is CR^{A1} and R^{A1} is H. In some embodiments, A^3 is CR^{A1} and R^{A1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{A1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{A1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{A1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{A1} are replaced by deuterium. In some embodiments, R^{A1} is H. In some embodiments, R^{A1} is methyl. In some embodiments, R^{A1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{A1} is CD_3 or CD_2CD_3. In some embodiments, R^{A1} is halogen. In some embodiments, R^{A1} is F. In some embodiments, A^3 is NR^{Y1}. In some embodiments, A^3 is NR^{Y1} and R^{Y1} is H. In some embodiments, A^3 is NR^{Y1} and R^{Y1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments,

R^{Y1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{Y1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{Y1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{Y1} are replaced by deuterium. In some embodiments, R^{Y1} is H. In some embodiments, R^{Y1} is methyl. In some embodiments, R^{Y1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{Y1} is CD_3 or CD_2CD_3. In some embodiments, A^3 is $N(CH_3)$.

[0169] In some embodiments, A^4 is CH, CH_2, $C(CH_3)$, N, O, or C(=O). In some embodiments, A^4 is CH. In some embodiments, A^4 is CH_2. In some embodiments, A^4 is $C(CH_3)$. In some embodiments, A^4 is $-S(=O)_2-$. In some embodiments, A^4 is N. In some embodiments, A^4 is O. In some embodiments, A^4 is C(=O). In some embodiments, A^4 is S. In some embodiments, A^4 is CR^{A1}. In some embodiments, A^4 is CR^{A1} and R^{A1} is H. In some embodiments, A^4 is CR^{A1} and R^{A1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{A1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{A1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{A1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{A1} are replaced by deuterium. In some embodiments, R^{A1} is H. In some embodiments, R^{A1} is methyl. In some embodiments, R^{A1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{A1} is CD_3 or CD_2CD_3. In some embodiments, R^{A1} is halogen. In some embodiments, R^{A1} is F. In some embodiments, A^4 is NR^{Y1}. In some embodiments, A^4 is NR^{Y1} and R^{Y1} is H. In some embodiments, A^4 is NR^{Y1} and R^{Y1} is substituted or unsubstituted C_1–C_6 alkyl. In some embodiments, R^{Y1} is C_1–C_6 alkyl that is optionally substituted with one or more halogen (such as F). In some embodiments, R^{Y1} is optionally substituted C_1–C_3 alkyl. In some embodiments, R^{Y1} is C_1–C_3 alkyl that is optionally substituted with one or more F. In some embodiments, one or more hydrogens in R^{Y1} are replaced by deuterium. In some embodiments, R^{Y1} is H. In some embodiments, R^{Y1} is methyl. In some embodiments, R^{Y1} is methyl, ethyl, CF_3, CHF_2, or CH_2CF_3. In some embodiments, R^{Y1} is CD_3 or CD_2CD_3.

[0170] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa')In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), W is substituted or unsubstituted C_1-C_3 alkylene. In some embodiments, W is $–CH_2–$. In some embodiments, W is $–CH_2CH_2–$. In some embodiments, W is $–CH_2CH_2CH_2–$. In some embodiments, W is substituted or unsubstituted C_1-C_2 heteroalkylene. In some embodiments, W is $–CH_2OCH_2–$. In some embodiments, W is $–CH_2O–$, wherein oxygen atom in W is attached to a carbon atom having R^{18} group. In some embodiments, W is substituted or unsubstituted C_3–C_8 cycloalkylene or substituted or unsubstituted C_2-C_3 alkenylene. In some

embodiments, W is substituted or unsubstituted C_3–C_8 cycloalkylene. In some embodiments, W is substituted or unsubstituted cyclopropylene. In some embodiments, W is substituted or unsubstituted C_2-C_3 alkenylene. In some embodiments, W is -CH=CH-.

[0171] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), R is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_5 cycloalkyl, or substituted or unsubstituted C_2–C_4 heterocycloalkyl. In some embodiments, R is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-C(OH)(CH_3)_2$, $-CH_2CN$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl, cyclobutyl, oxetanyl, aziridinyl, or azetidinyl. In some embodiments, R is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl, or oxetanyl. In some embodiments, R is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl, or oxetanyl. In some embodiments, R is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, cyclopropyl, or oxetanyl. In some embodiments, R is hydrogen, $-CH_3$, $-CH_2OH$, $-CH_2CN$, $-CHF_2$, $-CF_3$, or cyclopropyl. In some embodiments, R is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl, or oxetanyl. In some embodiments, R is $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, R is hydrogen.

[0172] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{15} and R^{18} are selected from hydrogen, deuterium, F, $-OR^{31}$, substituted or unsubstituted C_1–C_3 alkyl, substituted or unsubstituted C_1–C_3 fluoroalkyl, and substituted or unsubstituted C_1–C_3 heteroalkyl. In some embodiments, R^{15} and R^{18} are selected from hydrogen, deuterium, F, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In one embodiment, R^{15} and R^{18} are selected from hydrogen, deuterium, F, $-CH_3$, $-CH_2OH$, $-OCH_2CN$, -OH, $-OCH_3$, $-OCH_2CN$, $-OCF_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In some embodiments, R^{15} and R^{18} are selected from hydrogen, deuterium, F, $-CH_3$, $-OCH_3$, $-OCF_3$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In some embodiments, R^{15} and R^{18} are selected from hydrogen, deuterium, F, $-CH_3$, and $-OCH_3$. In some embodiments, R^{15} is F and R^{18} is hydrogen. In some embodiments, R^{15} is hydrogen and R^{18} is F. In some embodiments, R^{15} is hydrogen and R^{18} is CH_3. In some embodiments, R^{15} is CH_3 and R^{18} is hydrogen. In some embodiments, R^{15} and R^{18} are the same. In some embodiments, R^{15} and R^{18} are different.

[0173] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} is F. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} is F. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are F. In some embodiments, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} is F. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, and R^{17} is F. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, and R^{17} are F.

[0174] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{11} is H, D, or F. In some embodiments, R^{11} is D. In some embodiments, R^{11} is H. In some embodiments, R^{11} is F.

[0175] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{12} is H, D, or F. In some embodiments, R^{12} is D. In some embodiments, R^{12} is H. In some embodiments, R^{12} is F.

[0176] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{13} is H, D, or F. In some embodiments, R^{13} is D. In some embodiments, R^{13} is H. In some embodiments, R^{13} is F.

[0177] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{14} is H, D, or F. In some embodiments, R^{14} is D. In some embodiments, R^{14} is H. In some embodiments, R^{14} is F.

[0178] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{15} is H, D, F, CH_2F, CHF_2, CF_3, or CH_3. In some embodiments, R^{15} is H or D. In some embodiments, R^{15} is F, CH_2F, CHF_2, CF_3, or CH_3. In some embodiments, R^{15} is F, CF_3, CHF_2, or CH_2F. In some embodiments, R^{15} is F.

[0179] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{16} is H, D, or F. In some embodiments, R^{16} is D. In In some embodiments, R^{16} is H. some embodiments, R^{16} is F.

[0180] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{17} is H, D, or F. In some embodiments, R^{17} is D. In some embodiments, R^{17} is H. In some embodiments, R^{17} is F.

[0181] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{18} is H, D, F, CH_2F, CHF_2, CF_3, or CH_3. In some embodiments, R^{18} is H or D. In some embodiments, R^{18} is F, CH_2F, CHF_2, CF_3, or CH_3. In some embodiments, R^{18} is F, CF_3, CHF_2, or CH_2F. In some embodiments, R^{18} is F.

[0182] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} comprises a fluorine, e.g., F or C_1–C_4 fluoroalkyl such as CH_2F, CF_3, CHF_2, and CH_3CH_2F. In some embodiments, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is F or C_1–C_4 fluoroalkyl. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} comprises a fluorine. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} comprise a fluorine. In some embodiments, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, and R^{17} comprises a fluorine. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, and R^{17} comprises a fluorine. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, and R^{17} comprise a fluorine.

~~**[0183]**~~ In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, at least one of W, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} comprises a fluorine, e.g., F or C_1–C_4 fluoroalkyl such as CH_2F, CF_3, CHF_2, and CH_3CH_2F. In some embodiments, one of W, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} comprises a fluorine. In some embodiments, W comprises a fluorine.

[0184] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{11}, R^{12}, R^{19}, R^{20} and R^{16} are hydrogen.

[0185] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{19} is hydrogen. In some embodiments, R^{19} is H, F, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$. In some

embodiments, R^{19} is H, F, -OH, $-OCH_3$, $-OCF_3$, $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In some embodiments, R^{19} is F or $-OCH_3$.

[0186] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{20} is hydrogen. In some embodiments, R^{20} is H, F, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$. In some embodiments, R^{20} is H, F, -OH, $-OCH_3$, $-OCF_3$, $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In some embodiments, R^{20} is F or $-OCH_3$.

[0187] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{20} is H, D, or F. In some embodiments, R^{20} is D. In some embodiments, R^{20} is H. In some embodiments, R^{20} is F.

[0188] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{16} and R^{19} are H. In some embodiments, R^{16} and R^{19} are D. In some embodiments, R^{16} and R^{19} are F.

[0189] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{19} and R^{20} are H. In some embodiments, R^{19} and R^{20} are D. In some embodiments, R^{19} and R^{20} are F.

[0190] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{17} and R^{20} are H. In some embodiments, R^{17} and R^{20} are D. In some embodiments, R^{17} and R^{20} are F.

[0191] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{11}, R^{12}, R^{19}, R^{20} and R^{16} are hydrogen.

[0192] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{19} is hydrogen. In some embodiments, R^{19} is H, F, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$. In some

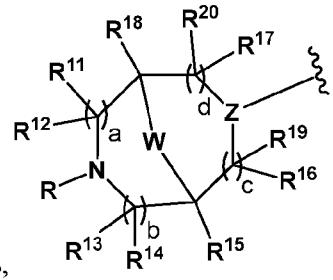
embodiments, R^{19} is H, F, -OH, $-OCH_3$, $-OCF_3$, $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In some embodiments, R^{19} is F or $-OCH_3$.

[0193] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, R^{20} is hydrogen. In some embodiments, R^{20} is H, F, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$. In some embodiments, R^{20} is H, F, -OH, $-OCH_3$, $-OCF_3$, $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$. In some embodiments, R^{20} is F or $-OCH_3$.

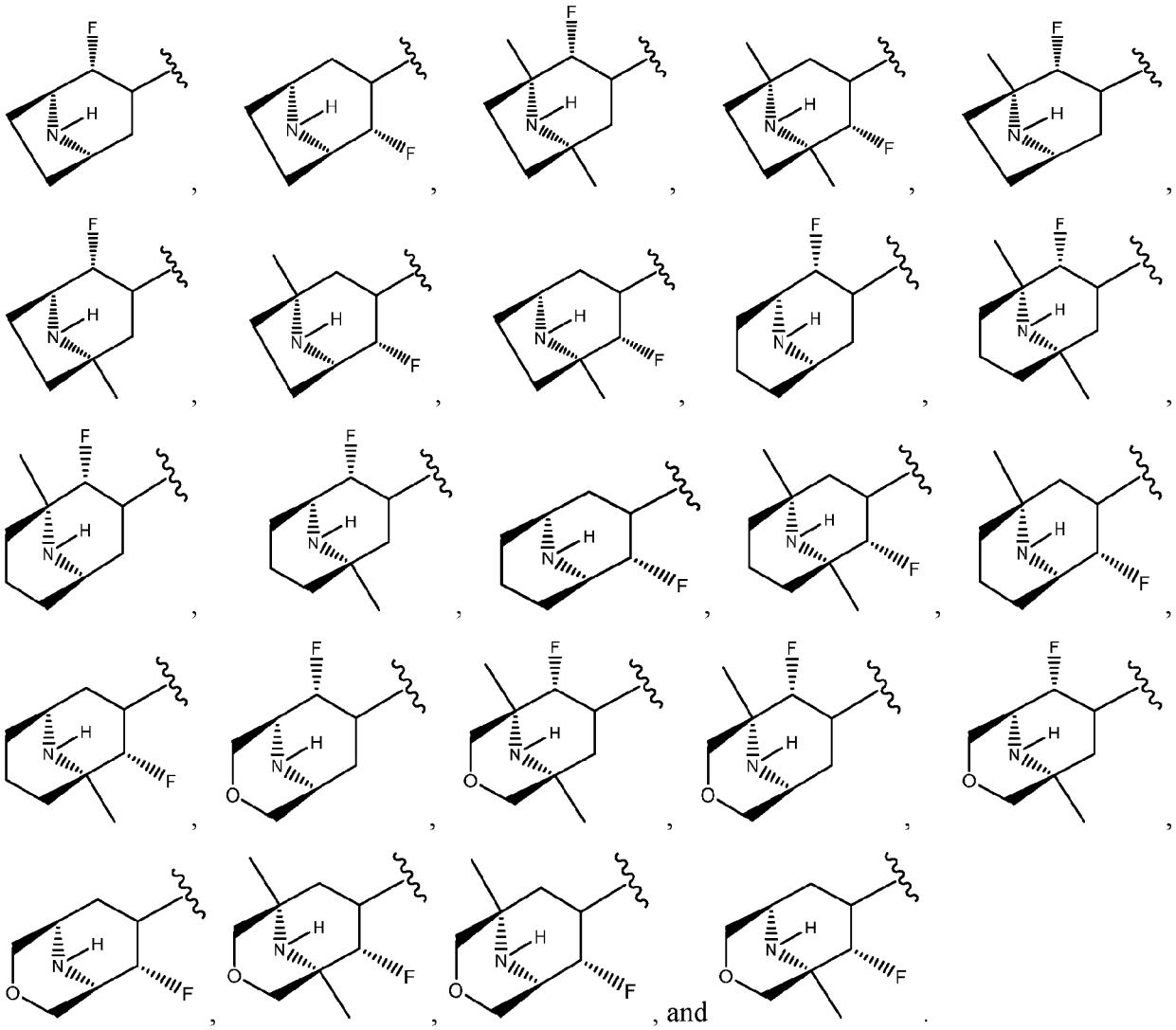
[0194] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} is F. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} is F. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} are F. In some embodiments, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{19}, R^{20}, and R^{17} is F. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{19}, R^{20}, and R^{17} is F. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{19}, R^{20}, and R^{17} are F.

[0195] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} comprises a fluorine, e.g., F or C_1–C_4 fluoroalkyl such as CH_2F, CF_3, CHF_2, and CH_3CH_2F. In some embodiments, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} is F or C_1–C_4 fluoroalkyl. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} comprises a fluorine. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} comprise a fluorine. In some embodiments, at least one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{19}, R^{20}, and R^{17} comprises a fluorine. In some embodiments, one of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{19}, R^{20}, and R^{17} comprises a fluorine. In some embodiments, at least two of R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, and R^{17} comprise a fluorine.

[0196] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof, at least one of W, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} comprises a fluorine, e.g., F or C_1–C_4 fluoroalkyl such as CH_2F, CF_3, CHF_2, and CH_3CH_2F. In some embodiments, one of W, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, and R^{18} comprises a fluorine. In some embodiments, W comprises a fluorine.



[0197] In some embodiments, is selected from the group consisting of



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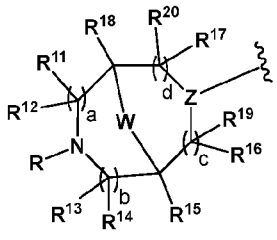
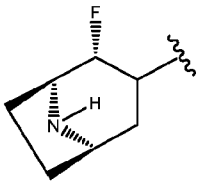


[0198] In some embodiments, is selected from the group consisting of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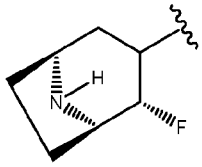
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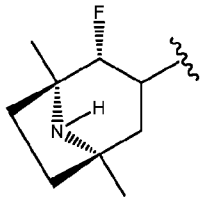
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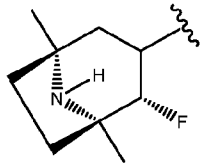
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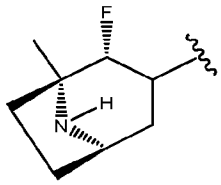
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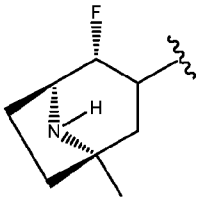
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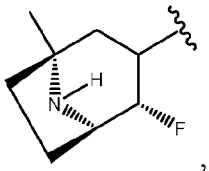
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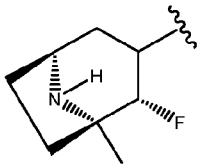
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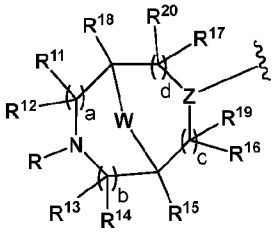
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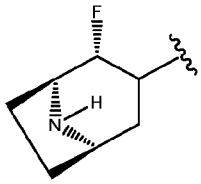
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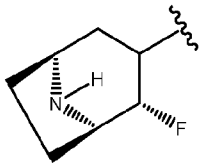
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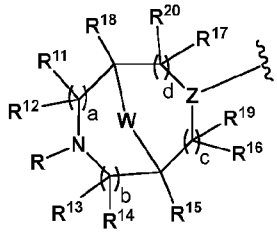

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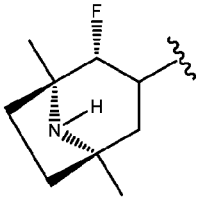
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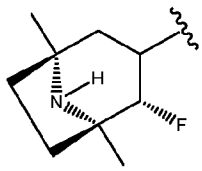
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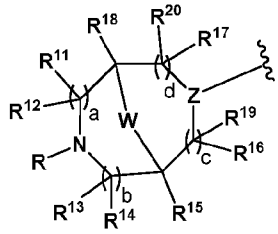
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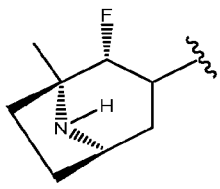
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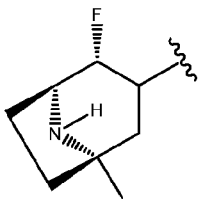
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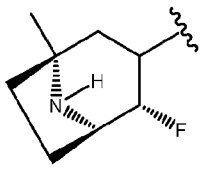
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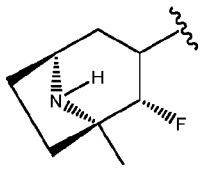
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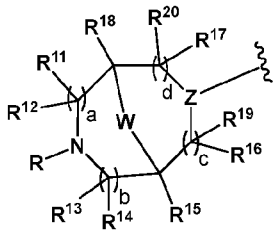

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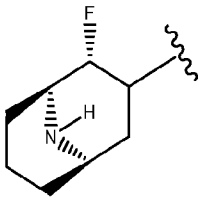
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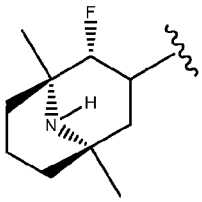
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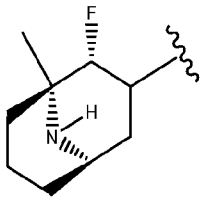
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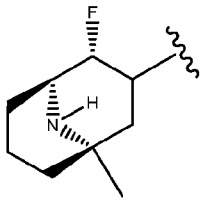
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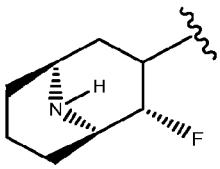
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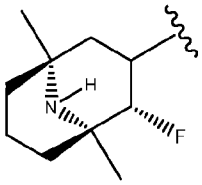
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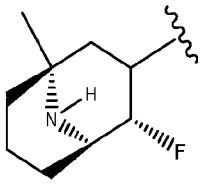
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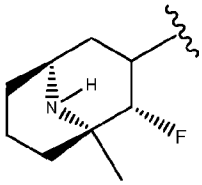
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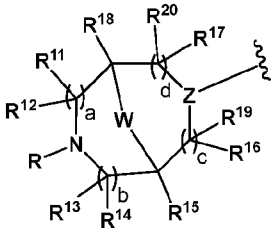
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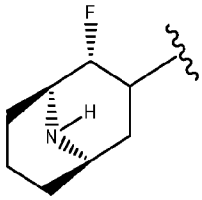
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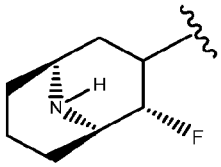
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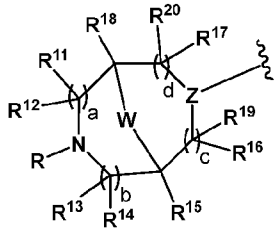
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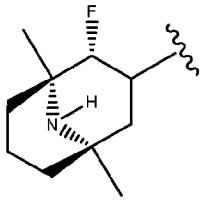
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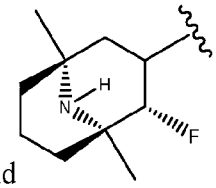
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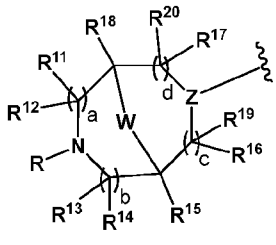
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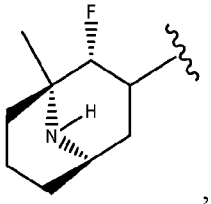
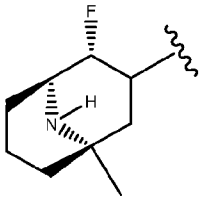
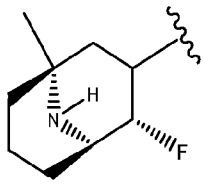
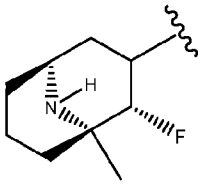
selected from the group consisting of  ,  ,  , and  .

[0200] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is absent.

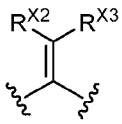
[0201] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is -O-.

[0202] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is -S-.

[0203] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is -C(=O)-.

[0204] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is $-NR^{X1}-$. In some embodiments, X is N-C_1-C_6 alkyl. In some embodiments, X is N-methyl. In some embodiments, X is N-C_1-C_6 cycloalkyl. In some embodiments, X is N-cyclopropyl.

[0205] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is $-CR^{X2}R^{X3}-$.

[0206] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is  .

[0207] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), X is or $=CR^{X1}-$.

[0208] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), Z is N.

[0209] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), Z is C.

[0210] In some embodiments of a compound of Formula (I), Formula (I'), Formula (I''), Formula (II), Formula (II'), Formula (II''), Formula (II*), or Formula (IIa'), Z is CR^5. In some embodiments, Z is CH.

[0211] In some embodiments, each R^{31} is independently hydrogen, deuterium, substituted or unsubstituted C_1–C_4 alkyl, $-CD_3$, or substituted or unsubstituted C_1–C_4 haloalkyl. In some embodiments, each R^{31} is independently hydrogen, deuterium, or C_1–C_4 alkyl. In some embodiments, each R^{31} is independently hydrogen, deuterium, or methyl. In some embodiments, R^{31} is H. In some embodiments, R^{31} is methyl.

[0212] In some embodiments, R1 is H. In some embodiments, R1 is halogen. In some embodiments, R1 is OH. In some embodiments, R1 is $–OR^{31}$. In some embodiments, R1 is CN. In some embodiments, R1 is substituted or unsubstituted alkyl. In some embodiments, R1 is substituted or unsubstituted haloalkyl. In some embodiments, R1 is substituted or unsubstituted heteroalkyl. In some embodiments, R1 is $–SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, $-NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, or $-P(=O)R^{31}R^{32}$.

[0213] In some embodiments, R1 is substituted or unsubstituted monocyclic aryl, substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted monocyclic cycloalkyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R1 is substituted or unsubstituted polycyclic aryl, substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic cycloalkyl, or substituted or unsubstituted polycyclic heteroaryl. In some embodiments, R1 is a fused ring. In some embodiments, R1 is a bridged ring. In some embodiments, R1 is a spiro ring.

[0214] In some embodiments, R2 is H. In some embodiments, R2 is halogen. In some embodiments, R2 is OH. In some embodiments, R2 is $–OR^{31}$. In some embodiments, R2 is CN. In some embodiments, R2 is substituted or unsubstituted alkyl. In some embodiments, R2 is substituted or unsubstituted haloalkyl. In some embodiments, R2 is substituted or unsubstituted heteroalkyl. In some embodiments, R2 is $–SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, $-NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, or $-P(=O)R^{31}R^{32}$.

[0215] In some embodiments, R2 is substituted or unsubstituted monocyclic aryl, substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted monocyclic cycloalkyl, or substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R2 is substituted or unsubstituted polycyclic aryl, substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic cycloalkyl, or substituted or unsubstituted polycyclic heteroaryl. In some

embodiments, R2 is a fused ring. In some embodiments, R2 is a bridged ring. In some embodiments, R2 is a spiro ring.

[0216] In some embodiments, a compound described herein, possesses one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In one aspect, stereoisomers are obtained by stereoselective synthesis.

EXAMPLES

[0217] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein. Compounds described herein can be synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology can be employed. Compounds can be prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions. The starting materials and reagents used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Acros Organics, Fluka, and Fischer Scientific. The starting materials can be available from commercial sources or can be readily prepared. By way of example only, provided are schemes for preparing the Examples described herein.

[0218] The following abbreviations are used: DCM – dichloromethane; DIPEA – N,N-diisopropylethylamine; DMSO - dimethyl sulfoxide; DMF - N,N-dimethylformamide; EDCI - N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide; Et2O - diethyl ether; EtOAc - ethyl acetate; EtOH - ethyl alcohol; HOBt – 1-hydroxybenzotriazole; LCMS – liquid chromatography mass spectrometer; MeCN – acetonitrile; MeOH - methyl alcohol; Ms – mesylate; MTBE – methyl tert-butyl ether; Selectfluor - 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); SFC - supercritical fluid chromatography; THFtetrahydrofuran; TMSCl – trimethylsilyl chloride; h – hour; min – minute; rt - room temperature (22-25 °C); g – grams; mL - milliliters; mg – milligrams; mmol – millimoles.

[0219] Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3 527–29074–5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0–19–509618–5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley–VCH, ISBN: 0–471–19031–4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0–471–60180–2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley–VCH, ISBN: 3–527–29871–1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0–471–93022–9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0–471–19095–0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley–Interscience, ISBN: 0–471–57456–2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3–527–29645–X, in 8 volumes; "Organic Reactions" (1942–2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[0220] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, in order to avoid their unwanted participation in reactions. A detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure).

Stereochemistry:

[0221] (±) or racemic indicates that the product is a racemic mixture of enantiomers. For example (±) (1*S*,2*S*,3*R*,5*R*) or racemic (1*S*,2*S*,3*R*,5*R*) indicates that the relative product stereochemistry shown is based on known stereochemistry of similar compounds and or reactions and the product is a racemic mixture of enantiomers of both (1*S*,2*S*,3*R*,5*R*) and (1*R*,2*R*,3*S*,5*S*) stereoisomers. A compound in which the absolute stereochemistry of separated enantiomers is undetermined is represented as being either of the single enantiomers, for example (1*S*,2*S*,3*R*,5*R*) or (1*R*,2*R*,3*S*,5*S*) or drawn as being either possible single enantiomer. In such cases, the product is pure and a single enantiomer, but absolute stereochemistry is not identified, but relative stereochemistry is known and indicated.

[0222] Example 1: Preparation of tert-butyl (1S,2R,3R,5R)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl)pyrazin-2-yl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0223] Step 1: Preparation of tert-butyl (1S,2R,3R,5R)-2-fluoro-3-((5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0224] To a stirred mixture of 2-bromo-5-(methylthio)pyrazine (1 g, 4.876 mmol) and tert-butyl (1S,2R,3R,5R)-3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (1.31 g, 5.364 mmol) in dimethyl sulfoxide (10 mL) was added N,N-diisopropylethylamine (2.52 g, 19.504 mmol) dropwise at room temperature under nitrogen. The resulting mixture was placed in a preheated oil bath and was stirred for 24 hours at 120°C then removed from heat, allowed to cool to room temperature and quenched with water/ice. The resulting mixture was extracted with ethyl acetate (3x60 mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, (ethyl acetate/petroleum ether: 1:3) which gave after isolation tert-butyl (1S,2R,3R,5R)-2-fluoro-3-((5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (340 mg, 18.92%) as a yellow solid, $[M\text{-}tBu+H]^+ = 313.1$.

[0225] Step 2: Preparation of tert-butyl (1S,2R,3R,5R)-2-fluoro-3-(methyl(5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0226] To a stirred mixture of tert-butyl (1S,2R,3R,5R)-2-fluoro-3-((5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (340 mg, 0.923 mmol) in dimethylformamide (4 mL) at 0°C under dry nitrogen was added portion-wise sodium hydride (44.28 mg, 1.108 mmol). The resulting mixture was stirred for 20 min at 0°C followed by the addition of methyl iodide (157.17 mg, 1.108 mmol) dropwise at 0°C. The cooling bath was removed, and the mixture was stirred for additional 1 hour at room temperature. The reaction was then cooled to 0°C and carefully quenched with water/ice. The resulting mixture was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with brine (2x40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether: 1:4) which gave after isolation tert-butyl (1S,2R,3R,5R)-2-fluoro-3-(methyl(5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (240 mg) as a yellow solid.

[0227] Step 3A: Preparation of tert-butyl (1S,2R,3R,5R)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl) pyrazin-2-yl)(methyl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate.

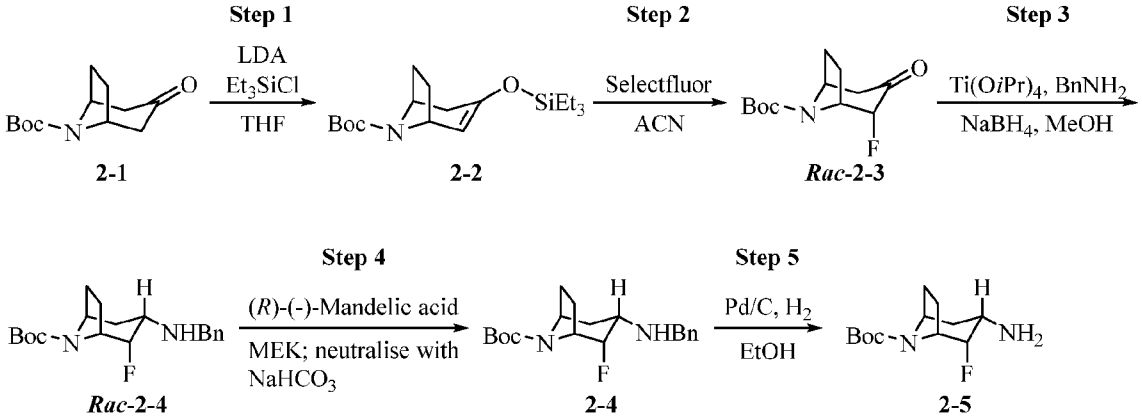
[0228] To a solution of tert-butyl (1S,2R,3R,5R)-2-fluoro-3-(methyl(5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.261 mmol) and 4-chloro-2-(methoxymethoxy)phenylboronic acid (169.74 mg, 0.783 mmol) in tetrahydrofuran (2.5 mL) under dry nitrogen was added copper(I)-3-methylsalicylate (168.39 mg, 0.783 mmol) and tetrakis(triphenylphosphine)palladium(0) (45.32 mg, 0.039 mmol). The resulting mixture was placed in a preheated oil bath and was stirred for 2 hours at 70°C then removed from heat, allowed to cool to room temperature under nitrogen. The desired product, tert-butyl (1S,2R,3R,5R)-3-((5-(4-chloro-2-(methoxymethoxy) phenyl)pyrazin-2-yl)(methyl)amino)-2-fluoro-8-azabicyclo[3.2.1] octane-8-carboxylate was observed by LCMS, $[M+H]^+ = 506.9$.

[0229] Step 3B: Preparation of tert-butyl (1S,2R,3R,5R)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl)pyrazin-2-yl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0230] To a solution of tert-butyl (1S,2R,3R,5R)-2-fluoro-3-(methyl(5-(methylthio)pyrazin-2-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.136 mmol) and 4-chloro-2-(methoxymethoxy)phenylboronic acid (88.10 mg, 0.408 mmol, 3.00) in tetrahydrofuran (1.5 mL) under dry nitrogen was added copper(I)-3-methylsalicylate (87.40 mg, 0.408 mmol, 3) and tetrakis(triphenylphosphine)palladium(0) (23.52 mg, 0.020 mmol, 0.15). The resulting mixture was

placed in a preheated oil bath and was stirred for 2 hours at 70°C then removed from heat, allowed to cool to room temperature under nitrogen. The desired product, tert-butyl (1S,2R,3R,5R)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl)pyrazin-2-yl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate was observed by LCMS, $[M+H]^+ = 492.9$.

[0231] Example 2: Synthesis of (1*R*,2*S*,3*S*,5*S*)-*tert*-Butyl 3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate.



[0232] Step 1: ***tert*-Butyl 3-((triethylsilyl)oxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (2-2).**

[0233] To a stirred solution of lithium diisopropylamide (15.0 L, 29.83 moles) in THF (14.4 L) at – 78 °C was added **2-1** (4.20 Kg, 21.30 moles) in THF (9.6 L) slowly over a period of 1 h keeping the temperature below -70 °C. The reaction mixture was stirred for 30 minutes at -78 °C (became deep yellow), triethylchlorosilane (3.53 Kg, 23.44 moles) was added for 15 minutes and the reaction mixture was stirred 10 minutes at -78 °C. The reaction mixture was allowed to warm to -15 °C to -10 °C and stirred for 2 h. After consumption of starting material by TLC, the reaction mass was quenched by adding 10% sodium bicarbonate solution (33.6 L) at 0 °C to 5 °C and extracted with MTBE (3 x 19.2 L) at room temperature. The combined organic extracts were washed with brine (26.4 L), dried over sodium sulphate, filtered and concentrated in vacuum to afford **2-2** (7.2 Kg, crude) as an orange oil which was used in the next step without further purification.

[0234] Step 2: *tert*-Butyl 2-fluoro-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (*Rac*-2-3).

[0235] To a solution of selectfluor (9.0 Kg, 25.44 moles) in acetonitrile (100 L) was added **2-2** (7.2 Kg, 21.20 moles) in acetonitrile (14.4 L) at -30 °C for 30 minutes under nitrogen. The reaction mixture was slowly warmed to 10 °C over a period of 1 h 30 minutes. After consumption of starting material by TLC, the reaction mixture was quenched by adding water (93.6 L) at 10 °C. The reaction mass was extracted with MTBE (3 x 28.8 L), and the combined organic extracts were washed with brine (2 x 36 L), dried over sodium sulphate and concentrated in vacuum to afford 4.5 Kg (crude) of **2-3**. This crude product was dissolved in petroleum ether (50.4 L), heated to 60 °C and stirred for 10

min. Undissolved solids were removed by filtration and the filtrate was concentrated to 2 volumes and stirred for 30 minutes at room temperature. Solids were collected by filtration and dried to obtain 3.8 Kg of crude **2-3**. The crude **2-3** was dissolved in acetonitrile (7.6 L) and water (22.8 L) was slowly added over 30 minutes and the precipitated solid was stirred for 2 h. This solid was filltered and dried to obtain *Rac*-**2-3** (3.2 Kg, 62%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 – 4.32 (m, 3H), 3.11 – 3.08 (m, 1H), 2.37-2.31 (m, 1H), 2.13 – 1.97 (m, 2H), 1.66 – 1.25 (m, 11H); Mass (*m/z*): 144 (M+H-Boc).

[0236] Step 3: *tert*-Butyl 3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (*Rac*-2-4).

[0237] To a stirred solution of *Rac*-**2-3** (1.3 Kg, 5.34 moles) in methanol (7.8 L) was added benzyl amine (0.63 Kg, 5.878 moles) at 0 °C for 30 minutes followed by titanium(IV) propan-2-olate (2.58 Kg, 9.080 moles) for 15 minutes. The reaction mixture was stirred at room temperature for 2 h, diluted with methanol (7.8 L), cooled to -15 °C and then sodiumborohydride (0.35 kg, 9.08 moles) was added portion wise. The reaction mixture was stirred for 30 minutes at 0 °C. After consumption of starting material by TLC, the reaction mixture was quenched by adding of 1N sodium hydroxide solution (16.9 L), diluted with toluene (13.0 L) and stirred vigorously for 30 minutes. The reaction mass was filtered through a celite pad and washed with toluene (6.5 L). Phases were separated and the aqueous layer was extracted with toluene (2 x 3.25 L). The combined organic extracts were washed with brine (6.5 L), dried over sodium sulphate, filtered and concentrated in vacuum to obtain *Rac*-**2-4** (1.7 Kg, 95%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.22 (m, 5H), 4.67 – 4.30 (m, 3H), 3.89 – 3.77 (m, 2H), 2.91-2.79 (m, 1H), 1.92 – 1.79 (m, 3H), 1.61 – 1.51 (m, 1H), 1.45 (s, 9H); Mass (*m/z*): 335 (M+H).

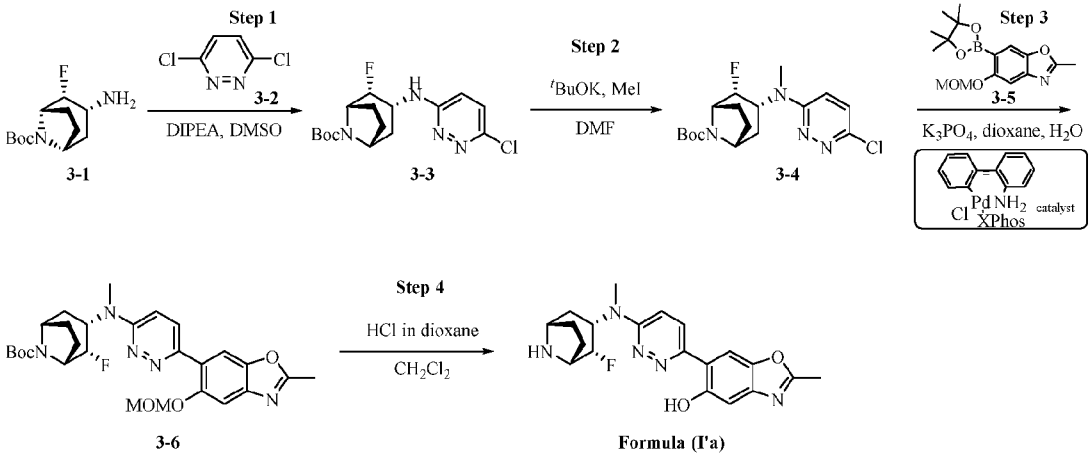
[0238] Step 4: (1*R*,2*S*,3*S*,5*S*)-*tert*-Butyl-3-(benzylamino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (2-4).

[0239] To a solution of Rac-**2-4** (1.0 Kg, 2.990 moles, 50% ee) in methyl ethyl ketone (12.0 L) was added *(R)-(-)*-mandelic acid (0.227 Kg, 1.495 moles) in methyl ethyl ketone (3.0 L) slowly over a period of 1 h at room temperature. The reaction mixture was heated to 60 °C, stirred for 3 h, cooled to room temperature and stirred for 18 h. The precipitated solid was filtered, washed with methyl ethyl ketone (1.0 L) and dried to obtain 0.45 Kg of salt. The salt was neutralised with sat $NaHCO_3$ solution and extracted with ethyl acetate (2 x 400 mL). The combined organic extracts were dried over sodium sulphate and concentrated under vacuum to obtain **2-4** (0.315 Kg, 88% chiral purity) as an off-white solid. The chiral resolution and free basing steps were repeated in an identical manner to provide the desired compound **4** as an off-white solid (0.225 kg, 98% chiral purity, 22.5%).

[0240] Step 5: (1*R*,2*S*,3*S*,5*S*)-*tert*-Butyl 3-amino-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (2-5).

[0241] To a solution of **2-4** (225.0 g, 1.524 moles) in ethanol (675 mL) was added 10% Pd/C (45.0 g) and the reaction mixture was stirred for 18 h under hydrogen atmosphere. After consumption of starting material by TLC, the reaction mixture was purged with nitrogen and filtered over celite, washing the celite pad with ethanol (1.0 L). Concentration in vacuo afforded **2-5** (157.1 g, 95%) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.40 – 4.28 (m, 2H), 4.06 (bs, 1H), 2.94 – 2.85 (m, 1H), 1.78 – 1.76 (m, 2H), 1.56 – 1.44 (m, 6H), 1.43 (s, 9H); ^{19}F NMR (500 MHz, DMSO-d_6): δ 199.2; Mass (*m/z*): 245.2 (M+H); GC purity: 98.03%.

[0242] Example 3: Synthesis of 6-(6-(((1*R*,2*R*,3*S*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-2-methylbenzo[d]oxazol-5-ol (Formula (I'a)).



[0243] Step 1: Synthesis of *tert*-Butyl 3-((6-chloropyridazin-3-yl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (3-3).

[0244] DIPEA (26.46 g, 2.5 eq) was added to a solution of 3,6-dichloropyridazine (14.6 g, 1.2 eq) and racemic-**3-1** (20.0 g, 81.9 mmol) in DMSO (200 mL) at RT. The mixture was stirred at 120 °C for about 24 h. After completion of the reaction (by TLC), the mixture was cooled to room temperature and quenched with H_2O (500 mL) and extracted with dichloromethane (3 x 200 mL). The combined organic extracts were concentrated to obtain a solid, which was triturated with EtOAc to yield **3-3** (15 g, 51 % yield) as a pale yellow solid.

[0245] Step 2: Synthesis of *tert*-butyl 3-((6-chloropyridazin-3-yl)(methyl)amino)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (3-4).

[0246] Potassium *t*-butoxide (4.74 g, 3.0 eq) was added to a stirred solution of **3-3** (5.0 g, 14.06 mmol) in 75 mL of DMF at 10 °C. After stirring for 1 h at 25 °C, methyl iodide (4.5 mL, 5.0 eq) was added to the mixture at 10 °C. The reaction was stirred at room temperature for 5 h, quenched with

75 mL of water to provide a solid. The solid was collected by filtration and dried in vacuo to provide **3-4** (4.2 g, 80% yield) as an off-white solid.

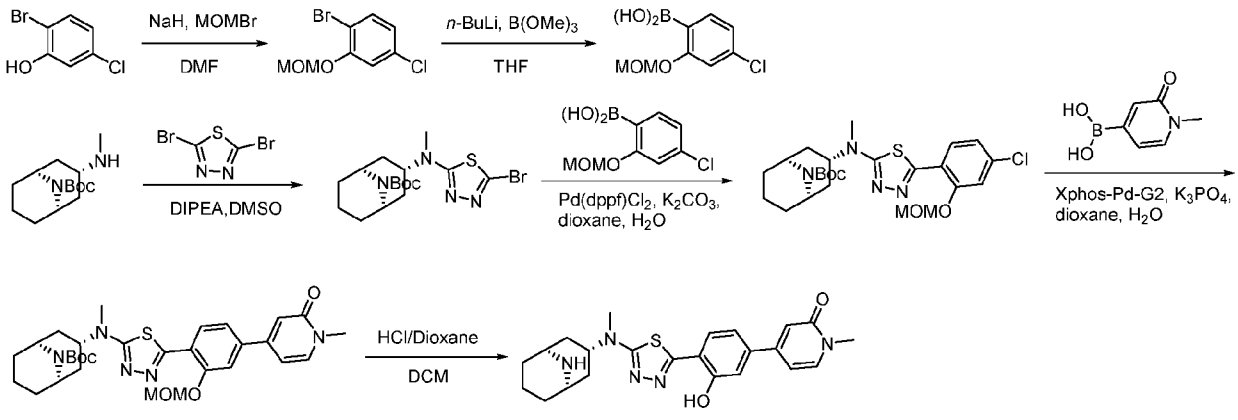
[0247] Step 3: Synthesis of *(1R,2S,3S,5S)*-*tert*-butyl 2-fluoro-3-((6-(5-(methoxymethoxy)-2-methylbenzo[*d*]oxazol-6-yl)pyridazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (3-6).

[0248] A mixture of **3-4** (13.0 g, 35.12 mmol), **3-5** (22.4 g, 2.0 eq) and K_3PO_4 (59.88 g, 8 eq) in 1,4-dioxane (292.0 mL) and water (98.0 mL) was degassed with nitrogen and Pd-X-Phos-G_2 (2.62 g, 0.1 eq) was added to reaction mixture. The resulting mixture was heated to 100 °C and stirred for 3 h at the same temperature. The mixture was cooled to RT, quenched with ice water and extracted with EtOAc (3 x 250 mL). The organic extracts were dried over sodium sulphate and concentrated to give a solid. The solid was crystalized from EtOAc/hexane to give **3-6** (17.0 g, 91% yield) as an off-white solid.

[0249] Step 4: Synthesis 6-(6-(((1*R*,2*R*,3*S*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-2-methylbenzo[d]oxazol-5-ol (Formula (I'a)).

[0250] TFA (136.0 mL) was slowly added to a stirred solution of **3-6** (17.0 g, 32.2 mmol) in DCM (170.0 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 16 h. The volatiles were distilled under vacuum and the residue was treated with cold saturated aqueous $NaHCO_3$ solution to a pH of 9 and extracted with ethyl acetate (3 x 500 mL). The combined organic extracts were washed with brine (500 mL), dried over sodium sulphate and concentrated to give a solid which was triturated with chilled *n*-hexane and the resulting solids were collected by filtration. This solid was slurried in IPA (4 vol) and heated to 40 °C, this temperature was maintained for 1 h. The suspension was cooled to 25 °C, stirred for 2 h, the solids were collected by filtration and dried to afford **Formula (I'a)** (8.6 g, 70% yield) as an off-white solid.

[0251] Example 4: Synthesis of 4-(4-(5-(((1*R*,3*s*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1*H*)-one.



[0252] Step 1: Synthesis of 1-bromo-4-chloro-2-(methoxymethoxy)benzene.

[0253] NaH (185 g, 46.3 mmol, 60% in mineral oil) was added to a stirred solution of 2-bromo-5-chlorophenol (8 g, 38.6 mmol) in 150 mL of DMF at 0 °C. After stirring at 0 °C for 30 min, MOMBr (7.25 g, 58 mmol) was added. The mixture was then stirred at room temperature for 2 h, quenched with NH_4Cl aqueous solution (15 mL), extracted with EtOAc (30 mL X 3). The combined organic solvents were dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to give 8.1 g of 1-bromo-4-chloro-2-(methoxymethoxy)benzene as colorless oil (84% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 8.4, 2.3 Hz, 1H), 5.24 (s, 2H), 3.51 (s, 3H). LCMS: t_R = 1.51 min.

[0254] Step 2: Synthesis of 4-chloro-2-(methoxymethoxy)phenylboronic acid.

[0255] *n*-BuLi (5.76 mL, 14.4 mmol) was added to a stirred solution of 1-bromo-4-chloro-2-(methoxymethoxy)benzene (3 g, 12 mmol) in 40 mL of THF under nitrogen at -78 °C. After stirring at -78 °C for 40 min, $B(OMe)_3$ (2 g, 19.2 mmol) was added. The mixture was allowed to warm up to room temperarture and stirred for 16 h. NH_4Cl aqueous solution (10 mL) was added to the mixture. The mxiture was extracted with EtOAc (20 mL X 3). The commbined orgainc solvents were washed with brine (10 mL), dried over Na_2SO_4, concentrated and recrystalized from 3% EtOAc/petroleum ether to give 1.6 g of 4-chloro-2-(methoxymethoxy)phenylboronic acid as off white solid (62% yield). LCMS: *m/z* 199.1 $[M\text{-}OH]^+$; t_R = 1.65 min.

[0256] Step 3: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-bromo-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

[0257] A mixture of *tert*-butyl (1*R*,3*s*,5*S*)-3-(methylamino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (2.2 g, 8.66 mmol), 2,5-dibromo-1,3,4-thiadiazole (2.54 g, 10.39 mmol) and DIPEA (3.35 g, 25.98 mmol) in 24 mL of DMSO was stirred at 130 °C for 4 h. After cooling to room temperature, the mixture was cooled to room temperature, diluted with H_2O (100 mL), extracted by EtOAc (100 mL x 3). After removal of solvent, the crude product was purified by silica gel column (30% EtOAc/petroleum ether) to give 3.2 g of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-bromo-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate as brown oil (89% yield). LCMS: *m/z* 363.0 $[M\text{-}55]^+$; t_R = 1.99 min.

[0258] Step 4: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

[0259] A mixture of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-bromo-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (300 mg, 1.87 mmol), 4-chloro-2-(methoxymethoxy)phenylboronic acid (444 mg, 2.06 mmol), $Pd(dppf)Cl_2$ (274 mg, 0.37 mmol), K_2CO_3 (516 mg, 3.74 mmol) in 6 mL of dioxane and 2 mL of H_2O. The mixture was degassed and

stirred at 100 °C for 1 h, concentrated and purified by silica gel column (20-30% EtOAc/petroleum ether) to give 250 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate as yellow solid (68% yield). LCMS: *m/z* 509.3 $[M+H]^+$; t_R = 2.12 min.

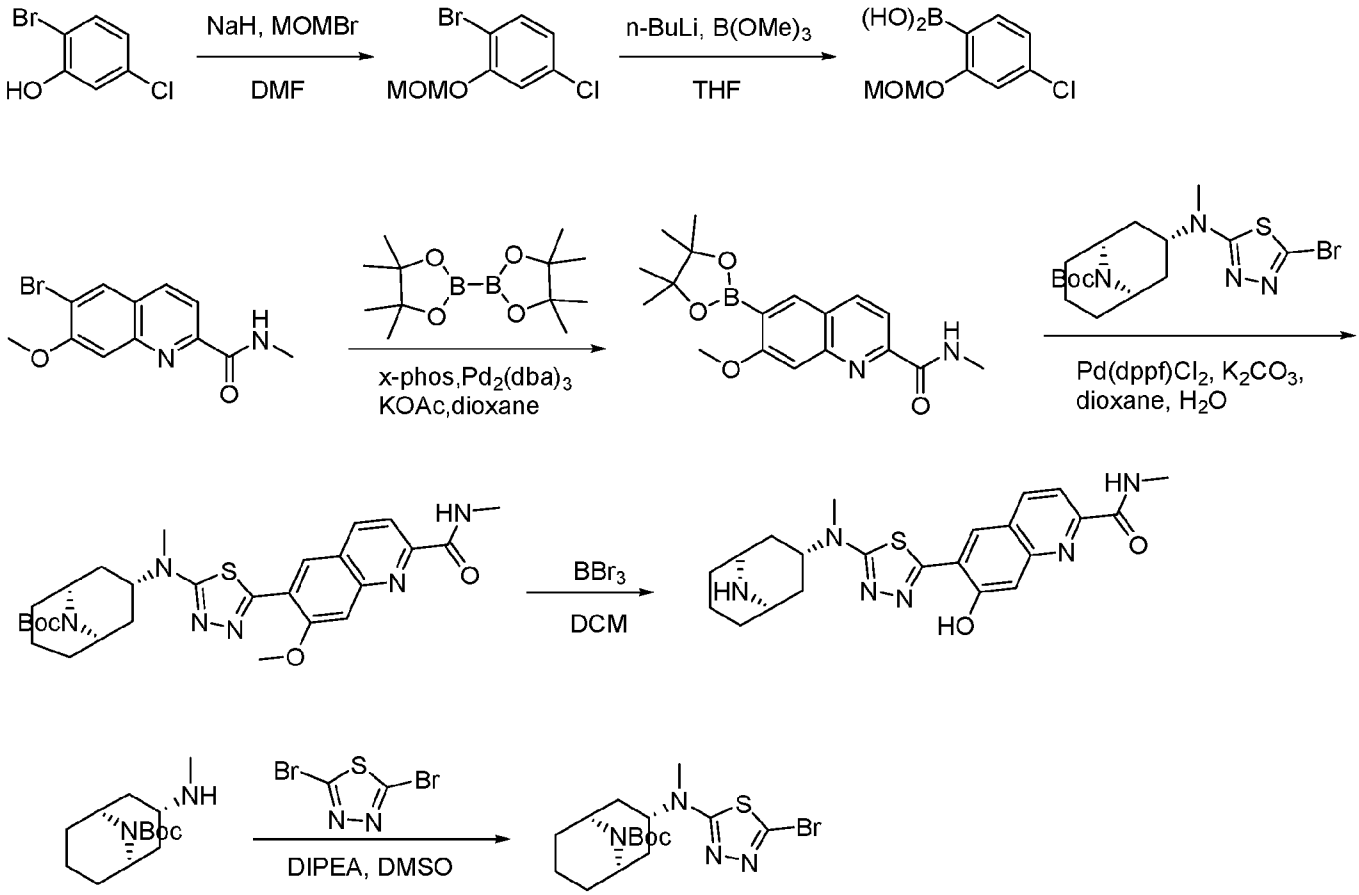
[0260] Step 5: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(2-(methoxymethoxy)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

[0261] A mixture of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(4-chloro-2-(methoxymethoxy)phenyl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (100 mg, 0.20 mmol), (1-methyl-2-oxo-1,2-dihydropyridin-4-yl)boronic acid (36 mg 0.24 mmol), Xphos-Pd-G2 (31 mg, 0.04 mmol) and K_3PO_4 (83 mg, 0.39 mmol) in 3 mL of dioxane and 1 mL of H_2O was added. The mixture was degassed and stirred at 100 °C for 1 h, concentrated and purified by silica gel column (75-85% EtOAc/petroleum ether) to give 100 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(2-(methoxymethoxy)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate as yellow oil (87% yield). LCMS: *m/z* 582.3 $[M+H]^+$; t_R = 1.85 min.

[0262] Step 6: Synthesis of 4-(4-(5-(((1*R*,3*s*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1*H*)-one.

[0263] 4 mL of HCl in dioxane (4 N) was added to a stirred solution of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(2-(methoxymethoxy)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (100 mg, 0.17 mmol) in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated, NH_3/MeOH (7 N) was added to make pH = 9, concentrated and purified by silica gel column (10-20% MeOH/CH_2Cl_2) to give 55 mg of 4-(4-(5-(((1*R*,3*s*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-3-hydroxyphenyl)-1-methylpyridin-2(1*H*)-one as yellow solid (73% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.39 – 7.23 (m, 2H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.59 (dd, *J* = 7.1, 2.0 Hz, 1H), 5.24 – 5.08 (m, 1H), 3.77 (s, 2H), 3.48 (s, 3H), 3.00 (s, 3H), 2.38 – 2.24 (m, 2H), 2.09 – 1.70 (m, 8H). LCMS: *m/z* 438.3 $[M+H]^+$; t_R=1.25 min.

[0264] Example 5: Synthesis of 6-(5-(((1*R*,3*s*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-7-hydroxy-*N*-methylquinoline-2-carboxamide.



[0265] Step 1: Synthesis of 1-bromo-4-chloro-2-(methoxymethoxy)benzene.

[0266] NaH (185 g, 46.3 mmol, 60% in mineral oil) was added to a stirred solution of 2-bromo-5-chlorophenol (8 g, 38.6 mmol) in 150 mL of DMF at 0 °C. After stirring at 0 °C for 30 min, MOMBr (7.25 g, 58 mmol) was added. The mixture was then stirred at room temperature for 2 h, quenched with NH_4Cl aqueous solution (15 mL), extracted with EtOAc (30 mL X 3). The combined organic solvents were dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to give 8.1 g of 1-bromo-4-chloro-2-(methoxymethoxy)benzene as colorless oil (84% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.24 (s, 2H), 3.51 (s, 3H). LCMS: t_R = 1.51 min.

[0267] Step 2: Synthesis of 4-chloro-2-(methoxymethoxy)phenylboronic acid.

[0268] *n*-BuLi (5.76 mL, 14.4 mmol) was added to a stirred solution of 1-bromo-4-chloro-2-(methoxymethoxy)benzene (3 g, 12 mmol) in 40 mL of THF under nitrogen at -78 °C. After stirring at -78 °C for 40 min, $B(OMe)_3$ (2 g, 19.2 mmol) was added. The mixture was allowed to warm up to room temperarture and stirred for 16 h. NH_4Cl aqueous solution (10 mL) was added to the mixture. The mxiture was extracted with EtOAc (20 mL X 3). The commbined orgainc solvents were washed

with brine (10 mL), dried over Na_2SO_4, concentrated and recrystalized from 3% EtOAc/petroleum ether to give 1.6 g of 4-chloro-2-(methoxymethoxy)phenylboronic acid as off white solid (62% yield). LCMS: *m/z* 199.1 $[M\text{-}OH]^+$; t_R = 1.65 min.

[0269] Step 3: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-bromo-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

[0270] The mixture of *tert*-butyl (1*R*,3*s*,5*S*)-3-(methylamino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (2.2 g, 8.66 mmol) in 24 mL of DMSO, 2,5-dibromo-1,3,4-thiadiazole (2.54 g, 10.39 mmol), DIPEA (3.35 g, 25.98 mmol) was added at room temperature, the mixture was stirred at 130 °C for 4 h, cooled to room temperature, diluted with H_2O (100 mL) and extracted by EtOAc (100 mLx3). After removal of solvent, the crude product was purified by silica gel column (30% EtOAc/petroleum ether) to give 3.2 g of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-bromo-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate as brown oil (89% yield). LCMS: *m/z* 363.0 $[M\text{-}55]^+$; t_R = 1.99 min.

[0271] Step 4: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(7-methoxy-2-(methylcarbamoyl)quinolin-6-yl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate.

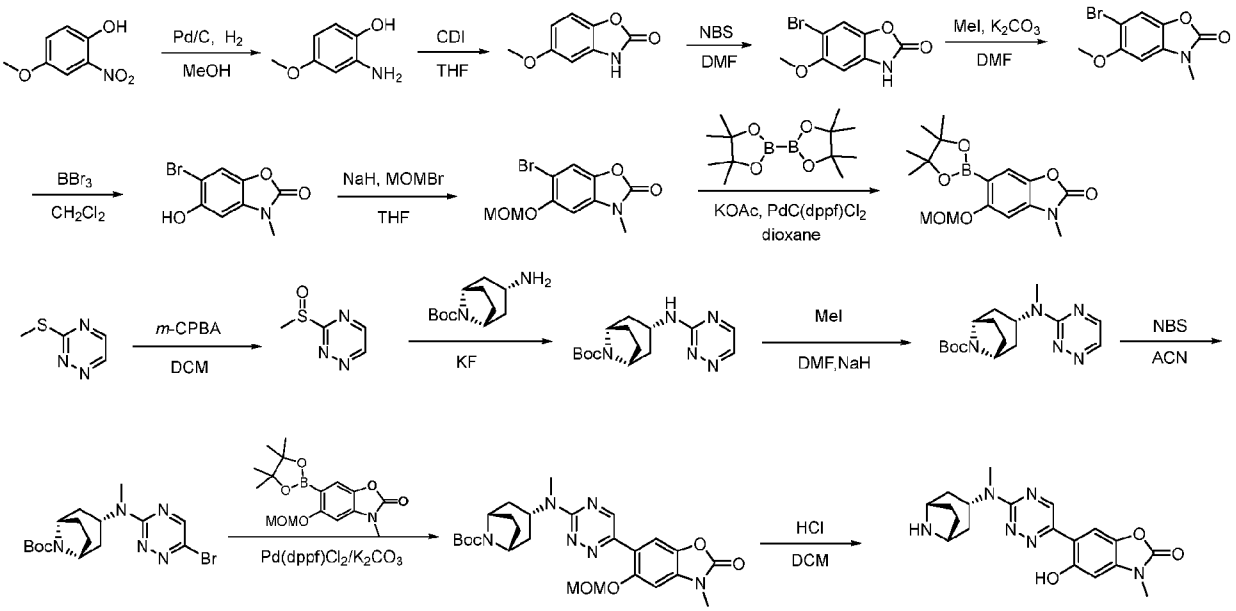
[0272] A mixture of 6-bromo-7-methoxy-*N*-methylquinoline-2-carboxamide (200 mg, 0.68 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (259 mg, 1.02 mmol), $Pd_2(dba)_3$ (125 mg, 0.14 mmol), x-Phos (130 mg, 0.27 mmol) and KOAc (133 mg, 1.36 mmol) in 6 mL of dioxane was degassed and stirred at 100 °C for 3 h. The mixture was cooled to room temerature, *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-bromo-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (227 mg, 0.54 mmol), $Pd(dppf)Cl_2$ (100 mg, 0.14 mmol), K_2CO_3 (188 mg, 1.36 mmol) in 9 mL of dioxane and 3 mL of H_2O was added. The mixture was degassed and stirred at 100 °C for 2 h, concentrated and purified by silica gel column (70-90% EtOAc/petroleum ether) to give 150 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(7-methoxy-2-(methylcarbamoyl)quinolin-6-yl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate as yellow solid (40% yield). LCMS: *m/z* 553.3 $[M+H]^+$; t_R = 1.97 min.

[0273] Step 5: Synthesis of 6-(5-(((1*R*,3*s*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-7-hydroxy-*N*-methylquinoline-2-carboxamide.

[0274] 10 mL of BBr_3 (17%) was added to a stirred solution of *tert*-butyl (1*R*,3*s*,5*S*)-3-((5-(7-methoxy-2-(methylcarbamoyl)quinolin-6-yl)-1,3,4-thiadiazol-2-yl)(methyl)amino)-9-azabicyclo[3.3.1]nonane-9-carboxylate (150 mg, 0.27 mmol) in 3 mL of CH_2Cl_2. The mixture was stirred at room temperature for 16 h, quenched with water (50 mL), added saturated aqueous sodium bicarbonate to adjust pH to 8~9 extracted with CH_2Cl_2 (50 mL X 3). The combined organic solvents

were washed with brine (100 mL), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column (0-20% MeOH/CH_2Cl_2) to give 20 mg of 6-(5-(((1*R*,3*s*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-7-hydroxy-*N*-methylquinoline-2-carboxamide as yellow solid (21% yield). LCMS: *m/z* 439.1 $[M+H]^+$; t_R = 1.36 min. ^1H NMR (400 MHz, MeOD-d_4) δ 8.50 (s, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 5.38 – 5.25 (m, 1H), 3.80 (s, 2H), 3.12 (s, 3H), 3.02 (s, 3H), 2.44 – 2.31 (m, 2H), 2.24 – 1.95 (m, 8H).

[0275] Example 6: Synthesis of 6-(3-(((1*R*,3*s*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-5-hydroxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one.



[0276] Step 1: Synthesis of 2-amino-4-methoxyphenol.

[0277] A mixture of 4-methoxy-2-nitrophenol (10 g, 59.17 mmol) and Pd/C (3 g, 10% on activated carbon) in MeOH (25 mL) was stirred at room temperature for 5 h under H_2 atmosphere. Then the mixture was filtered and concentrated to give 8.5 g of 2-amino-4-methoxyphenol as yellow oil (97% yield), which was used directly to next step. LCMS: *m/z* 140.1 $[M+H]^+$; t_R = 0.35 min.

[0278] Step 2: Synthesis of 5-methoxybenzo[d]oxazol-2(3H)-one.

[0279] A mixture of 2-amino-4-methoxyphenol (18.5 g, 133 mmol) and CDI (28.05 g, 172.9 mmol) in THF (50 ml) was stirred at 70 °C for 2 hours. After cooling to room temperature, the mixture was quenched with water (400 mL), extracted with EtOAc (500 mL X 3). The combined organic solvents were washed with brine (400 ml X 3), dried over anhydrous Na_2SO_4 and concentrated to give 31.5 g of 5-methoxybenzo[d]oxazol-2(3*H*)-one as colorless oil (98% yield), which was used directly to next step. LCMS: *m/z* 166.2 $[M+H]^+$; t_R = 1.61 min.

[0280] Step 3: Synthesis of 6-bromo-5-methoxybenzo[d]oxazol-2(3*H*)-one.

[0281] NBS (20.0 g, 112.1 mmol) was added to a mixture of 5-methoxybenzo[d]oxazol-2(3*H*)-one (18.5 g, 112.1 mmol) and in DMF (50 ml). The mixture was stirred at room temperature for 1 hour, quenched with water (200 mL) and extracted with EtOAc (250 mL X 3). The combined organic solvents were washed with LiCl aqueous solution (200 mL X 3), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to give 22.8 g of 6-bromo-5-methoxybenzo[*d*]oxazol-2(3*H*)-one as brown solid (91% yield). LCMS: *m/z* 245.9 $[M+H]^+$; t_R = 1.76 min.

[0282] Step 4: Synthesis of 6-bromo-5-methoxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one.

[0283] MeI (26.5 g, 0.18 mol) was added to a mixture of 6-bromo-5-methoxybenzo[d]oxazol-2(3*H*)-one (22.8 g, 0.09 mol) and K_2CO_3 (25.8 g, 0.18 mol) in DMF (100 mL). The mixture was stirred at room temperature overnight, quenched with water (200 mL) and extracted with EtOAc (80 mL X 3). The combined organic solvents were washed with LiCl aqueous solution (200 ml X 3), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatography (0-30% EtOAc/petroleum ether) to give 23.2 g of 6-bromo-5-methoxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one as brown solid (96% yield). LCMS: *m/z* 259.0 $[M+H]^+$; t_R = 1.72 min.

[0284] Step 5: Synthesis of 6-bromo-5-hydroxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one.

[0285] To a solution of 6-bromo-5-methoxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one (2.3 g, 8.91 mmol) in CH_2Cl_2 (20 mL) was added BBr_3 (20 mL, 1N in CH_2Cl_2). The mixure was stirred at room temperature for 1 hour, quenched with water (100 mL) and pH value was adjusted to 9~10 with K_2CO_3. The mixture was extracted with CH_2Cl_2/MeOH (10:1, v/v, 120 mL X 3). The combined organic layers were wash with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2 g of 6-bromo-5-hydroxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one as yellow oil (71% yield), which was used directly to next step. LCMS: *m/z* 245.9 $[M+H]^+$; t_R = 1.51 min.

[0286] Step 6: Synthesis of 6-bromo-5-(methoxymethoxy)-3-methylbenzo[*d*]oxazol-2(3*H*)-one.

[0287] NaH (656 g, 16.4 mmol, 60% in mineral oil) was added to a stirred solution of 6-bromo-5-hydroxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one (2.0 g, 8.2 mmol) in 20 mL of DMF at 0 °C. After stirring at 0 °C for 30 min, MOMBr (2.0g, 16.4 mmol) was added. The mixture was then stirred at room temperature for 2 h, quenched with NH_4Cl aqueous solution (50 mL), extracted with EtOAc (80 mL X 3). The combined organic solvents were with LiCl aqueous solution (50 mL X 3), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatography (0-10% EtOAc/petroleum ether) to give 2.0 g of 6-bromo-5-(methoxymethoxy)-3-methylbenzo[*d*]oxazol-2(3*H*)-one as yellow oil (72% yield). LCMS: 289.0 $[M+H]^+$; t_R = 1.72 min.

[0288] Step 7: Synthesis of 5-(methoxymethoxy)-3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazol-2(3*H*)-one.

[0289] A mixture of 6-bromo-5-(methoxymethoxy)-3-methylbenzo[d]oxazol-2(3H)-one (2 g, 6.94 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.65 g, 10.41 mmol), $Pd(dppf)Cl_2$ (51 mg, 0.694 mmol) and KOAc (2.04 g, 20.82 mmol) in 30 mL of dioxane was degassed and stirred at 100 °C for 2 h. After cooling to room temperature, the mixture was concentrated and purified by silica gel column (0-50% EtOAc/petroleum ether) to give 2.0 g of 5-(methoxymethoxy)-3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazol-2(3*H*)-one as yellow oil (87% yield). LCMS: *m/z* 336.2 $[M+H]^+$; t_R = 1.81.

[0290] Step 8: Synthesis of 3-(methylsulfinyl)-1,2,4-triazine.

[0291] *m*-CPBA (24 g, 137.79 mmol) was added to a solution of 3-(methylthio)-1,2,4-triazine (5 g, 39.37 mmol) in DCM (500 mL) at 0 ^{0}C and the mixture was stirred at 0 ^{0}C for 1 h. The mixture was quenched with H_2O (200 ml), filtered, extracted with DCM (500ml X 3). The combined organic solvents were washed with saturated $NaHCO_3$ aqueous solution (200 ml), dried over anhydrous Na_2SO_4 and concentrated to give 5 g of 3-(methylsulfinyl)-1,2,4-triazine as yellow solid (89% yield), which was used directly to next step. LCMS: *m/z* 144.2$[M+H]^+$; t_R = 0.48 min.

[0292] Step 9: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((1,2,4-triazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0293] A mixture of *tert*-butyl (1*R*,3*s*,5*S*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (2.0 g, 8.85 mmol), 3-(methylsulfinyl)-1,2,4-triazine (4.7 g, 31.57 mmol) and KF (1.5 g, 26.55 mmol) in DMSO (30 ml) was stirred at 100 °C for 2 h. After cooling to room temperature, the mixture was quenched with H_2O (40 ml), extracted with EtOAc (30 ml X 3). The organic phases washed with brine (100 ml), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column (0-25% EtOAc / petroleum ether) to give 600 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-((1,2,4-triazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (22% yield). LCMS: *m/z* 250.2 $[M-55]^+$; t_R = 1.69 min.

[0294] Step 10: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-(methyl(1,2,4-triazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0295] NaH (216 mg, 5.41 mmol, 60% in mineral oil) was added to a solution of *tert*-butyl (1*R*,3*s*,5*S*)-3-((1,2,4-triazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (550 mg, 1.80 mmol) in DMF (6 ml) and stirred at room temperature for 30 min. Then CH_3I (512 mg, 3.61 mmol) was added and the reaction was stirred for another 1 h. The mixture was quenched with H_2O (30 ml), extracted with EtOAc (20 ml X 3). The organic phases washed with saturated LiCl aqueous solution (50 ml), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column (0-20% EtOAc/petroleum ether) to give 600 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-(methyl(1,2,4-triazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (96% yield). LCMS: *m/z* 264.1 $[M-55]^+$; t_R = 1.81 min.

[0296] Step 11: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-bromo-1,2,4-triazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0297] A mixture of *tert*-butyl (1*R*,3*s*,5*S*)-3-(methyl(1,2,4-triazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (580 mg, 1.82 mmol) and NBS (356 mg, 2.00 mmol) in acetonitrile (6 ml) was stirred at 60 °C for 4 h. The mixture was quenched with H_2O (30 ml), extracted with EtOAc (20 ml X 3). The organic phases washed with saturated LiCl aqueous solution (50 ml), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column (0-25% MeOH/EtOAc) to give 500 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-bromo-1,2,4-triazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (75% yield). LCMS: *m/z* 342.0 $[M-55]^+$; t_R = 2.00 min.

[0298] Step 12: Synthesis of *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-(5-(methoxymethoxy)-3-methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)-1,2,4-triazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate.

[0299] A mixture of (1*R*,3*s*,5*S*)-*tert*-butyl 3-((6-bromo-1,2,4-triazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (178 mg, 0.45 mmol), 5-(methoxymethoxy)-3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazol-2(3*H*)-one (150 mg, 0.45 mmol), $Pd(dppf)Cl_2$ (33 mg, 0.04 mmol) and K_2CO_3 (124 mg, 0.90 mmol) in 6 mL of 1,4-dioxane and 2 mL of H_2O. The resulting mixture was stirred at 100 °C for 3 hours under nitrogen atmosphere and concentrated. The resiude was purified by silica gel column (20~40% EtOAc/petroleum ether) to give 100 mg of *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-(5-(methoxymethoxy)-3-methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)-1,2,4-triazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (42% yield) as a yellow solid. LCMS: *m/z* 527.2 $[M+H]^+$; t_R = 1.96 min.

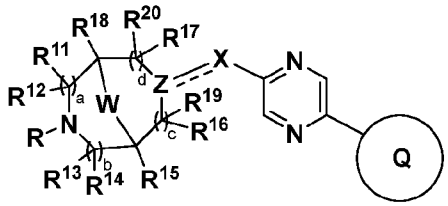
[0300] Step 13: Synthesis of 6-(3-(((1*R*,3*s*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-5-hydroxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one.

[0301] To a solution of *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-(5-(methoxymethoxy)-3-methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)-1,2,4-triazin-3-yl)(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.19 mmol) in dichloromethane (3 mL) was added HCl (4M in dioxane, 1 mL) and the mixture was stirred at room temperature for 2 hours and concentrated. The residues was purified by Prep-HPLC (ACN and H_2O with 0.05% NH_4HCO_3 as mobile phase, Column: Xtimate 10um 150A 21.2 × 250mm) to give 20 mg of 6-(3-(((1*R*,3*s*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-5-hydroxy-3-methylbenzo[*d*]oxazol-2(3*H*)-one as yellow solid (yield 28%). LCMS: *m/z* 383.3 $[M+H]^+$; t_R = 1.31 min. ^1H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 7.80 (s, 1H), 6.83 (s, 1H), 5.12 – 5.06 (m, 1H), 3.56 – 3.52 (m, 2H), 3.32 (s, 3H), 3.04 (s, 3H), 1.87 – 1.67 (m, 6H), 1.57 – 1.53 (m, 2H).

CLAIMS

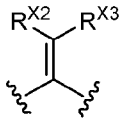
What is claimed is:

1. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

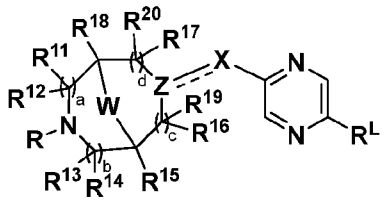


Formula (I)

wherein,

Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; X is absent, -O-, -S-, -C(=O)-, $-NR^{X1}-$, $-CR^{X2}R^{X3}-$,  , or $=CR^{X1}-$; R^{X1} is hydrogen, –CN, substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, substituted or unsubstituted C_2–C_6 heterocycloalkyl, substituted or unsubstituted C_1–C_6 haloalkyl, substituted or unsubstituted C_1–C_6 heteroalkyl, or -C_1-C_4 alkylene-OR^{31}; each R^{X2} and R^{X3} is independently hydrogen, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 haloalkyl, or substituted or unsubstituted C_1–C_4 heteroalkyl; each ---- is independently a single or a double bond; Z is N, C or CR^5; R^5 is hydrogen, substituted or unsubstituted C_1–C_4 alkyl, or substituted or unsubstituted C_1–C_4 haloalkyl; W is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_2-C_3 alkenylene, substituted or unsubstituted C_3–C_8 cycloalkylene, or substituted or unsubstituted C_2–C_7 heterocycloalkylene; each R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R^{17}, R^{19}, and R^{20} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; each R^{15} and R^{18} is independently selected from the group consisting of hydrogen, F, $–OR^{31}$, substituted or unsubstituted C_1–C_4 alkyl, a substituted or unsubstituted C_1–C_4 fluoroalkyl, and substituted or unsubstituted C_1–C_4 heteroalkyl; R is

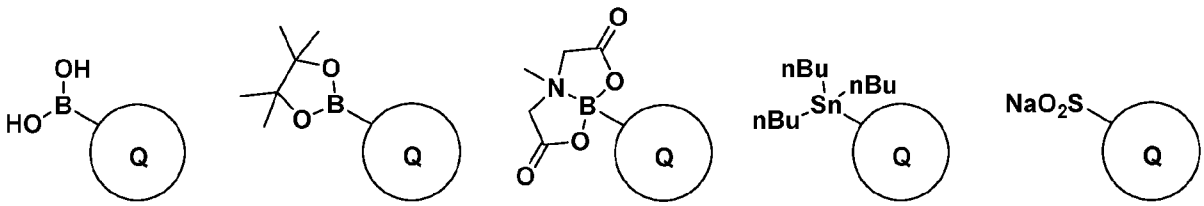
hydrogen, substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 fluoroalkyl, substituted or unsubstituted C_1–C_4 heteroalkyl, substituted or unsubstituted C_3–C_6 cycloalkyl, or substituted or unsubstituted C_2–C_5 heterocycloalkyl; a is 0, 1, 2, or 3; b is 0, 1, 2, or 3; c is 0, 1, 2, or 3; and d is 0, 1, 2, or 3, comprising the step of reacting a compound of Formula (II)



Formula (II)

wherein R^L is halogen, $-O(C=O)R^{L1}$, $-SR^{L1}$, $-S(=O)R^{L1}$, $-S(=O)_2R^{L1}$, or $-S(=O)(=NR^{L1})R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and wherein each other variable in Formula (II) is as described above for Formula (I);

with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI)

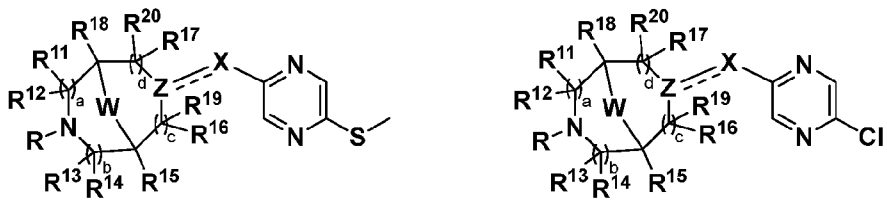


Formula (III) Formula (IV) Formula (IVa) Formula (V) Formula (VI)

to produce a compound of Formula (I);

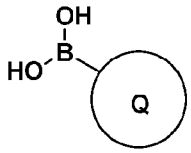
wherein each variable within Formula (III), Formula (IV), Formula (IVa), Formula (V), and Formula (VI) is as described above for Formula (I).

2. The process of claim 1, wherein a compound of Formula (II) has a structure of Formula (IIa) or Formula (IIb):



Formula (IIa) Formula (IIb).

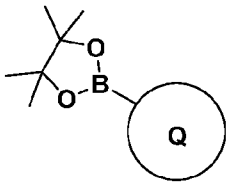
3. The process of claim 1 or claim 2, comprising the step of reacting the compound of Formula (II) with a compound of Formula (III)



Formula (III)

to produce a compound of Formula (I).

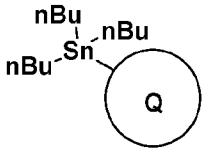
4. The process of claim 1 or claim 2, comprising the step of reacting the compound of Formula (II) with the compound of Formula (IV)



Formula (IV)

to produce a compound of Formula (I).

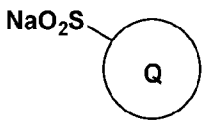
5. The process of claim 1 or claim 2, comprising the step of reacting the compound of Formula (II) with the compound of Formula (V)



Formula (V)

to produce a compound of Formula (I).

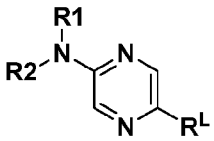
6. The process of claim 1 or claim 2, comprising the step of reacting a compound of Formula (II) with a compound of Formula (VI)



Formula (VI)

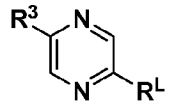
to produce a compound of Formula (I).

7. A process for preparing a compound of Formula (VII)



Formula (VII)

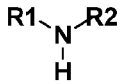
comprising reacting a compound of Formula (VIII)



Formula (VIII)

wherein R^3 is a halogen, such as Cl, Br, or I; or O-CH_2CF_3;R^L is halogen, -O(C=O)R^{L1}, -SR^{L1}, -S(=O)R^{L1}, or -S(=O)$_2R^{L1}$; and each R^{L1} is independently substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted C_1–C_8 heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

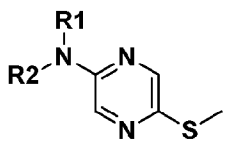
with a compound of Formula (IX)



Formula (IX)

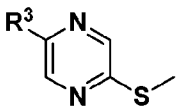
to produce a compound of Formula (VII), wherein each R1 and R2 is independently hydrogen, halogen, -OH, –OR^{31}, –CN,–SR^{31}, -S(=O)R^{31}, -SO_2R^{31}, -N$R^{31}R^{32}$, -NR^{31}S(=O)(=NR^{31})R^{32}, -NR^{31}S(=O)$_2R^{31}R^{32}$, -SO_2N$R^{31}R^{32}$, -C(=O)R^{31}, -OC(=O)R^{31}, -C(=O)OR^{31}, -OC(=O)OR^{31}, -C(=O)N$R^{31}R^{32}$, -OC(=O)N$R^{31}R^{32}$, -NR^{31}C(=O)R^{32}, -P(=O)$R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

8. The process of claim 7, wherein a compound of Formula (VII) has a structure of Formula (VIIa):



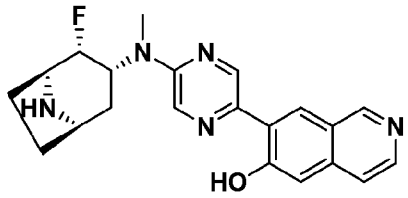
Formula (VIIa);

and wherein a compound of Formula (VIII) has a structure of Formula (VIIIa):



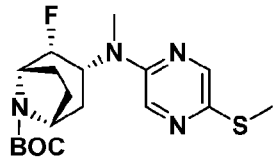
Formula (VIIIa).

9. The process of any one of claims 1-6, wherein a compound of Formula (I) is a compound of Formula (Ia)



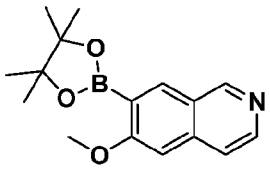
Formula (Ia).

10. The process of any one of claims 1-6, wherein a compound of Formula (II) is a compound of Formula (IIaaa)



Formula (IIaaa).

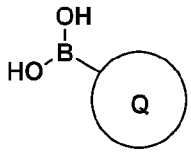
11. The process of claim 4, wherein a compound of Formula (IV) is a compound of Formula (IVaaa)



Formula (IVaaa).

12. The process of any one of claims 1-6 further comprising the steps of reacting a compound of Formula (II) with a compound of Formula (III), Formula (IV), Formula (IVa), Formula (V), or Formula (VI) in the presence of a palladium catalyst, tetrahydrofuran or dimethylformamide, and a copper (I) salt of 3-methyl salicylic acid or 2-Thienyl carboxylic acid.

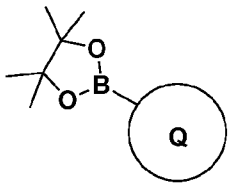
13. A compound of Formula (III)



Formula (III)

wherein Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

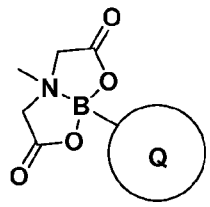
14. A compound of Formula (IV)



Formula (IV)

wherein Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

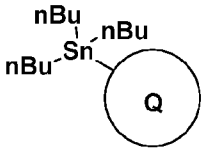
15. A compound of Formula (IVa)



Formula (IVa)

wherein Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

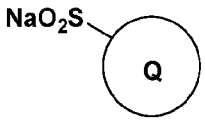
16. A compound of Formula (V)



Formula (V)

wherein Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

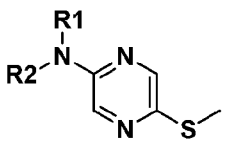
17. A compound of Formula (VI)



Formula (VI)

wherein Ring Q is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

18. A compound of Formula (VII)



Formula (VII)

wherein each R1 and R2 is independently hydrogen, halogen, -OH, $-OR^{31}$, –CN,$–SR^{31}$, $-S(=O)R^{31}$, $-SO_2R^{31}$, $-NR^{31}R^{32}$, $-NR^{31}S(=O)(=NR^{31})R^{32}$, $-NR^{31}S(=O)_2R^{31}R^{32}$, $-SO_2NR^{31}R^{32}$, $-C(=O)R^{31}$, $-OC(=O)R^{31}$, $-C(=O)OR^{31}$, $-OC(=O)OR^{31}$, $-C(=O)NR^{31}R^{32}$, $-OC(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-P(=O)R^{31}R^{32}$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted monocyclic aryl, or substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted polycyclic aryl, or substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic alkyl, substituted or unsubstituted polycyclic heteroalkyl; and each R^{31} and R^{32} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

19. The compound of claim 18, wherein R1 is substituted or unsubstituted monocyclic aryl, substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted monocyclic cycloalkyl, or substituted or unsubstituted monocyclic heteroaryl.
20. The compound of claim 18, wherein R1 is substituted or unsubstituted polycyclic aryl, substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic cycloalkyl, or substituted or unsubstituted polycyclic heteroaryl.
21. The compound of claim 18, wherein R2 is substituted or unsubstituted monocyclic aryl, substituted or unsubstituted monocyclic heteroaryl, substituted or unsubstituted monocyclic cycloalkyl, or substituted or unsubstituted monocyclic heteroaryl.
22. The compound of claim 18, wherein R2 is substituted or unsubstituted polycyclic aryl, substituted or unsubstituted polycyclic heteroaryl, substituted or unsubstituted polycyclic cycloalkyl, or substituted or unsubstituted polycyclic heteroaryl.