

COMPOUNDS, COMPOSITIONS, AND METHODS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application Serial Number 63/580,981, filed September 6, 2023, the contents of which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates generally to small molecule modulators of Sterile Alpha and TIR Motif containing 1 (SARM1) protein, and their use as therapeutic agents.

BACKGROUND

[0003] Neurodegenerative diseases are a class of progressive neurological disorders, in which nerve cells malfunction and ultimately die. The degradation of neurons in those suffering from a neurodegenerative disease can present as a wide variety of symptoms, including changes in mood and behavior, agitation, sensory disturbances, motor and cognitive difficulties, and memory loss, which can progress to inability to move or speak, dementia, and ultimately death.

[0004] Axonal degeneration has been identified as an important pathology in most neurodegenerative diseases. Axons are vulnerable to both mechanical injury (Wallerian degeneration) and disease (Wallerian-like degeneration).

[0005] In healthy axons, SARM1's N-terminus interacts with the TIR domain, preventing TIR dimerization and subsequent enzymatic cleavage of NAD⁺. However, under neuronal injury or disease conditions, SARM1's N-terminus-TIR domain interaction is disrupted, allowing TIR multimerization to occur, followed by a rapid loss of NAD⁺ and associated axon degeneration.

DESCRIPTION

[0006] Provided herein are compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, that are useful in treating and/or preventing diseases mediated, at least in part, by SARM1.

[0007] In certain embodiments, provided are compounds that inhibit SARM1.

[0008] In another embodiment, provided is a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier.

[0009] In another embodiment, provided is a method for treating a disease or condition mediated, at least in part, by SARM1, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0010] The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, methods of using (or administering) and making the

compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and intermediates thereof.

[0011] The disclosure further provides compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or compositions thereof for use in a method of treating a disease, disorder, or condition that is mediated, at least in part, by SARMI.

[0012] Moreover, the disclosure provides uses of the compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or compositions thereof in the manufacture of a medicament for the treatment of a disease, disorder, or condition that is mediated, at least in part, by SARMI.

[0013] The description herein sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

1. Definitions

[0014] A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-C(O)NH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.

[0015] The prefix “C_{u-v}” indicates that the following group has from u to v carbon atoms. For example, “C₁₋₆ alkyl” indicates that the alkyl group has from 1 to 6 carbon atoms.

[0016] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 1\%$. Also, to the term “about X” includes description of “X”. Also, the singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0017] “Alkyl” refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C₁₋₂₀ alkyl), 1 to 12 carbon atoms (i.e., C₁₋₁₂ alkyl), 1 to 8 carbon atoms (i.e., C₁₋₈ alkyl), 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl) or 1 to 4 carbon atoms (i.e., C₁₋₄ alkyl). Examples of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example,

“butyl” includes n-butyl (i.e., $-(\text{CH}_2)_3\text{CH}_3$), sec-butyl (i.e., $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), isobutyl (i.e., $-\text{CH}_2\text{CH}(\text{CH}_3)_2$), and tert-butyl (i.e., $-\text{C}(\text{CH}_3)_3$); and “propyl” includes n-propyl (i.e., $-(\text{CH}_2)_2\text{CH}_3$) and isopropyl (i.e., $-\text{CH}(\text{CH}_3)_2$).

[0018] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, a divalent heteroaryl group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group (for example, methylenyl, ethylenyl, and propylenyl), an “arylene” group or an “arylenyl” group (for example, phenylenyl or naphthylenyl, or quinoliny for heteroarylene), respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl or aralkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0019] “Alkenyl” refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 12 carbon atoms (i.e., C_{2-12} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0020] “Alkynyl” refers to an alkyl group containing at least one (e.g., 1-3, or 1) carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 12 carbon atoms (i.e., C_{2-12} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term “alkynyl” also includes those groups having one triple bond and one double bond.

[0021] “Alkoxy” refers to the group “alkyl-O-”. Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0022] “Alkoxyalkyl” refers to the group “alkyl-O-alkyl”.

[0023] “Alkylthio” refers to the group “alkyl-S-”. “Alkylsulfinyl” refers to the group “alkyl-S(O)-”. “Alkylsulfonyl” refers to the group “alkyl-S(O)₂-”. “Alkylsulfonylalkyl” refers to -alkyl-S(O)₂-alkyl.

[0024] “Acyl” refers to a group $-\text{C}(\text{O})\text{R}^y$, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0025] “Amido” refers to both a “C-amido” group which refers to the group $-\text{C}(\text{O})\text{NR}^y\text{R}^z$ and an “N-amido” group which refers to the group $-\text{NR}^y\text{C}(\text{O})\text{R}^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0026] “Amino” refers to the group $-NR^yR^z$ wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0027] “Amidino” refers to $-C(NR^y)(NR^z_2)$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0028] “Aryl” refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl regardless of point of attachment. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl regardless of point of attachment. If one or more aryl groups are fused with a cycloalkyl, the resulting ring system is cycloalkyl regardless of point of attachment.

[0029] “Arylalkyl” or “Aralkyl” refers to the group “aryl-alkyl”.

[0030] “Carbamoyl” refers to both an “O-carbamoyl” group which refers to the group $-O-C(O)NR^yR^z$ and an “N-carbamoyl” group which refers to the group $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0031] “Carboxyl ester” or “ester” refer to both $-OC(O)R^x$ and $-C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0032] “Cyanoalkyl” refers to refers to an alkyl group as defined above, wherein one or more (e.g., 1 or 2) hydrogen atoms are replaced by a cyano ($-CN$) group.

[0033] “Cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 14 ring carbon atoms (i.e., C_{3-14} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalanyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also

includes “spirocycloalkyl” when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0034] “Cycloalkylalkyl” refers to the group “cycloalkyl-alkyl”.

[0035] “Imino” refers to a group $-C(NR^y)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0036] “Imido” refers to a group $-C(O)NR^yC(O)R^z$, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0037] “Halogen” or “halo” refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0038] “Haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0039] “Haloalkoxy” refers to an alkoxy group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0040] “Haloalkoxyalkyl” refers to an alkoxyalkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0041] “Hydroxyalkyl” refers to an alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a hydroxy group.

[0042] “Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms), excluding any terminal carbon atom(s), are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y$ -, $-O$ -, $-S$ -, $-S(O)$ -, $-S(O)_2$ -, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, etc.), thioethers (e.g., $-CH_2SCH_3$, $-CH(CH_3)SCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2SCH_2CH_2SCH_3$, etc.), sulfones (e.g., $-CH_2S(O)_2CH_3$, $-CH(CH_3)S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_3$, etc.), and amines (e.g., $-CH_2NR^yCH_3$, $-CH(CH_3)NR^yCH_3$, $-CH_2CH_2NR^yCH_3$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_3$, etc., where R^y is hydrogen, alkyl,

alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 2 to 10 carbon atoms, 2 to 8 carbon atoms, or 2 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0043] “Heteroaryl” refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C₁₋₂₀ heteroaryl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heteroaryl), or 3 to 8 carbon ring atoms (i.e., C₃₋₈ heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothiophenyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolyl, quinuclidinyl, isoquinolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolyl, isoquinolyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound *via* either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0044] “Heteroarylalkyl” refers to the group “heteroaryl-alkyl-”.

[0045] “Heterocyclyl” refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro, and may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide (-O⁺) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein,

heterocyclyl has 2 to 20 ring carbon atoms (i.e., C₂₋₂₀ heterocyclyl), 2 to 12 ring carbon atoms (i.e., C₂₋₁₂ heterocyclyl), 2 to 10 ring carbon atoms (i.e., C₂₋₁₀ heterocyclyl), 2 to 8 ring carbon atoms (i.e., C₂₋₈ heterocyclyl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heterocyclyl), 3 to 8 ring carbon atoms (i.e., C₃₋₈ heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C₃₋₆ heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidiny, azepiny, benzodioxoly, benzo[b][1,4]dioxepiny, 1,4-benzodioxany, benzopyrany, benzodioxiny, benzopyranony, benzofuranony, dioxolany, dihydropyrany, hydropyrany, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanony, imidazoliny, imidazolidiny, indoliny, indoliziny, isoindoliny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, oxazolidiny, oxirany, oxetany, phenothiaziny, phenoxaziny, piperidiny, piperaziny, 4-piperidony, pyrrolidiny, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofury, tetrahydropyrany, trithianyl, tetrahydroquinoliny, thiophenyl (i.e., thienyl), thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, and 1,1-dioxo-thiomorpholiny. The term “heterocyclyl” also includes “spiroheterocyclyl” when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as oxabicyclo[2.2.2]octany, 2-oxa-7-azaspiro[3.5]nonany, 2-oxa-6-azaspiro[3.4]octany, and 6-oxa-1-azaspiro[3.3]heptany. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinoliny, 4,5,6,7-tetrahydrothieno[2,3-c]pyridiny, indoliny, and isoindoliny, where the heterocyclyl can be bound *via* either ring of the fused system.

[0046] “Heterocyclylalkyl” refers to the group “heterocyclyl-alkyl-.”

[0047] “Oxime” refers to the group -CR^y(=NOH) wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0048] “Sulfonyl” refers to the group -S(O)₂R^y, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0049] “Sulfinyl” refers to the group -S(O)R^y, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl, and toluenesulfinyl.

[0050] “Sulfonamido” refers to the groups -SO₂NR^yR^z and -NR^ySO₂R^z, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0051] The terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term “optionally substituted” refers to

any one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0052] The term “substituted” used herein means any of the above groups (i.e., alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, and/or heteroalkyl) wherein at least one (e.g., 1 to 5 or 1 to 3) hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -NHNH₂, =NNH₂, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, -S(O)OH, -S(O)₂OH, sulfonamido, thiol, thioxo, N-oxide, or -Si(R^y)₃, wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

[0053] In certain embodiments, “substituted” includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, -NR^gR^h, -NR^gC(O)R^h, -NR^gC(O)NR^gR^h, -NR^gC(O)OR^h, -NR^gS(O)₁₋₂R^h, -C(O)R^g, -C(O)OR^g, -OC(O)OR^g, -OC(O)R^g, -C(O)NR^gR^h, -OC(O)NR^gR^h, -OR^g, -SR^g, -S(O)R^g, -S(O)₂R^g, -OS(O)₁₋₂R^g, -S(O)₁₋₂OR^g, -NR^gS(O)₁₋₂NR^gR^h, =NSO₂R^g, =NOR^g, -S(O)₁₋₂NR^gR^h, -SF₅, -SCF₃, or -OCF₃. In certain embodiments, “substituted” also means any of the above groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are replaced with -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -CH₂SO₂R^g, or -CH₂SO₂NR^gR^h. In the foregoing, R^g and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl. In certain embodiments, “substituted” also means any of the above groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxy, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^g and R^h and Rⁱ are taken together with the atoms to which they are attached to form a heterocyclyl ring optionally substituted with oxo, halo, or alkyl optionally substituted with oxo, halo, amino, hydroxy, or alkoxy.

[0054] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such

impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term “substituted” may describe other chemical groups defined herein.

[0055] In certain embodiments, as used herein, the phrase “one or more” refers to one to five. In certain embodiments, as used herein, the phrase “one or more” refers to one to three.

[0056] Any compound or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. These forms of compounds may also be referred to as “isotopically enriched analogs.” Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0057] The term “isotopically enriched analogs” includes “deuterated analogs” of compounds described herein in which one or more hydrogens is/are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, “Deuterium Isotope Effects in Studies of Drug Metabolism,” *Trends Pharmacol. Sci.* 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0058] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements, and/or an improvement in therapeutic index. An ^{18}F , ^3H , or ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0059] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen,” the position is understood to have hydrogen at

its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0060] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino, and/or carboxyl groups, or groups similar thereto.

[0061] Provided are also a pharmaceutically acceptable salt, isotopically enriched analog, deuterated analog, stereoisomer, mixture of stereoisomers, and prodrugs of the compounds described herein.

“Pharmaceutically acceptable” or “physiologically acceptable” refer to compounds, salts, compositions, dosage forms, and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0062] The term “pharmaceutically acceptable salt” of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. “Pharmaceutically acceptable salts” or “physiologically acceptable salts” include, for example, salts with inorganic acids, and salts with organic acids. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic or organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, such as alkyl amines (i.e., $\text{NH}_2(\text{alkyl})$), dialkyl amines (i.e., $\text{HN}(\text{alkyl})_2$), trialkyl amines (i.e., $\text{N}(\text{alkyl})_3$), substituted alkyl amines (i.e., $\text{NH}_2(\text{substituted alkyl})$), di(substituted alkyl) amines (i.e., $\text{HN}(\text{substituted alkyl})_2$), tri(substituted alkyl) amines (i.e., $\text{N}(\text{substituted alkyl})_3$), alkenyl amines (i.e., $\text{NH}_2(\text{alkenyl})$), dialkenyl amines (i.e., $\text{HN}(\text{alkenyl})_2$), trialkenyl amines (i.e., $\text{N}(\text{alkenyl})_3$), substituted alkenyl amines (i.e., $\text{NH}_2(\text{substituted alkenyl})$), di(substituted alkenyl) amines (i.e., $\text{HN}(\text{substituted alkenyl})_2$), tri(substituted alkenyl) amines (i.e., $\text{N}(\text{substituted alkenyl})_3$), mono-, di- or tri- cycloalkyl amines (i.e., $\text{NH}_2(\text{cycloalkyl})$, $\text{HN}(\text{cycloalkyl})_2$, $\text{N}(\text{cycloalkyl})_3$), mono-, di- or tri- arylamines (i.e., $\text{NH}_2(\text{aryl})$, $\text{HN}(\text{aryl})_2$, $\text{N}(\text{aryl})_3$), or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl)

amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0063] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0064] The compounds of the disclosure, or their pharmaceutically acceptable salts include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and/or fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

[0065] A “stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers, or mixtures thereof, and includes “enantiomers,” which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[0066] “Diastereomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

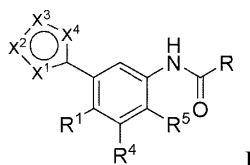
[0067] Relative centers of the compounds as depicted herein are indicated graphically using the “thick bond” style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[0068] “Prodrugs” means any compound which releases an active parent drug according to a structure described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound described herein are prepared by modifying functional groups present in the compound described herein in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds described herein wherein a hydroxy, amino, carboxyl, or sulfhydryl group in a compound described herein is bonded to any group that may be cleaved *in vivo* to

regenerate the free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), amides, guanidines, carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds described herein, and the like. Preparation, selection, and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

2. Compounds

[0069] Provided herein are compounds that are inhibitors of SARM1. In certain embodiments, provided is a compound of Formula I:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N, NR^{8a}, O, S, or CR^{6a};

X² is N, NR^{8b}, O, S, or CR^{6b};

X³ is N, NR^{8c}, or CR^{6c};

X⁴ is N or CR^{6d};

provided that at least one of X¹, X², X³, and X⁴ is N, and the ring containing X¹, X², X³, and X⁴ is aromatic;

R is -NR³R³, -OR⁷, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl is optionally substituted with one to five Z¹;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R³ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

or R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^7 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8a} and R^{6b} , or R^{8b} and R^{6c} , or R^{6b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

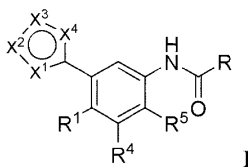
each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, $-L$ -heterocyclyl, $-L$ -aryl, or $-L$ -heteroaryl; and

each L is independently $-O-$, $-NH-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(C_{1-6} \text{ alkyl})-$, $-N(C_{2-6} \text{ alkenyl})-$, $-N(C_{2-6} \text{ alkynyl})-$, $-N(C_{1-6} \text{ haloalkyl})-$, $-N(C_{3-10} \text{ cycloalkyl})-$, $-N(\text{heterocyclyl})-$, $-N(\text{aryl})-$, $-N(\text{heteroaryl})-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N(C_{1-6} \text{ alkyl})-$, $-C(O)N(C_{2-6} \text{ alkenyl})-$, $-C(O)N(C_{2-6} \text{ alkynyl})-$, $-C(O)N(C_{1-6} \text{ haloalkyl})-$, $-C(O)N(C_{3-10} \text{ cycloalkyl})-$, $-C(O)N(\text{heterocyclyl})-$, $-C(O)N(\text{aryl})-$, $-C(O)N(\text{heteroaryl})-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHC(O)NH-$, $-NHS(O)-$, or $-S(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0070] In certain embodiments, provided is a compound of Formula I:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^1 is N, NR^{8a} , O, S, or CR^{6a} ;

X^2 is N, NR^{8b} , O, S, or CR^{6b} ;

X^3 is N, NR^{8c} , or CR^{6c} ;

X^4 is N or CR^{6d} ;

provided that at least one of X^1 , X^2 , X^3 , and X^4 is N, and the ring containing X^1 , X^2 , X^3 , and X^4 is aromatic;

R is $-NR^3R^3$, $-OR^7$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl is optionally substituted with one to five Z^1 ;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five Z^1 ;

R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^3 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

or R^2 and R^3 together form a heterocyclyl, which may further be optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^7 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8a} and R^{6b} , or R^{8b} and R^{6c} , or R^{6b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each Z^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, $-L$ -heterocyclyl, $-L$ -aryl, or $-L$ -heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

with the proviso that at least one of A, B, C, D, or E occurs:

A. X¹ is N and X² is NR^{8b}; and

- when R is C₁₋₆ alkyl; the C₁₋₆ alkyl is substituted with halo or C₃₋₁₀ cycloalkyl and optionally one to four Z¹; and/or
- R^{8b} is other than hydrogen; and/or
- when R is -OR⁷; then R⁷ is not methyl, ethyl, *iso*-propyl, *tert*-butyl, 2-bromoethyl, 2-methoxyethyl, 2-cyanoethyl, 2-phenylethyl, benzyl, or 9*H*-fluoren-9-ylmethyl;

and the compound is not:

- | | |
|--------------|---|
| 129628-21-3 | [2,4-dichloro-5-[4-chloro-1-methyl-5-(methylthio)-1H-pyrazol-3-yl]phenyl]-carbamic acid 2-methyl-2-propenyl ester, |
| 945236-54-4 | 1-(1,3-benzodioxol-5-yl)-N-[4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl]cyclopropanecarboxamide, |
| 142622-93-3 | N-[2,4-dichloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]phenyl]-2,2,2-trifluoroacetamide, |
| 142621-98-5 | N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide, |
| 2231121-13-2 | N-[4-bromo-2-fluoro-5-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2H-tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide, |
| 2231119-31-4 | N-[4-bromo-3-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2H-tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide, |
| 159291-92-6 | 1-bromo-N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorophenyl]cyclopropanecarboxamide, or |
| 141576-10-5 | N-[2-chloro-5-[4-chloro-1-methyl-5-(methylsulfonyl)-1H-pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide; |

B. X² is or NR^{8b}; and R is -NR²R³; and

- R² and R³ are not simultaneously methyl; and/or
- when X¹ is O; then at least one of R^{8b}, R^{8c}, R^{6c}, or R^{6d} is other than hydrogen;

and the compound is not:

- 1150100-88-1 N'-[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-N-phenyl-N-4-piperidinylurea,
- 938467-87-9 N'-[4-chloro-3-(2-methyl-2H-tetrazol-5-yl)phenyl]-N-(3,3-diphenylpropyl)-N-[2-(4-morpholinyl)ethyl]-urea,
- 1808766-39-3 4-(3-chlorophenyl)-N-[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide,
- 1071521-28-2 4-(3-fluorobenzoyl)-N-[4-fluoro-3-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]phenyl]-1-piperazinecarboxamide,
- 1071521-22-6 4-(3-fluorobenzoyl)-N-[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide,
- 1095716-86-1 N-[4-chloro-3-ethyl-5-(1-methyl-1H-pyrazol-4-yl)phenyl]-7,8-dihydro-4-(2-methylphenyl)-2-(3-pyridinyl)pyrido[4,3-d]pyrimidine-6(5H)-carboxamide, or
- 1150100-22-3 N-[4-[[5-[[4-[[[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]amino]carbonyl]phenylamino]-1-piperidinyl]methyl]-6-methyl-2-pyridinyl]oxy]phenyl]methanesulfonamide;

- C. X^1 is N or CR^{6a}, X^2 is O, X^3 is N or CR^{6c}, and X^4 is N; and
- where R is C₁₋₆ alkyl, the C₁₋₆ alkyl is substituted with one to five Z¹; and/or
 - R^{6c} is not 4-amino-2-[(3,4,5-trimethoxyphenyl)amino]-5-thiazolyl, [[4-(1-pyrrolidinylmethyl)phenyl]amino]-5-thiazolyl, or [[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino]-5-thiazolyl; and/or
 - when R is -OR⁷; then R⁷ is not *iso*-butyl or *tert*-butyl;

and the compound is not:

- 2024618-95-7 (α R,5R,8S)-N-[4-chloro-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5,6,7,8-tetrahydro- α ,2,5-trimethyl-8-quinolineacetamide;

D. X^1 is O, X^2 is N or CR^{6b}, X^3 is CR^{6c}, X^4 is N, R^{6c} is other than hydrogen; and R is -NR²R³, wherein R² and R³ together form a heterocyclyl, which may further be independently optionally substituted with one to five Z¹; and at least one of the following a.-d. occurs:

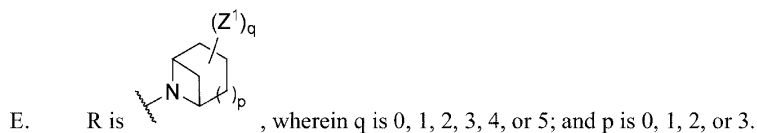
- X^2 is N; or
- R¹ is other than methyl; or
- R² and R³ form an optionally substituted bridged heterocyclyl, which is optionally fused to an aryl or heteroaryl ring; or
- R² and R³ form an optionally substituted monocyclic 7-membered heterocyclyl, which is optionally fused to an aryl or heteroaryl ring;

and the compound is not:

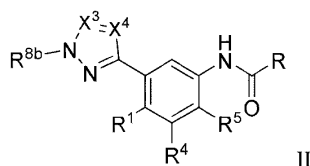
2433600-20-3	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-7-azabicyclo[2.2.1]heptane-7-carboxamide,
1950533-91-1	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide,
1956717-19-3	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3,9-diazabicyclo[4.2.1]nonane-9-carboxamide,
1951851-26-5	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-azabicyclo[3.2.1]octane-8-carboxamide,
1950762-35-2	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide,
1948326-39-3	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxamide,
2390318-25-7	2-thia-5-azabicyclo[2.2.1]heptane-5-carboxamide, N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-, 2-oxide, (1S,4S)-,
2134719-79-0	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxamide,
1951235-51-0	1,3,3a,4,5,6,7,7a-octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-etheno-2H-isoindole-2-carboxamide,
2128457-53-2	N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4-azatricyclo[4.3.1.1 ^{3,8}]undecane-4-carboxamide,
1943194-72-6	(3aR,7aS)-1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
1954930-48-3	octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
1950392-13-8	1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
2127527-42-6	octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
2321449-65-2	rel-(3aR,4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
1943187-21-0	(4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
2128457-20-3	hexahydro-2-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
2129297-32-9	hexahydro-3,5-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,

- 2430356-12-8 hexahydro-4-methoxy-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2135054-93-0 hexahydro-3,3-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2130442-49-6 hexahydro-4,4-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2134261-73-5 hexahydro-2,6-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide, or
- 1944921-02-1 hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-azepine-1-carboxamide; .

and/or



[0071] In certain embodiments, provided is a compound of Formula II:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X³ is N or CR^{6c};

X⁴ is N or CR^{6d};

R is -NR²R³, -OR⁷, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl; wherein the C₁₋₆ alkyl is substituted with halo or C₃₋₁₀ cycloalkyl, and optionally one to four Z¹; and wherein the C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl is optionally substituted with one to five Z¹;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R³ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

or R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R⁵ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6c} and R^{6d} are each independently hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

R⁷ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{8b} is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

or R^{8b} and R^{6c}, or R^{6c} and R^{6d}, together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

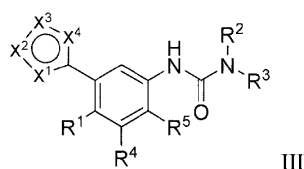
provided that:

when R is -OR⁷; then R⁷ is not methyl, ethyl, *iso*-propyl, *tert*-butyl, 2-bromoethyl, 2-methoxyethyl, 2-cyanoethyl, 2-phenylethyl, benzyl, or 9*H*-fluoren-9-ylmethyl; and the compound is not:

- | | |
|-------------|---|
| 129628-21-3 | [2,4-dichloro-5-[4-chloro-1-methyl-5-(methylthio)-1 <i>H</i> -pyrazol-3-yl]phenyl]-carbamic acid 2-methyl-2-propenyl ester, |
| 945236-54-4 | 1-(1,3-benzodioxol-5-yl)-N-[4-methyl-3-(1-methyl-1 <i>H</i> -pyrazol-3-yl)phenyl]cyclopropanecarboxamide, |
| 142622-93-3 | N-[2,4-dichloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-3-yl]phenyl]-2,2,2-trifluoroacetamide, |

- 142621-98-5 N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide,
- 2231121-13-2 N-[4-bromo-2-fluoro-5-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2H-tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide,
- 2231119-31-4 N-[4-bromo-3-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2H-tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide,
- 159291-92-6 1-bromo-N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorophenyl]cyclopropanecarboxamide, or
- 141576-10-5 N-[2-chloro-5-[4-chloro-1-methyl-5-(methylsulfonyl)-1H-pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide.

[0072] In certain embodiments, provided is a compound of Formula III:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N, NR^{8a}, O, S, or CR^{6a};

X² is N or NR^{8b};

X³ is N, NR^{8c}, or CR^{6c};

X⁴ is N or CR^{6d};

provided that the ring containing X¹, X², X³, and X⁴ is aromatic;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R³ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

or R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂,

$-\text{NR}^{11}\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{11})_2$, or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{11})_2$, $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{11})_2$, or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{11})_2$, $-\text{OR}^{10}$, $-\text{SR}^{10}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{11})_2$, or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{6a} and R^{8b} , R^{8b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{12})_2$, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{S}(\text{O})\text{R}^{12}$, $-\text{S}(\text{O})_2\text{R}^{12}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{S}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{C}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{S}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{N}(\text{R}^{12})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{12})_2$, or $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{13})_2$, $-\text{OR}^{13}$, $-\text{SR}^{13}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{R}^{13}$, $-\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{13})_2$, or $-\text{NR}^{13}\text{C}(\text{O})\text{OR}^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{L}-\text{C}_{1-6}$ alkyl, $-\text{L}-\text{C}_{2-6}$ alkenyl, $-\text{L}-\text{C}_{2-6}$ alkynyl, $-\text{L}-\text{C}_{1-6}$ haloalkyl, $-\text{L}-\text{C}_{3-10}$ cycloalkyl, $-\text{L}-\text{heterocyclyl}$, $-\text{L}-\text{aryl}$, or $-\text{L}-\text{heteroaryl}$; and

each L is independently $-\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{C}_{1-6} \text{ alkyl})-$, $-\text{N}(\text{C}_{2-6} \text{ alkenyl})-$, $-\text{N}(\text{C}_{2-6} \text{ alkynyl})-$, $-\text{N}(\text{C}_{1-6} \text{ haloalkyl})-$, $-\text{N}(\text{C}_{3-10} \text{ cycloalkyl})-$, $-\text{N}(\text{heterocyclyl})-$, $-\text{N}(\text{aryl})-$, $-\text{N}(\text{heteroaryl})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6} \text{ alkenyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6} \text{ alkynyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ haloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{3-10} \text{ cycloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{heterocyclyl})-$, $-\text{C}(\text{O})\text{N}(\text{aryl})-$, $-\text{C}(\text{O})\text{N}(\text{heteroaryl})-$, $-\text{NHC}(\text{O})-$, $-\text{NHC}(\text{O})\text{O}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NHS}(\text{O})-$, or $-\text{S}(\text{O})_2\text{NH}-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{SF}_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl;

provided that:

R^2 and R^3 are not simultaneously methyl;

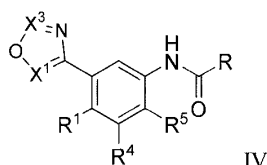
when X^1 is O ; then at least one of R^{8b} , R^{8c} , R^{6c} , or R^{6d} is other than hydrogen; and

the compound is not:

- | | |
|--------------|---|
| 1150100-88-1 | N' -[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]- N -phenyl- N -4-piperidinylurea, |
| 938467-87-9 | N' -[4-chloro-3-(2-methyl-2H-tetrazol-5-yl)phenyl]- N -(3,3-diphenylpropyl)- N -[2-(4-morpholinyl)ethyl]-urea, |
| 1808766-39-3 | 4-(3-chlorophenyl)- N -[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide, |
| 1071521-28-2 | 4-(3-fluorobenzoyl)- N -[4-fluoro-3-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]phenyl]-1-piperazinecarboxamide, |
| 1071521-22-6 | 4-(3-fluorobenzoyl)- N -[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide, |
| 1095716-86-1 | N -[4-chloro-3-ethyl-5-(1-methyl-1H-pyrazol-4-yl)phenyl]-7,8-dihydro-4-(2- |

1150100-22-3 methylphenyl)-2-(3-pyridinyl)pyrido[4,3-d]pyrimidine-6(5H)-carboxamide, or N-[4-[[5-[[4-[[[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]amino]carbonyl]phenylamino]-1-piperidinyl]methyl]-6-methyl-2-pyridinyl]oxy]phenyl]methanesulfonamide.

[0073] In certain embodiments, provided is a compound of Formula IV:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N or CR^{6a};

X³ is N or CR^{6c};

R is -NR²R³, -OR⁷, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl; wherein the C₁₋₆ alkyl is substituted with one to five Z¹; and wherein the C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl is optionally substituted with one to five Z¹;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R³ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

or R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R⁵ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂,

-NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6a} and R^{6c} are each independently hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹:

R⁷ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b}.

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

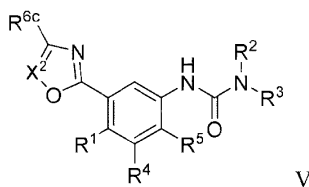
provided that:

R^{6c} is not 4-amino-2-[(3,4,5-trimethoxyphenyl)amino]-5-thiazolyl, [[4-(1-pyrrolidinylmethyl)phenyl]amino]-5-thiazolyl, or [[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino]-5-thiazolyl;

when R is -OR⁷; then R⁷ is not *iso*-butyl or *tert*-butyl; and the compound is not:

2024618-95-7 (α R,5R,8S)-N-[4-chloro-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5,6,7,8-tetrahydro- α ,2,5-trimethyl-8-quinolineacetamide.

[0074] In certain embodiments, provided is a compound of Formula V:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^2 is N or CR^{6b};

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z^1 ;

R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z^1 ;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂,

-NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R⁵ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{bb} is hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

R^{6c} is halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹:

or R^{6b} and R^{6c} together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

provided that one or more of the following occurs:

X² is N;

R¹ is other than methyl;

R² and R³ form an optionally substituted bridged heterocyclyl, which is optionally fused to an aryl or heteroaryl ring; or

R² and R³ form an optionally substituted monocyclic 7-membered heterocyclyl, which is optionally fused to an aryl or heteroaryl ring;

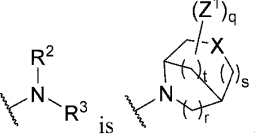
and the compound is not:

2433600-20-3 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-7-azabicyclo[2.2.1]heptane-7-carboxamide,

1950533-91-1 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide,

- 1956717-19-3 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3,9-diazabicyclo[4.2.1]nonane-9-carboxamide,
- 1951851-26-5 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-azabicyclo[3.2.1]octane-8-carboxamide,
- 1950762-35-2 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide,
- 1948326-39-3 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxamide,
- 2390318-25-7 2-thia-5-azabicyclo[2.2.1]heptane-5-carboxamide, N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-, 2-oxide, (1S,4S)-,
- 2134719-79-0 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxamide,
- 1951235-51-0 1,3,3a,4,5,6,7,7a-octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-etheno-2H-isoindole-2-carboxamide,
- 2128457-53-2 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4-azatricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide,
- 1943194-72-6 (3aR,7aS)-1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1954930-48-3 octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1950392-13-8 1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
- 2127527-42-6 octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
- 2321449-65-2 rel-(3aR,4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1943187-21-0 (4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 2128457-20-3 hexahydro-2-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2129297-32-9 hexahydro-3,5-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2430356-12-8 hexahydro-4-methoxy-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2135054-93-0 hexahydro-3,3-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2130442-49-6 hexahydro-4,4-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-

- carboxamide,
- 2134261-73-5 hexahydro-2,6-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide, or
- 1944921-02-1 hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-azepine-1-carboxamide.

[0075] In certain embodiments, R or the moiety  is fused to a C₆ aryl; wherein:

q is 0, 1, 2, or 3;

r is 0 or 1;

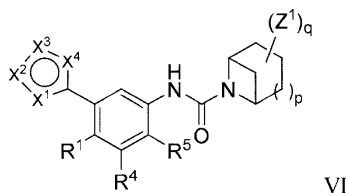
s is 0, 1, or 2;

t is 1 or 2;

X is CH₂, CHZ¹, C(Z¹)₂, NR⁹, O, or S; and

R⁹ is H or Z¹.

[0076] In certain embodiments, provided is a compound of Formula VI:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N, NR^{8a}, O, S, or CR^{6a};

X² is N, NR^{8b}, O, S, or CR^{6b};

X³ is N, NR^{8c}, or CR^{6c};

X⁴ is N or CR^{6d};

provided that at least one of X¹, X², X³, and X⁴ is N, and the ring containing X¹, X², X³, and X⁴ is aromatic;

q is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, or 3;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂,

$-\text{NR}^{11}\text{C}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{11})_2$, or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{11})_2$, $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{11})_2$, or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{11})_2$, $-\text{OR}^{10}$, $-\text{SR}^{10}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{C}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})\text{N}(\text{R}^{11})_2$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{N}(\text{R}^{11})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{11})_2$, or $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8a} and R^{6b} , or R^{8b} and R^{6c} , or R^{6b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{12})_2$, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{S}(\text{O})\text{R}^{12}$, $-\text{S}(\text{O})_2\text{R}^{12}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{S}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{C}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{S}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{N}(\text{R}^{12})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{12})_2$, or $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0077] In certain embodiments of the Formulas disclosed herein, each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

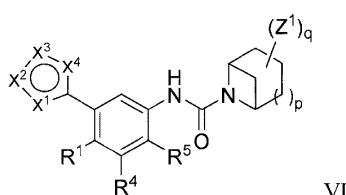
each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each Z^{1a} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0078] In certain embodiments, provided is a compound of Formula VI:



VI

or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^1 is N, NR^{8a} , O, S, or CR^{6a} ;

X^2 is N, NR^{8b} , O, S, or CR^{6b} ;

X^3 is N, NR^{8c} , or CR^{6c} ;

X^4 is N or CR^{6d} ;

provided that at least one of X^1 , X^2 , X^3 , and X^4 is N, and the ring containing X^1 , X^2 , X^3 , and X^4 is aromatic;

q is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, or 3;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each independently hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

R^{8a}, R^{8b}, and R^{8c} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

or R^{8a} and R^{6b}, or R^{8b} and R^{6c}, or R^{6b} and R^{6c}, or R^{8c} and R^{6d}, or R^{6c} and R^{6d}, together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

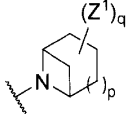
each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

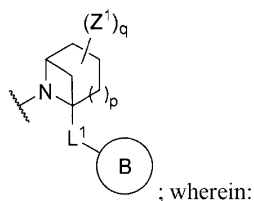
each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0079] In certain embodiments, R, the moiety , or the moiety  is

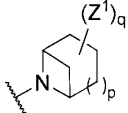


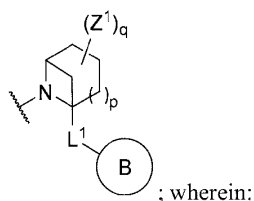
q is 0, 1, 2, 3, or 4;

p is 0, 1, 2, or 3;

Ring B is C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹; and

L¹ is a bond, C₁₋₄ alkylene, C₂₋₄ alkenylene, or C₂₋₄ alkynylene.

[0080] In certain embodiments, R, the moiety , or the moiety  is



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

p is 0, 1, 2, or 3;

Ring B is C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^{1b}; and

L¹ is a bond, C₁₋₄ alkylene, C₂₋₄ alkenylene, or C₂₋₄ alkynylene.

[0081] In certain embodiments, p is 1.

[0082] In certain embodiments, q is 1 or 2.

[0083] In certain embodiments, R¹ is halo, cyano, C₁₋₃ alkyl, C₁₋₃ haloalkyl, or C₃₋₆ cycloalkyl optionally substituted with cyano or methyl.

[0084] In certain embodiments, R¹ is fluoro, chloro, cyano, methyl, ethyl, iso-propyl, difluoromethyl, trifluoromethyl, cyclobutyl, or cyclopropyl optionally substituted with cyano or methyl.

[0085] In certain embodiments, R¹ is chloro, cyano, or trifluoromethyl.

[0086] In certain embodiments, L¹ is a bond or C₁₋₄ alkylene. In certain embodiments, L¹ is a bond or C₁₋₂ alkylene. In certain embodiments, L¹ is a bond or -CH₂-. In certain embodiments, L¹ is a bond.

[0087] In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1a}. In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1a}, and L¹ is a bond or C₁₋₂ alkylene. In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1a}, and L¹ is a bond or CH₂. In certain embodiments, Ring B is heteroaryl and L¹ is a bond. In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1a}, L¹ is a bond, q is 1, and Z¹ is C₁₋₆ alkyl.

[0088] In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1b}. In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1b}, and L¹ is a bond or C₁₋₂ alkylene. In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1b}, and L¹ is a bond or CH₂. In certain embodiments, Ring B is heteroaryl and L¹ is a bond. In certain embodiments, Ring B is heteroaryl optionally substituted with one to five Z^{1b}, L¹ is a bond, q is 1, and Z¹ is C₁₋₆ alkyl.

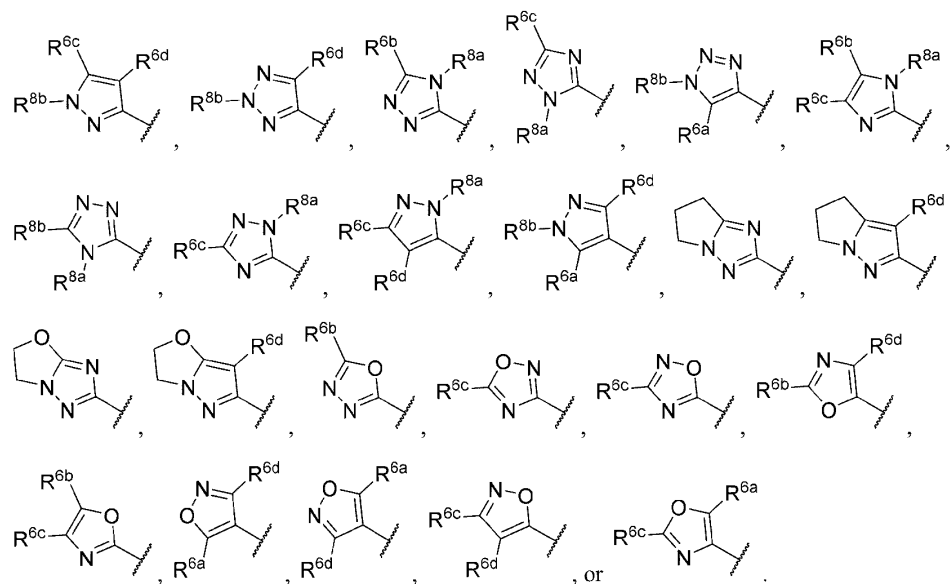
[0089] In certain embodiments, R⁴ is hydrogen or C₁₋₆ alkyl.

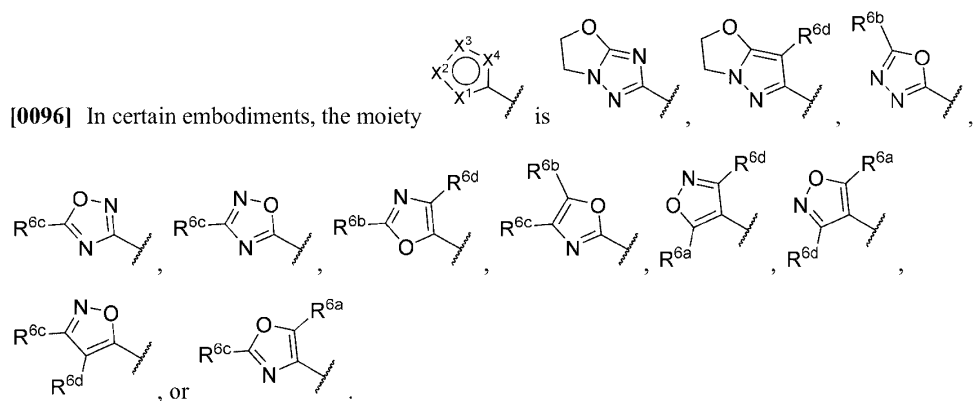
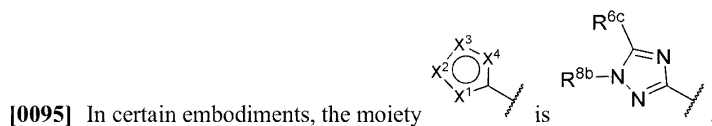
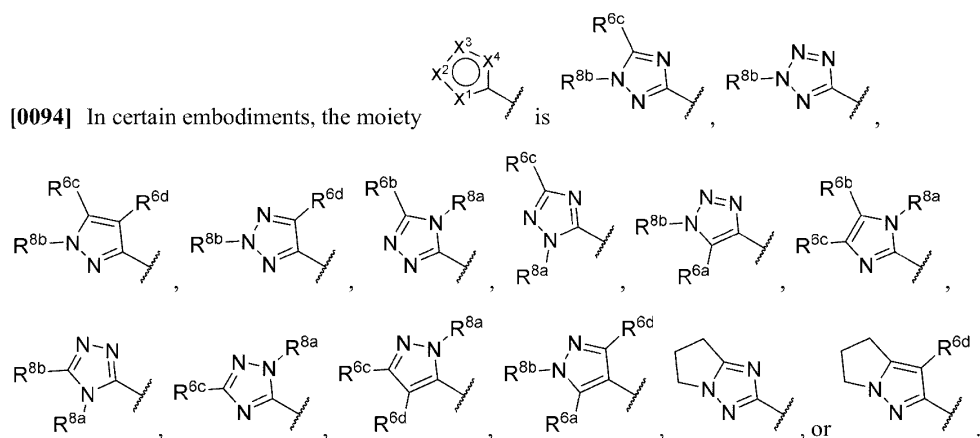
[0090] In certain embodiments, R⁴ is hydrogen or methyl.

[0091] In certain embodiments, R⁵ is hydrogen or halo.

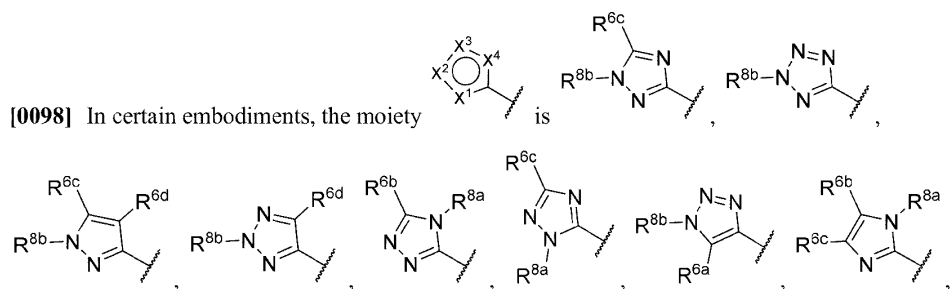
[0092] In certain embodiments, R⁵ is hydrogen or fluoro.

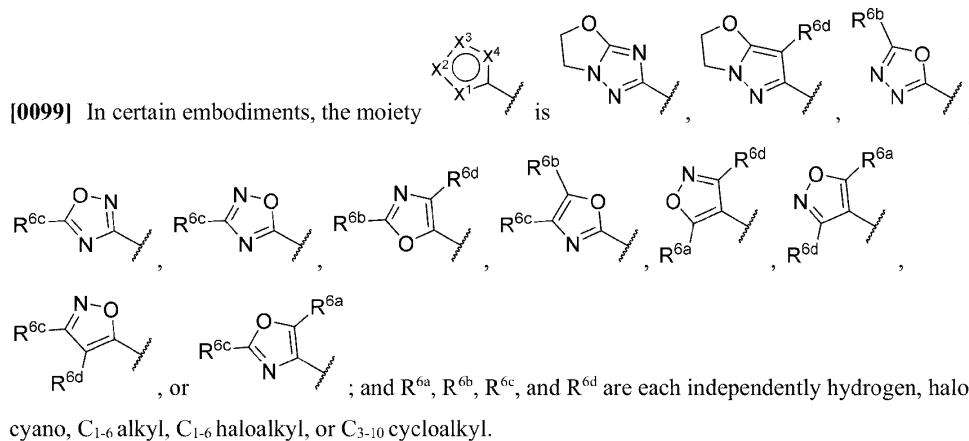
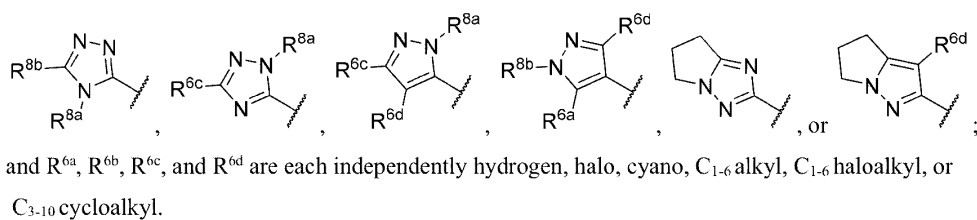
[0093] In certain embodiments, the moiety





[0097] In certain embodiments, R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₃₋₁₀ cycloalkyl.





[0100] In certain embodiments, R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, fluoro, cyano, methyl, ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-methoxyethyl, cyclopropyl, or cyclopropylmethyl.

[0101]

[0102] In certain embodiments, each Z^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, heteroaryl, $-OR^{12}$, or $-C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{1-6} haloalkyl, heteroaryl is independently optionally substituted with one to five hydroxy, methoxy, or methyl.

[0103] In certain embodiments, R is $-OR^7$.

[0104] In certain embodiments, R is $-OR^7$, and R^7 is benzyl or cyclobutyl.

[0105] In certain embodiments, R is $-NR^2R^3$.

[0106] In certain embodiments, R is $-NR^2R^3$, and R^2 and R^3 together form a heterocyclyl, which may further be independently optionally substituted with one to five Z^1 .

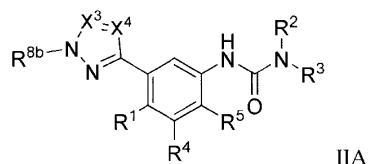
[0107] In certain embodiments, R is $-NR^2R^3$, and R^2 and R^3 together form a heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ; where each Z^1 is independently fluoro, bromo, cyano, methyl, trifluoromethyl, methoxy, cyclopropyl, cyclobutyl, bicyclo[1.1.1]pentan-1-yl, or phenyl.

[0108] In certain embodiments, R is C_{1-6} alkyl optionally substituted with one to five Z^1 .

[0109] In certain embodiments, R is C_{1-6} alkyl optionally substituted with one to five Z^1 ; where each Z^1 is independently fluoro, methyl, trifluoromethyl, cyclopropyl, cyclobutyl, bicyclo[1.1.1]pentan-1-yl, phenyl, or pyridyl.

[0110] In certain embodiments, each Z^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, heteroaryl, C_{1-6} alkoxy, or $-C(O)O-C_{1-6}$ alkyl; wherein each C_{1-6} alkyl, C_{1-6} haloalkyl, heteroaryl is independently optionally substituted with one to five hydroxy, methoxy, or methyl.

[0111] In certain embodiments, provided is a compound of Formula IIA:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^3 is N or CR^{6c} ;

X^4 is N or CR^{6d} ;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five Z^1 ;

R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^3 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^2 and R^3 together form a heterocyclyl, which may further be optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6c} and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$,

-S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

R^{8b} is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

or R^{8b} and R^{6c}, or R^{6c} and R^{6d}, together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

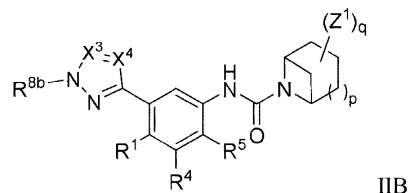
each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0112] In certain embodiments, provided is a compound of Formula IIB:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

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

p is 0, 1, 2, or 3;

X³ is N or CR^{6c};

X⁴ is N or CR^{6d};

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R⁵ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6c} and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^{8b} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8b} and R^{6c} , or R^{6c} and R^{6d} , together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

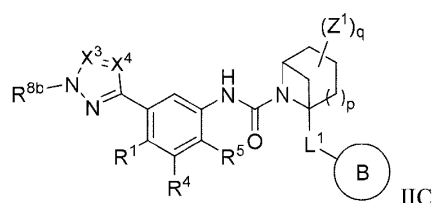
each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0113] In certain embodiments, provided is a compound of Formula IIC:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

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

p is 0, 1, 2, or 3;

L¹ is a bond, C₁₋₄ alkylene, C₂₋₄ alkenylene, or C₂₋₄ alkynylene;

Ring B is C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^{1b} ;

X³ is N or CR^{6c};

X⁴ is N or CR^{6d};

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z^{1c} ;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^{1c} ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6c} and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^{8b} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8b} and R^{6c} , or R^{6c} and R^{6d} , together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein

each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L- C_{1-6} alkyl, -L- C_{2-6} alkenyl, -L- C_{2-6} alkynyl, -L- C_{1-6} haloalkyl, -L- C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0114] In certain embodiments, L^1 is a bond.

[0115] In certain embodiments, R^1 is halo or C_{1-6} alkyl optionally substituted with one to five halo.

[0116] In certain embodiments, R^1 is halo or C_{1-6} haloalkyl. In certain embodiments, R^1 is halo or CF₃.

[0117] In certain embodiments, R^4 is hydrogen.

[0118] In certain embodiments, R^5 is hydrogen or halo.

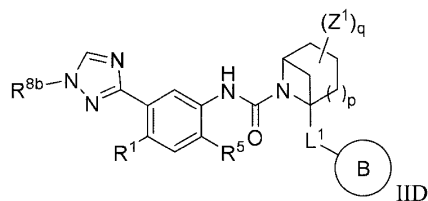
[0119] In certain embodiments, X^3 is CR^{6c}.

[0120] In certain embodiments, X^4 is N.

[0121] In certain embodiments, X^3 is CR^{6c}; and X^4 is N.

[0122] In certain embodiments, R^{8b} is C_{1-6} alkyl. In certain embodiments, R^{8b} is methyl.

[0123] In certain embodiments, provided is a compound of Formula IID:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

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

p is 0, 1, 2, or 3;

L^1 is a bond, C_{1-4} alkylene, C_{2-4} alkenylene, or C_{2-4} alkynylene;

Ring B is C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^{1b} ;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five Z^1 ;

R^5 is hydrogen or halo;

R^{8b} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

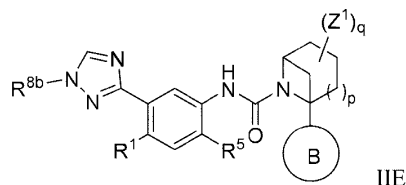
each Z^{1b} is independently halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, $-L$ -heterocyclyl, $-L$ -aryl, or $-L$ -heteroaryl; and

each L is independently $-O-$, $-NH-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(C_{1-6} \text{ alkyl})-$, $-N(C_{2-6} \text{ alkenyl})-$, $-N(C_{2-6} \text{ alkynyl})-$, $-N(C_{1-6} \text{ haloalkyl})-$, $-N(C_{3-10} \text{ cycloalkyl})-$, $-N(\text{heterocyclyl})-$, $-N(\text{aryl})-$, $-N(\text{heteroaryl})-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N(C_{1-6} \text{ alkyl})-$, $-C(O)N(C_{2-6} \text{ alkenyl})-$, $-C(O)N(C_{2-6} \text{ alkynyl})-$, $-C(O)N(C_{1-6} \text{ haloalkyl})-$, $-C(O)N(C_{3-10} \text{ cycloalkyl})-$, $-C(O)N(\text{heterocyclyl})-$, $-C(O)N(\text{aryl})-$, $-C(O)N(\text{heteroaryl})-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHC(O)NH-$, $-NHS(O)-$, or $-S(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five

substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0124] In certain embodiments, provided is a compound of Formula IIE:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

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

p is 0, 1, 2, or 3;

Ring B is C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^{1b};

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R⁵ is hydrogen or halo;

R^{8b} is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L- C_{1-6} alkyl, -L- C_{2-6} alkenyl, -L- C_{2-6} alkynyl, -L- C_{1-6} haloalkyl, -L- C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

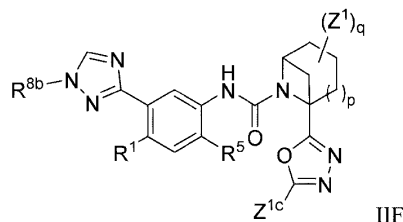
wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0125] In certain embodiments, R^{8b} is C_{1-6} alkyl. In certain embodiments, R^{8b} is methyl.

[0126] In certain embodiments, Ring B is oxadiazole optionally substituted with one to five Z^{1b} .

[0127] In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 0. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2. In certain embodiments, q is 3.

[0128] In certain embodiments, provided is a compound of Formula IIF:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

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

p is 0, 1, 2, or 3;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five Z^1 ;

R^5 is hydrogen or halo;

R^{8b} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, $-L$ -heterocyclyl, $-L$ -aryl, or $-L$ -heteroaryl; and Z^{1c} is hydrogen or Z^{1b} ;

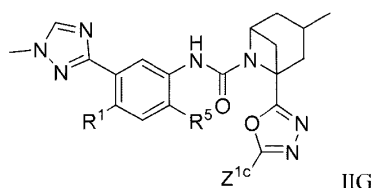
each L is independently $-O-$, $-NH-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(C_{1-6} \text{ alkyl})-$, $-N(C_{2-6} \text{ alkenyl})-$, $-N(C_{2-6} \text{ alkynyl})-$, $-N(C_{1-6} \text{ haloalkyl})-$, $-N(C_{3-10} \text{ cycloalkyl})-$, $-N(\text{heterocyclyl})-$, $-N(\text{aryl})-$, $-N(\text{heteroaryl})-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N(C_{1-6} \text{ alkyl})-$, $-C(O)N(C_{2-6} \text{ alkenyl})-$, $-C(O)N(C_{2-6} \text{ alkynyl})-$, $-C(O)N(C_{1-6} \text{ haloalkyl})-$, $-C(O)N(C_{3-10} \text{ cycloalkyl})-$, $-C(O)N(\text{heterocyclyl})-$, $-C(O)N(\text{aryl})-$, $-C(O)N(\text{heteroaryl})-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHC(O)NH-$, $-NHS(O)-$, or $-S(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0129] In certain embodiments, each Z^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, heteroaryl, $-OR^{12}$, or $-C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{1-6} haloalkyl, heteroaryl is independently optionally substituted with one to five hydroxy, methoxy, or methyl.

[0130] In certain embodiments, each Z^{1b} is independently halo, cyano, C_{1-6} alkyl, or C_{1-6} haloalkyl; wherein each C_{1-6} alkyl or C_{1-6} haloalkyl is independently optionally substituted with hydroxy or methoxy.

[0131] In certain embodiments, provided is a compound of Formula IIG:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five halo;

R^5 is hydrogen or halo;

Z^{1c} is hydrogen or Z^{1b} ;

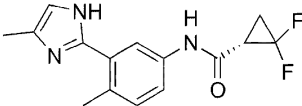
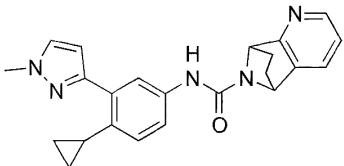
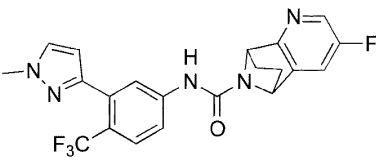
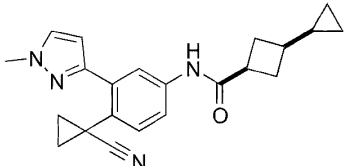
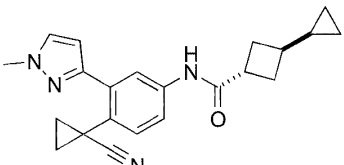
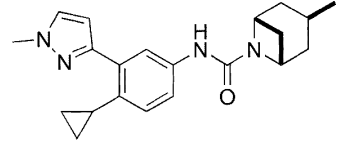
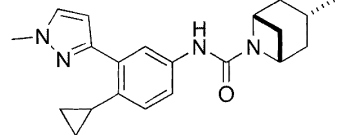
Z^{1b} is halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, $-L$ -heterocyclyl, $-L$ -aryl, or $-L$ -heteroaryl; and

each L is independently $-O-$, $-NH-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(C_{1-6}$ alkyl)-, $-N(C_{2-6}$ alkenyl)-, $-N(C_{2-6}$ alkynyl)-, $-N(C_{1-6}$ haloalkyl)-, $-N(C_{3-10}$ cycloalkyl)-, $-N$ (heterocyclyl)-, $-N$ (aryl)-, $-N$ (heteroaryl)-, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N(C_{1-6}$ alkyl)-, $-C(O)N(C_{2-6}$ alkenyl)-, $-C(O)N(C_{2-6}$ alkynyl)-, $-C(O)N(C_{1-6}$ haloalkyl)-, $-C(O)N(C_{3-10}$ cycloalkyl)-, $-C(O)N$ (heterocyclyl)-, $-C(O)N$ (aryl)-, $-C(O)N$ (heteroaryl)-, $-NHC(O)-$, $-NHC(O)O-$, $-NHC(O)NH-$, $-NHS(O)-$, or $-S(O)_2NH-$;

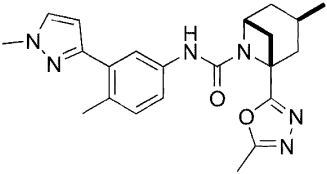
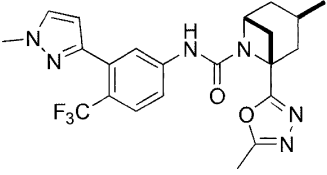
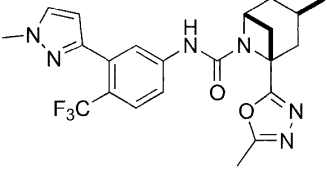
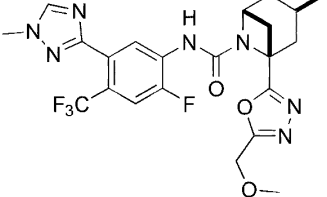
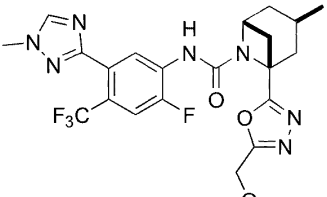
wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl.

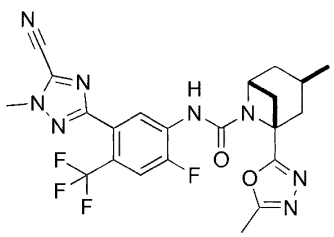
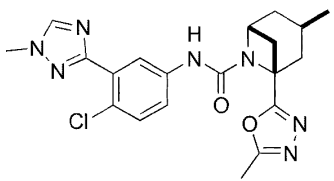
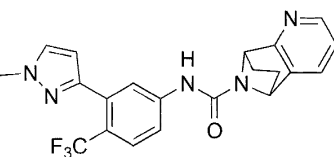
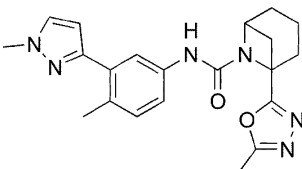
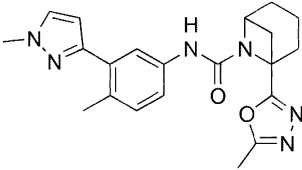
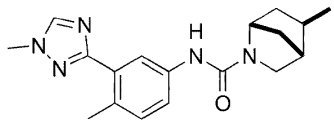
[0132] In certain embodiments, provided is a compound selected from Table 1, or a pharmaceutically acceptable salt, isotopically enriched analog, prodrug, stereoisomer, or a mixture of stereoisomers thereof:

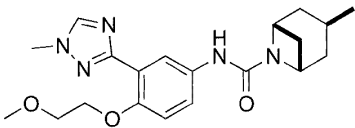
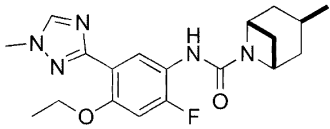
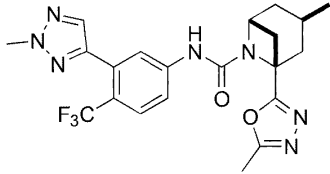
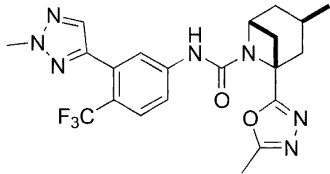
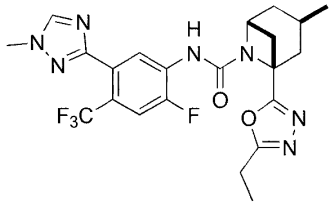
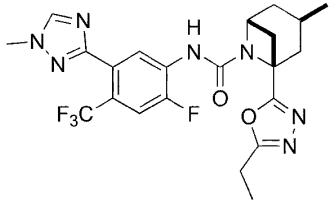
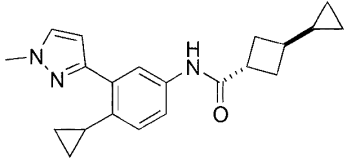
Table 1

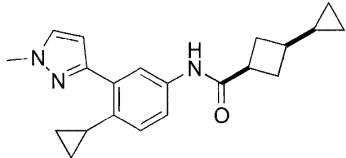
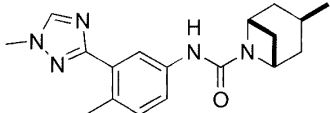
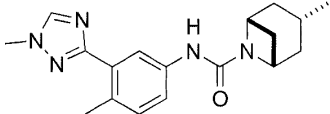
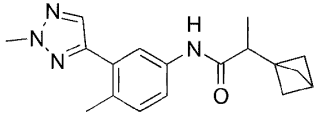
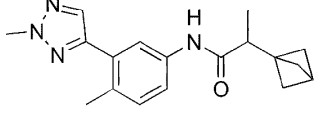
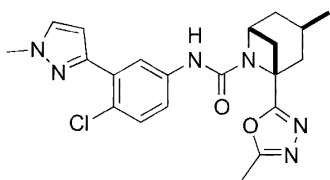
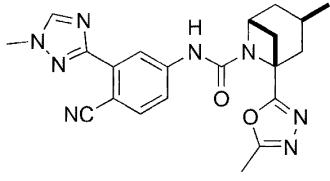
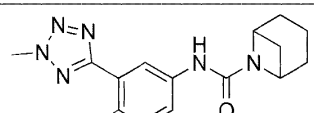
Ex.	Structure
A-1	
A-2	 Mixture of enantiomers
A-3	 Mixture of enantiomers
A-4	
A-5	
A-6	
A-7	

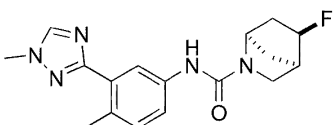
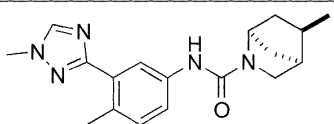
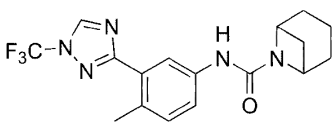
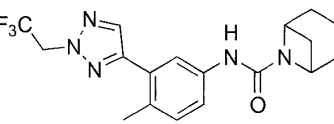
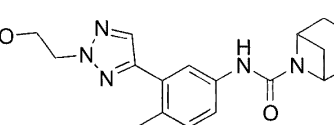
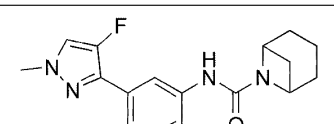
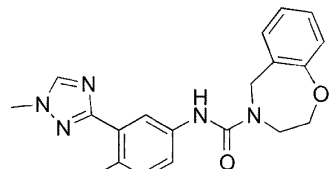
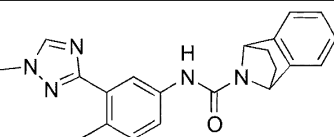
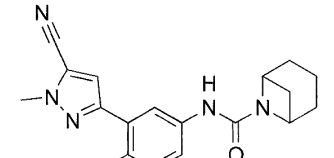
Ex.	Structure
A-8	
A-9	
A-10	
A-11	
A-12	
A-13	
A-14	
A-15	
A-16	

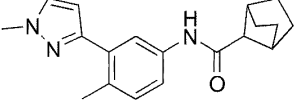
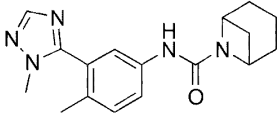
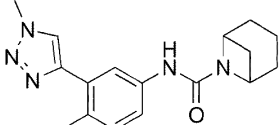
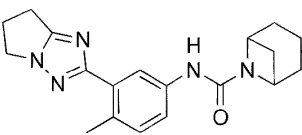
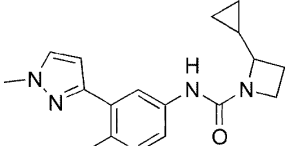
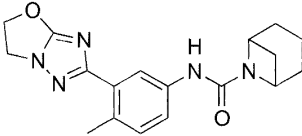
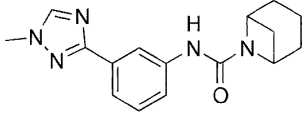
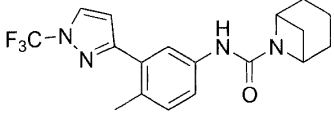
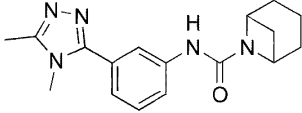
Ex.	Structure
A-17	 Single unknown enantiomer, second eluting
A-18	 Single unknown enantiomer, first eluting
A-19	 Single unknown enantiomer, second eluting
A-20	 Single unknown enantiomer, first eluting
A-21	 Single unknown enantiomer, second eluting

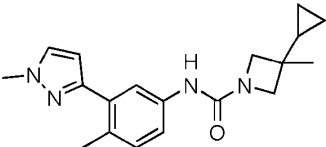
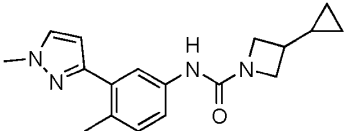
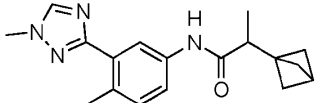
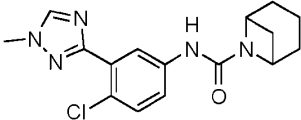
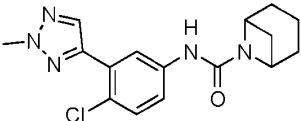
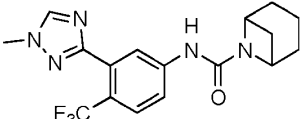
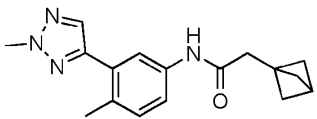
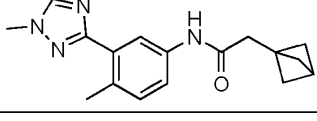
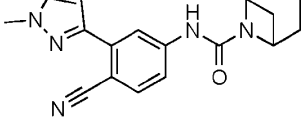
Ex.	Structure
A-22	 Single unknown enantiomer prepared from intermediate 34
A-23	 Single unknown enantiomer prepared from intermediate 34
A-24	 Mixture of enantiomers
A-25	 Single unknown enantiomer, first eluting
A-26	 Single unknown enantiomer, second eluting
A-27	 Mixture of enantiomers

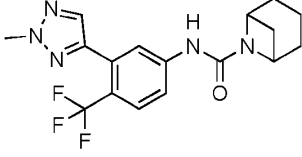
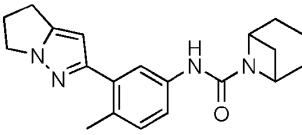
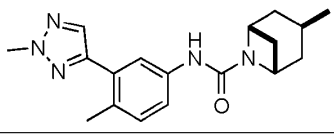
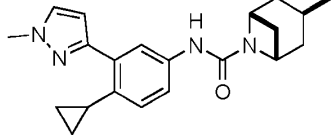
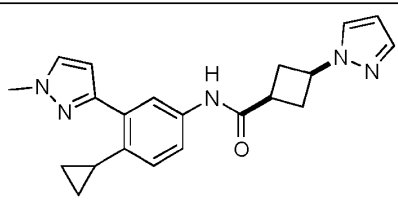
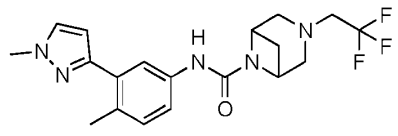
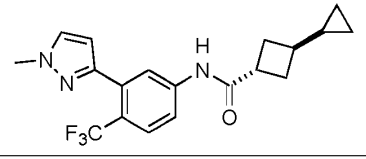
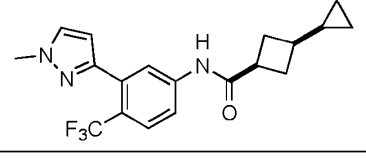
Ex.	Structure
A-28	
A-29	
A-30	 Single unknown enantiomer, first eluting
A-31	 Single unknown enantiomer, second eluting
A-32	 Single unknown enantiomer, first eluting
A-33	 Single unknown enantiomer, second eluting
A-34	

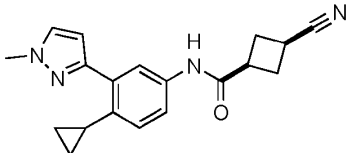
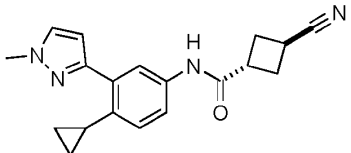
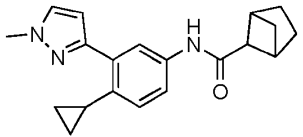
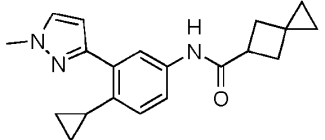
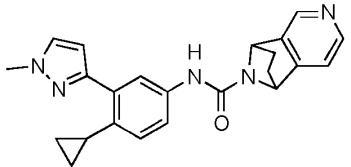
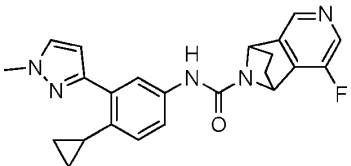
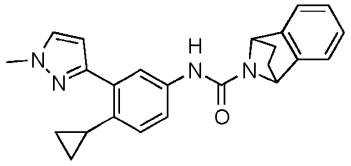
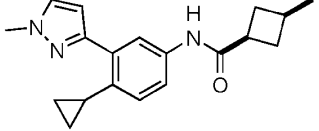
Ex.	Structure
A-35	
A-36	
A-37	
A-38	 Single unknown enantiomer, first eluting
A-39	 Single unknown enantiomer, second eluting
A-40	 Single unknown enantiomer prepared from Intermediate 34
A-41	 Single unknown enantiomer prepared from Intermediate 34
A-42	

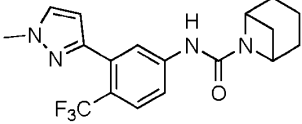
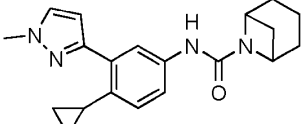
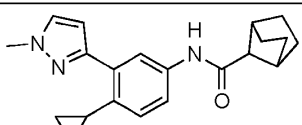
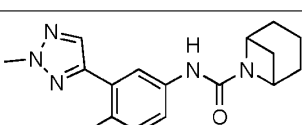
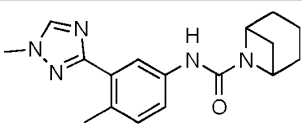
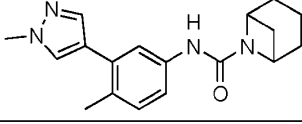
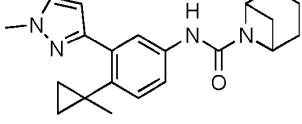
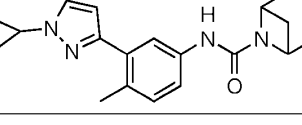
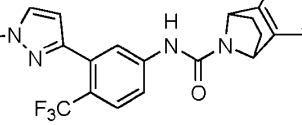
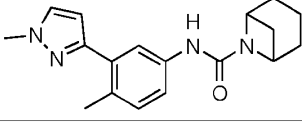
Ex.	Structure
A-43	 Mixture of enantiomers
A-44	 Mixture of enantiomers
A-45	
A-46	
A-47	
A-48	
A-49	
A-50	
A-51	

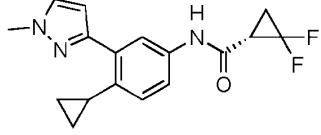
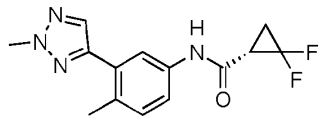
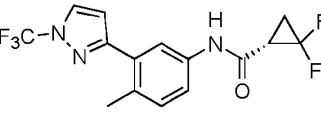
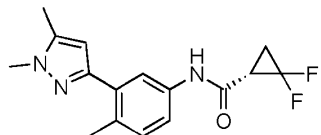
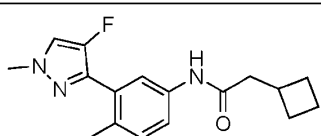
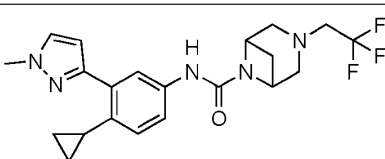
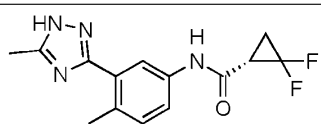
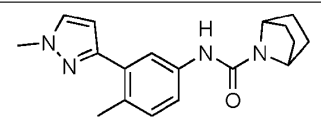
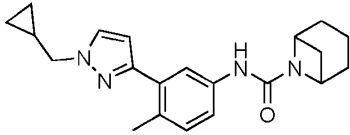
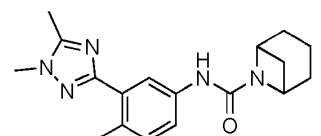
Ex.	Structure
A-52	
A-53	
A-54	
A-55	
A-56	 Mixture of enantiomers
A-57	
A-58	
A-59	
A-60	

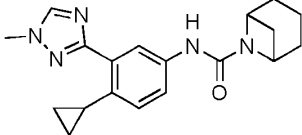
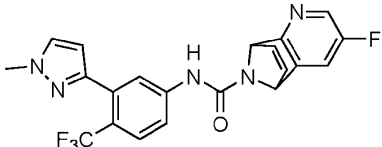
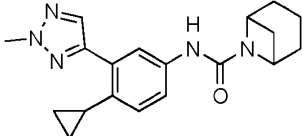
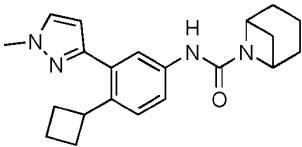
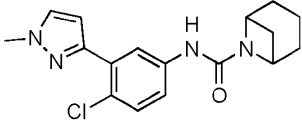
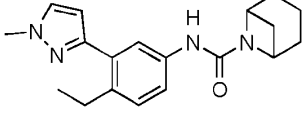
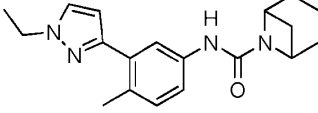
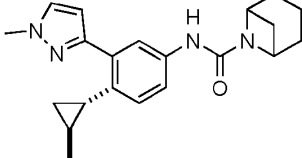
Ex.	Structure
A-61	
A-62	
A-63	 Mixture of enantiomers
A-64	
A-65	
A-66	
A-67	
A-68	
A-69	

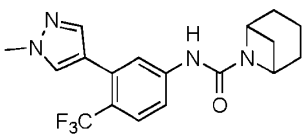
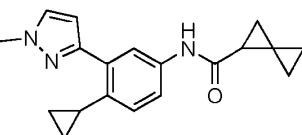
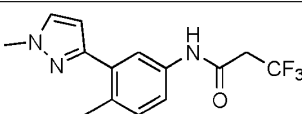
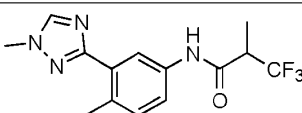
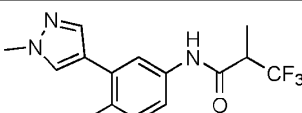
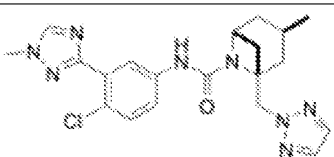
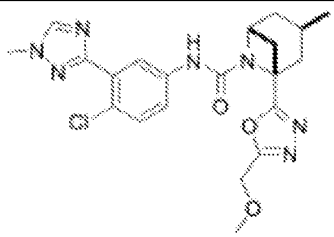
Ex.	Structure
A-70	
A-71	
A-72	
A-73	
A-74	
A-75	
A-76	
A-77	

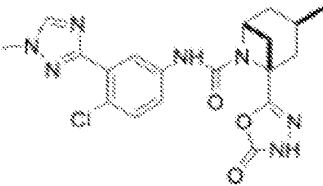
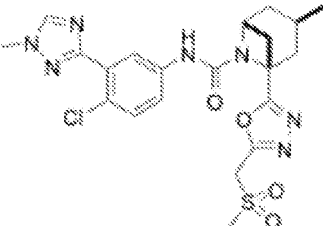
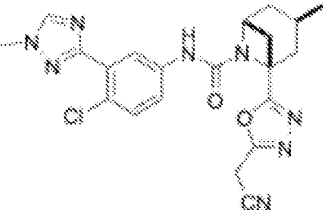
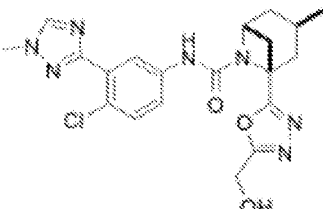
Ex.	Structure
A-78	
A-79	
A-80	
A-81	
A-82	 Mixture of enantiomers
A-83	 Mixture of enantiomers
A-84	
A-85	

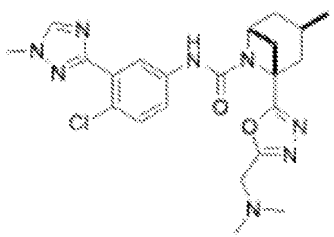
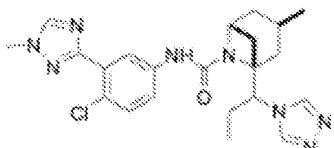
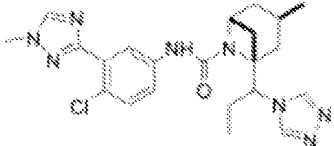
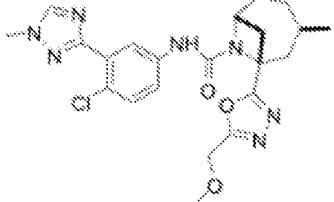
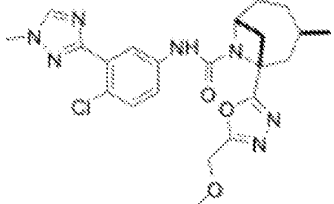
Ex.	Structure
A-86	
A-87	
A-88	
A-89	
A-90	
A-91	
A-92	
A-93	
A-94	
A-95	

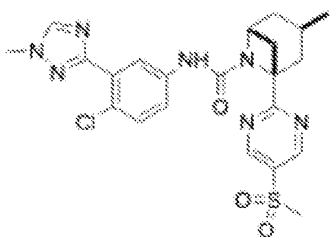
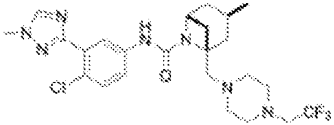
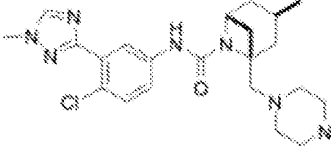
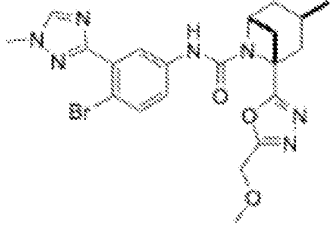
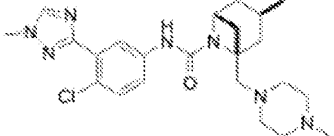
Ex.	Structure
A-96	
A-97	
A-98	
A-99	
A-100	
A-101	
A-102	
A-103	
A-104	
A-105	

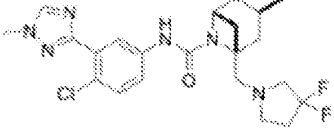
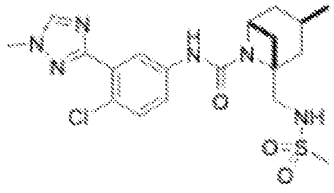
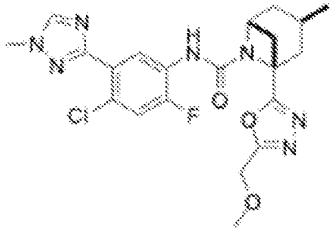
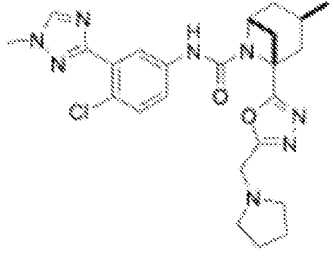
Ex.	Structure
A-106	
A-107	 Mixture of enantiomers
A-108	
A-109	
A-110	
A-111	
A-112	
A-113	 Mixture of enantiomers

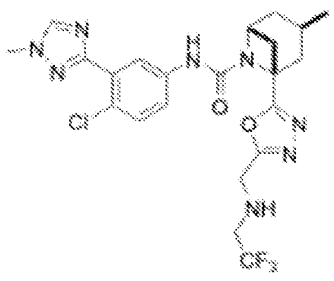
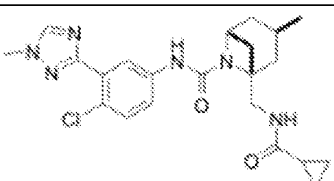
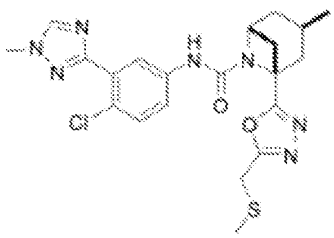
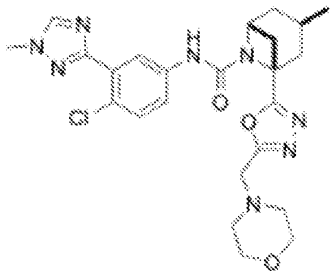
Ex.	Structure
A-114	
A-115	 Mixture of enantiomers
A-116	
A-117	 Mixture of enantiomers
A-118	 Mixture of enantiomers
A-119	 Single unknown enantiomer prepared from Intermediate 31
A-120	 Single unknown enantiomer prepared from Intermediate 34

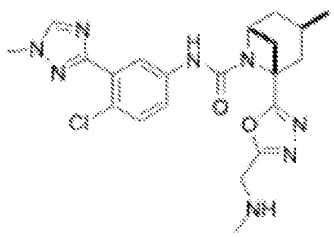
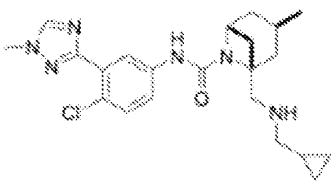
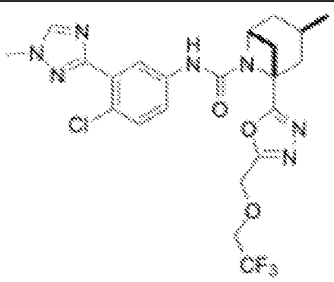
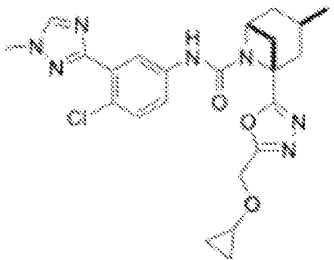
Ex.	Structure
A-121	 Single unknown enantiomer prepared from Intermediate 34
A-122	 Single unknown enantiomer prepared from Intermediate 34
A-123	 Single unknown enantiomer prepared from Intermediate 34
A-124	 Single unknown enantiomer prepared from Intermediate 34

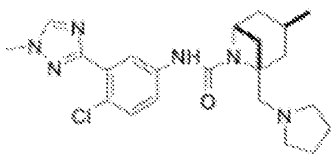
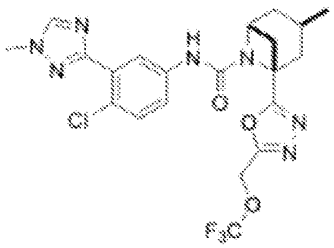
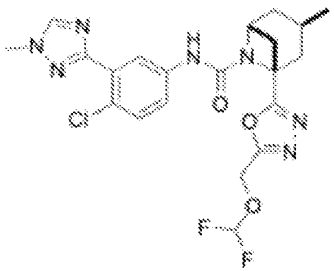
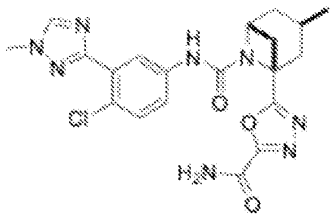
Ex.	Structure
A-125	 Single unknown enantiomer prepared from Intermediate 34
A-126	 Single unknown enantiomer, first eluting
A-127	 Single unknown enantiomer, second eluting
A-128	 Single unknown enantiomer, first eluting
A-129	 Single unknown enantiomer, second eluting

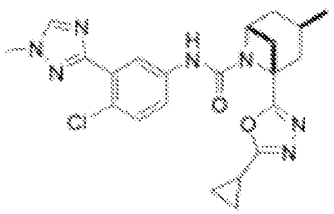
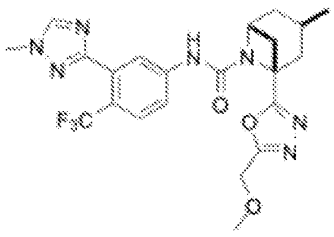
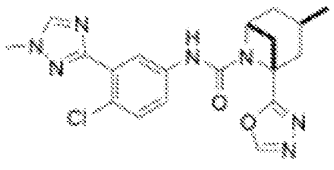
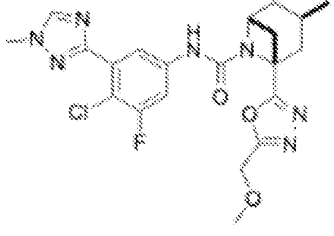
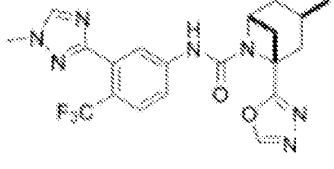
Ex.	Structure
A-130	 Single unknown enantiomer prepared from Intermediate 31
A-131	 Single unknown enantiomer prepared from Intermediate 31
A-132	 Single unknown enantiomer prepared from Intermediate 31
A-133	 Single unknown enantiomer prepared from Intermediate 31
A-134	 Single unknown enantiomer prepared from Intermediate 31

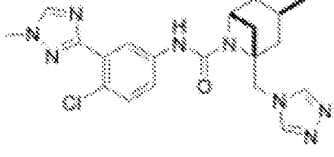
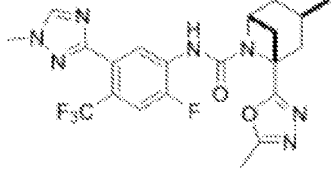
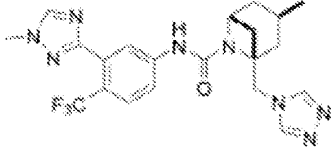
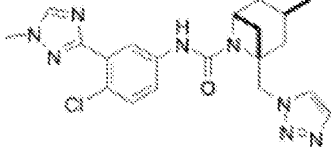
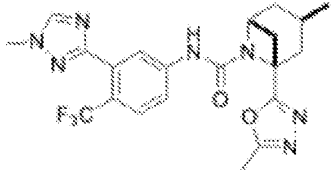
Ex.	Structure
A-135	 Single unknown enantiomer prepared from Intermediate 31
A-136	 Single unknown enantiomer prepared from Intermediate 31
A-137	 Single unknown enantiomer prepared from Intermediate 31
A-138	 Single unknown enantiomer prepared from Intermediate 31

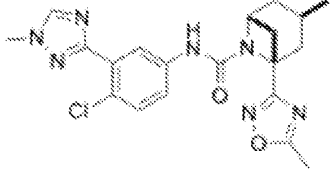
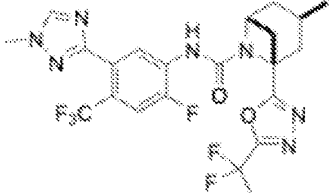
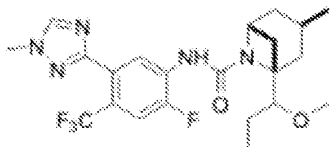
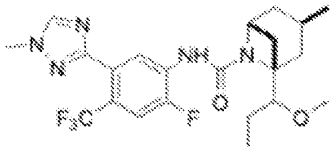
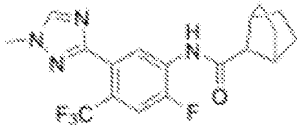
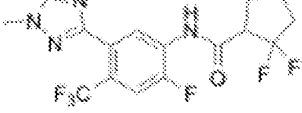
Ex.	Structure
A-139	 Single unknown enantiomer prepared from Intermediate 31
A-140	 Single unknown enantiomer prepared from Intermediate 31
A-141	 Single unknown enantiomer prepared from Intermediate 31
A-142	 Single unknown enantiomer prepared from Intermediate 31

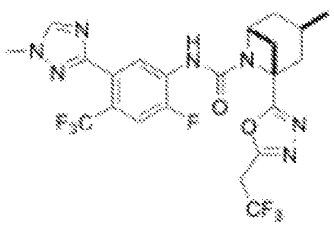
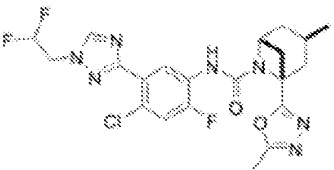
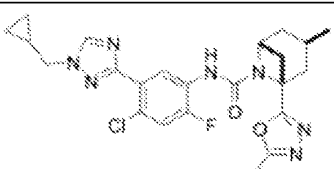
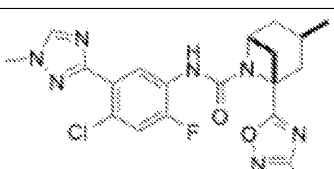
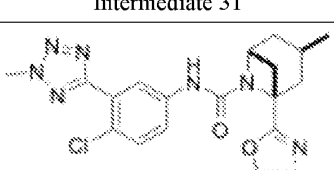
Ex.	Structure
A-143	 Single unknown enantiomer prepared from Intermediate 31
A-144	 Single unknown enantiomer prepared from Intermediate 31
A-145	 Single unknown enantiomer prepared from Intermediate 31
A-146	 Single unknown enantiomer prepared from Intermediate 31

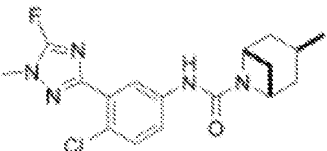
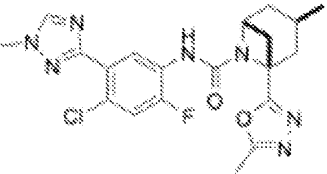
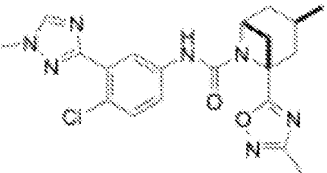
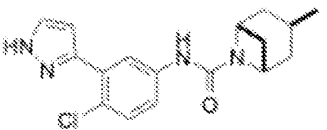
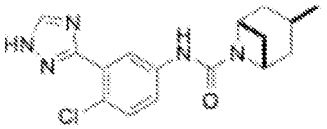
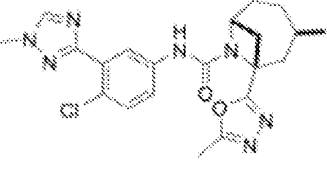
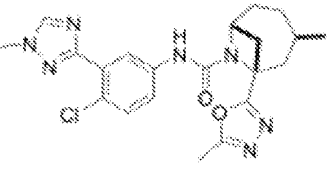
Ex.	Structure
A-147	 Single unknown enantiomer prepared from Intermediate 31
A-148	 Single unknown enantiomer prepared from Intermediate 31
A-149	 Single unknown enantiomer prepared from Intermediate 31
A-150	 Single unknown enantiomer prepared from Intermediate 31

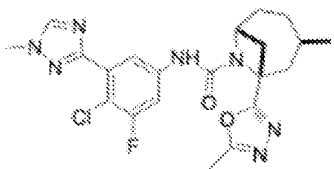
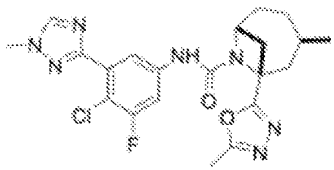
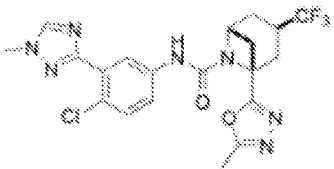
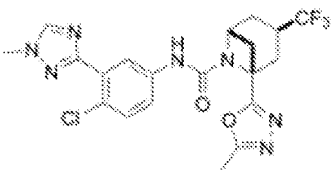
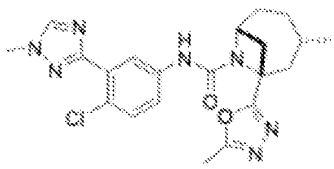
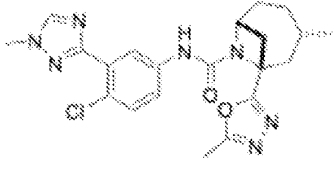
Ex.	Structure
A-151	 Single unknown enantiomer prepared from Intermediate 31
A-152	 Single unknown enantiomer prepared from Intermediate 31
A-153	 Single unknown enantiomer prepared from Intermediate 31
A-154	 Single unknown enantiomer prepared from Intermediate 31
A-155	 Single unknown enantiomer prepared from Intermediate 31

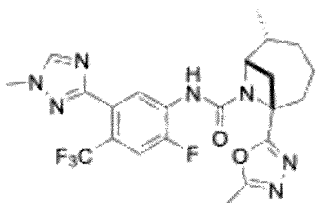
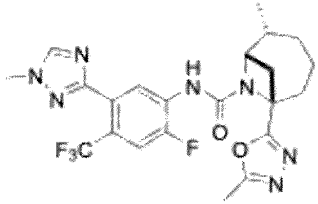
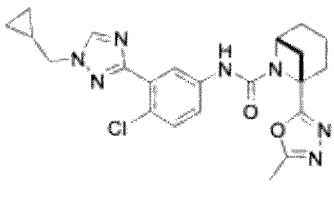
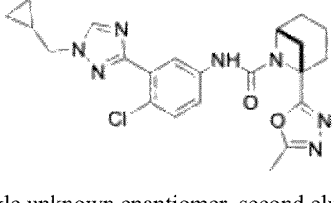
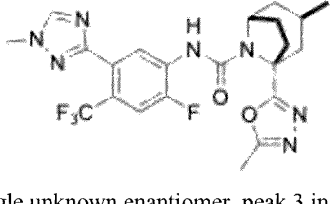
Ex.	Structure
A-156	 Single unknown enantiomer prepared from Intermediate 31
A-157	 Single unknown enantiomer prepared from Intermediate 31
A-158	 Single unknown enantiomer prepared from Intermediate 31
A-159	 Single unknown enantiomer prepared from Intermediate 31
A-160	 Single unknown enantiomer prepared from Intermediate 31

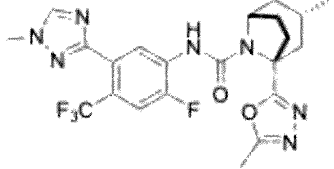
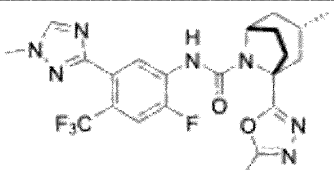
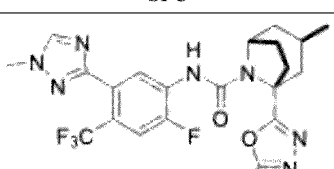
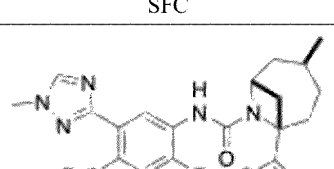
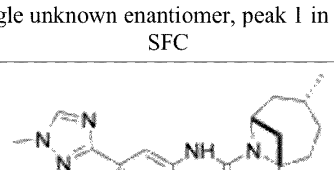
Ex.	Structure
A-161	 Single unknown enantiomer prepared from Intermediate 31
A-162	 Single unknown enantiomer prepared from Intermediate 31
A-163	 Single unknown diastereomer, from Intermediate 47
A-164	 Single unknown diastereomer, from Intermediate 48
A-165	
A-166	 Mixture of enantiomers

Ex.	Structure
A-167	 Single unknown enantiomer prepared from Intermediate 31
A-168	 Single unknown enantiomer prepared from Intermediate 31
A-169	 Single unknown enantiomer prepared from Intermediate 31
A-170	 Single unknown enantiomer prepared from Intermediate 31
A-171	 Single unknown enantiomer prepared from Intermediate 31

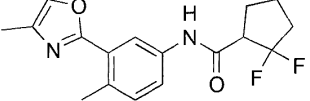
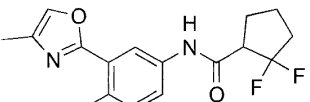
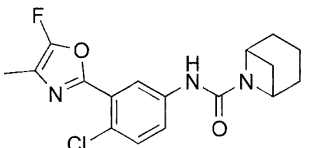
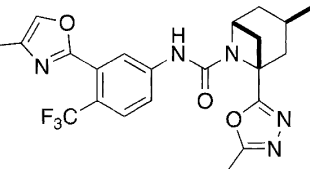
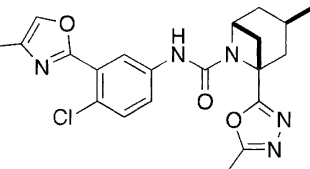
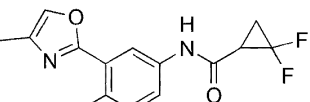
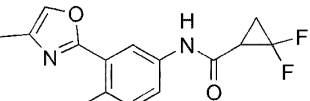
Ex.	Structure
A-172	
A-173	 Single unknown enantiomer prepared from Intermediate 31
A-174	 Single unknown enantiomer prepared from Intermediate 31
A-175	
A-176	
A-177	 Single unknown enantiomer, first eluting
A-178	 Single unknown enantiomer, second eluting

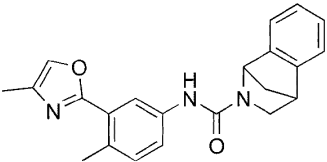
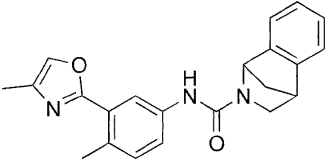
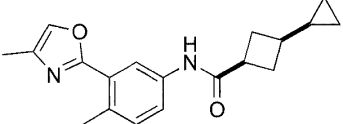
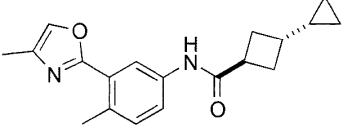
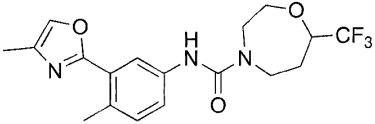
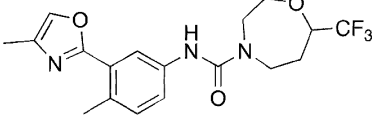
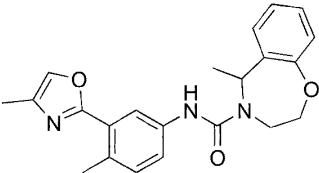
Ex.	Structure
A-179	 Single unknown enantiomer, first eluting
A-180	 Single unknown enantiomer, second eluting
A-181	 Single unknown enantiomer, first eluting
A-182	 Single unknown enantiomer, second eluting
A-183	 Single unknown enantiomer, first eluting
A-184	 Single unknown enantiomer, second eluting

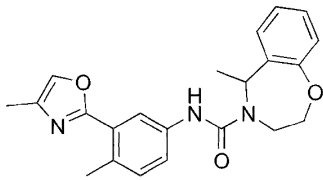
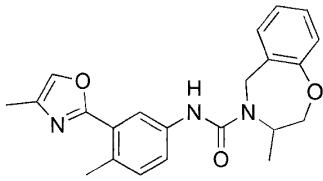
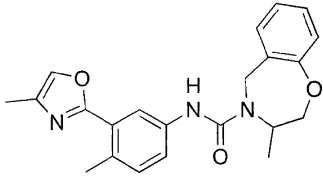
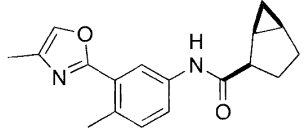
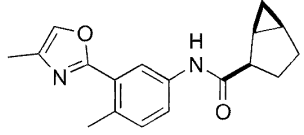
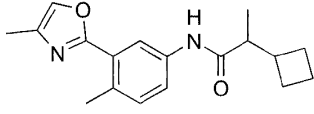
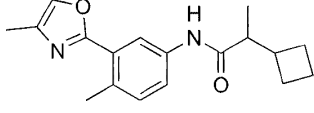
Ex.	Structure
A-185	 Single unknown enantiomer, first eluting
A-186	 Single unknown enantiomer, second eluting
A-187	 Single unknown enantiomer, first eluting
A-188	 Single unknown enantiomer, second eluting
A-189	 Single unknown enantiomer, peak 3 in first SFC

Ex.	Structure
A-190	 Single unknown enantiomer, peak 4 in first SFC
A-191	 Single unknown enantiomer, peak 1 in second SFC
A-192	 Single unknown enantiomer, peak 2 in second SFC
A-193	 Single unknown enantiomer, peak 1 in first SFC
A-194	 Single unknown enantiomer, peak 3 in first SFC

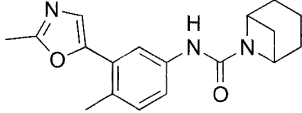
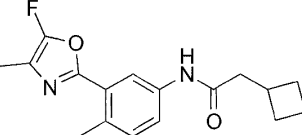
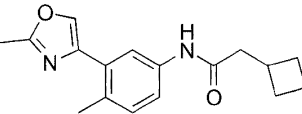
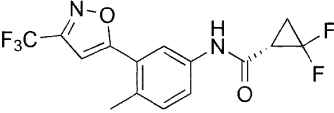
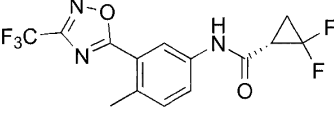
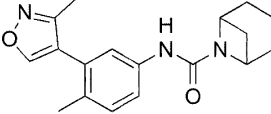
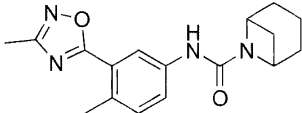
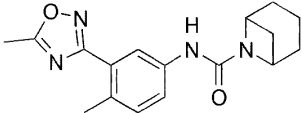
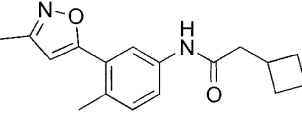
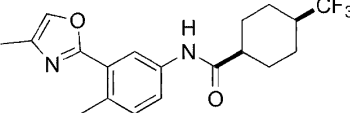
Ex.	Structure
A-195	Single unknown enantiomer, peak 1 in second SFC
A-196	Single unknown enantiomer, peak 3 in second SFC
A-197	Single unknown enantiomer, peak 1 in third SFC
A-198	Single unknown enantiomer, peak 2 in third SFC
B-1	
B-2	

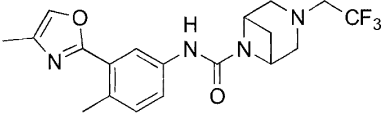
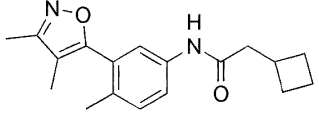
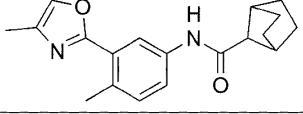
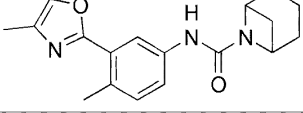
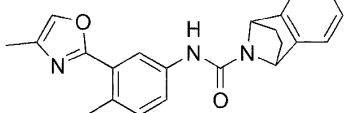
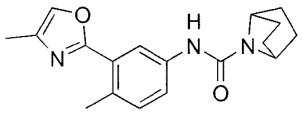
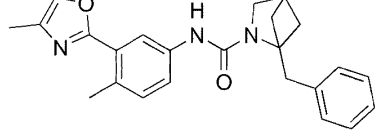
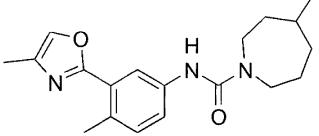
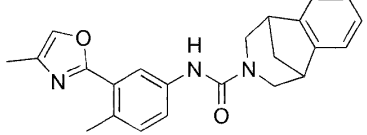
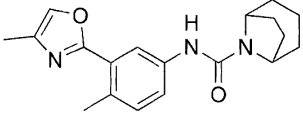
Ex.	Structure
B-3	 Single unknown enantiomer, first eluting
B-4	 Single unknown enantiomer, second eluting
B-5	 Single unknown enantiomer, first eluting
B-6	 Single unknown enantiomer from Intermediate 34
B-7	 Single unknown enantiomer from Intermediate 34
B-8	 Single unknown enantiomer, first eluting
B-9	 Single unknown enantiomer, second eluting

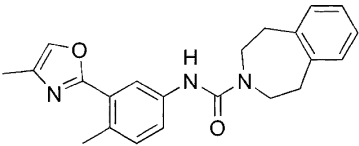
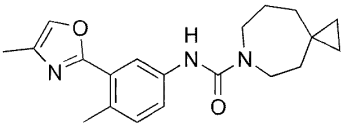
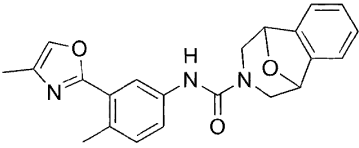
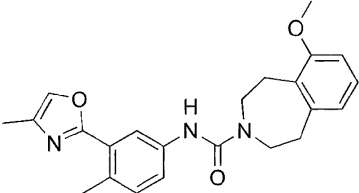
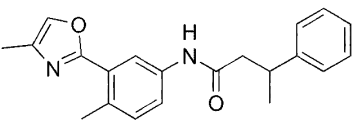
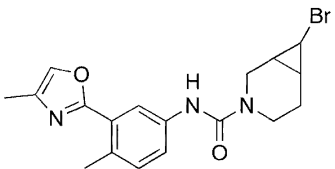
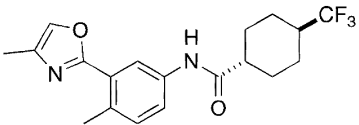
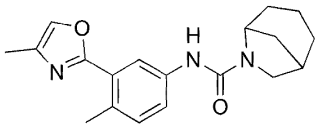
Ex.	Structure
B-10	 Single unknown enantiomer, first eluting
B-11	 Single unknown enantiomer, second eluting
B-12	 Single unknown enantiomer, first eluting
B-13	 Single unknown enantiomer, second eluting
B-14	 Single unknown enantiomer, first eluting
B-15	 Single unknown enantiomer, second eluting
B-16	 Single unknown enantiomer, first eluting

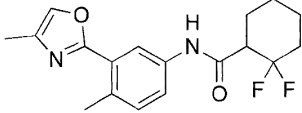
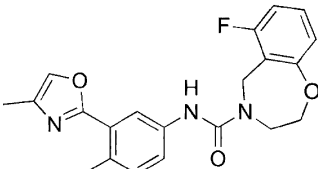
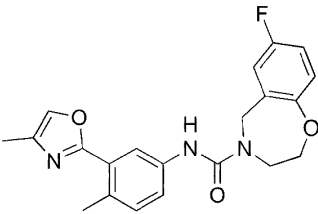
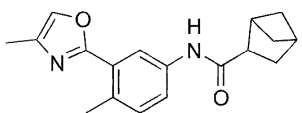
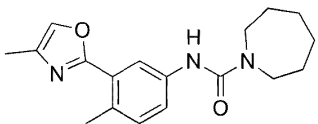
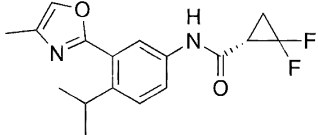
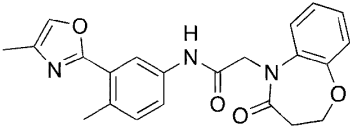
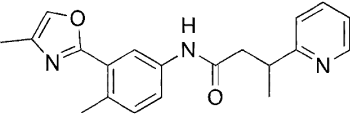
Ex.	Structure
B-17	 Single unknown enantiomer, second eluting
B-18	 Single unknown enantiomer, first eluting
B-19	 Single unknown enantiomer, second eluting
B-20	 Single unknown enantiomer, first eluting
B-21	 Single unknown enantiomer, second eluting
B-22	 Single unknown enantiomer, first eluting
B-23	 Single unknown enantiomer, second eluting

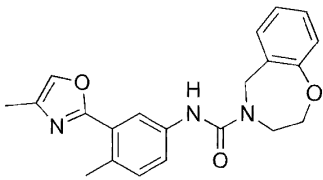
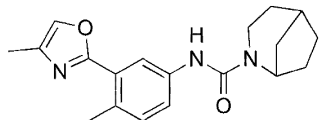
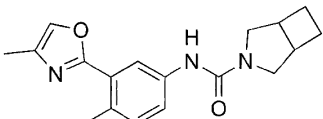
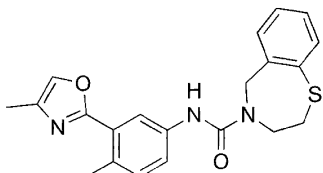
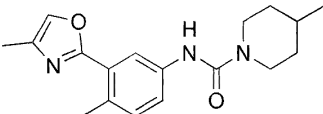
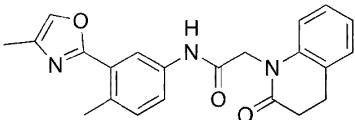
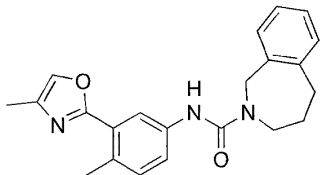
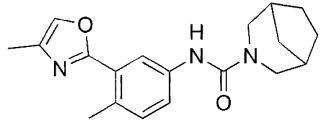
Ex.	Structure
B-24	Single unknown enantiomer, first eluting
B-25	Single unknown enantiomer, second eluting
B-26	Single unknown enantiomer, first eluting
B-27	Single unknown enantiomer, second eluting
B-28	Single unknown enantiomer, first eluting
B-29	Single unknown enantiomer, second eluting
B-30	Single unknown enantiomer, first eluting
B-31	Single unknown enantiomer, second eluting

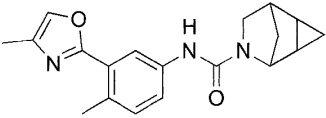
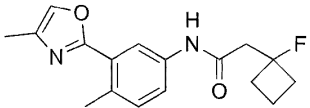
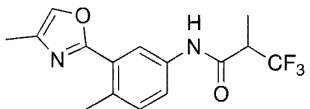
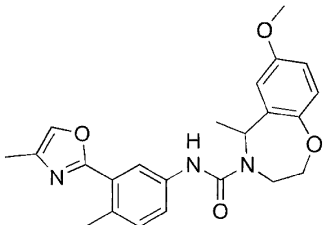
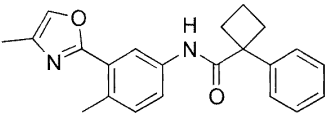
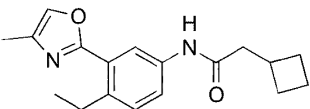
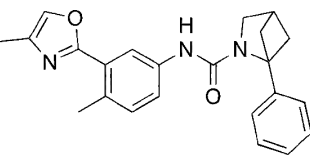
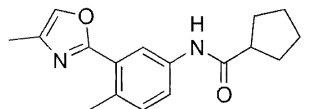
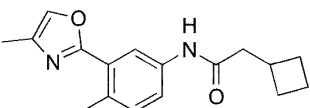
Ex.	Structure
B-32	
B-33	
B-34	
B-35	
B-36	
B-37	
B-38	
B-39	
B-40	
B-41	

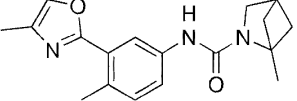
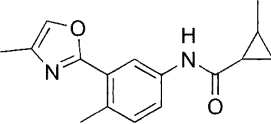
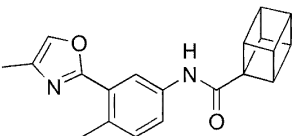
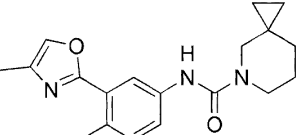
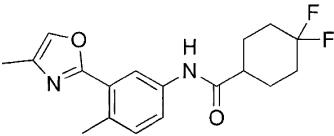
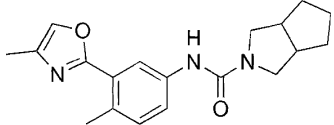
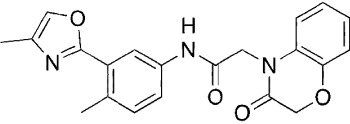
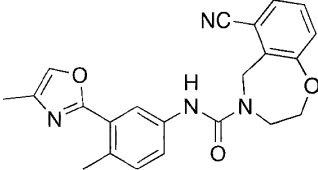
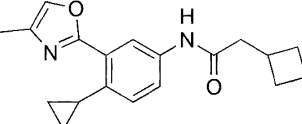
Ex.	Structure
B-42	
B-43	
B-44	
B-45	
B-46	
B-47	
B-48	
B-49	 Mixture of enantiomers
B-50	
B-51	

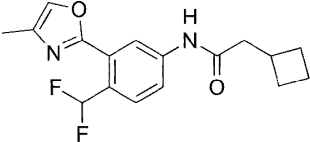
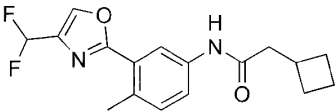
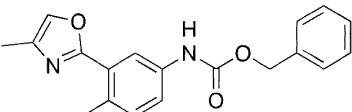
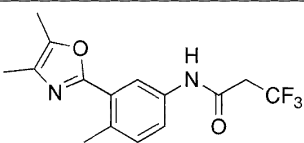
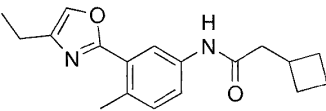
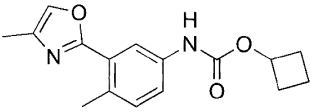
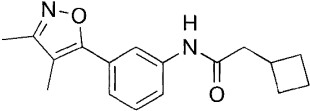
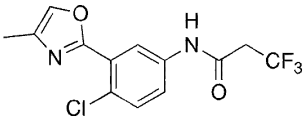
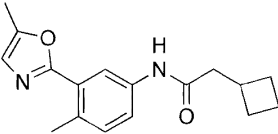
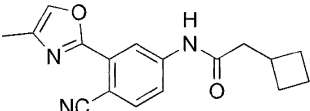
Ex.	Structure
B-52	
B-53	
B-54	
B-55	
B-56	 Mixture of enantiomers
B-57	 Mixture of diastereomers
B-58	
B-59	 Mixture of enantiomers

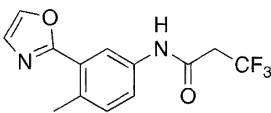
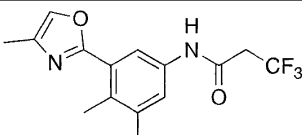
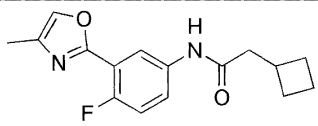
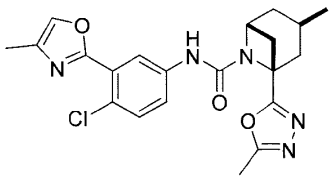
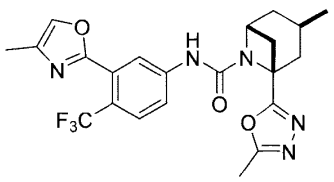
Ex.	Structure
B-60	 Mixture of enantiomers
B-61	
B-62	
B-63	 Mixture of enantiomers
B-64	
B-65	
B-66	
B-67	 Mixture of enantiomers

Ex.	Structure
B-68	
B-69	 Mixture of enantiomers
B-70	
B-71	
B-72	
B-73	
B-74	
B-75	

Ex.	Structure
B-76	 Mixture of diastereomers
B-77	 Mixture of diastereomers
B-78	 Mixture of enantiomers
B-79	 Mixture of enantiomers
B-80	 Mixture of enantiomers
B-81	 Mixture of enantiomers
B-82	 Mixture of enantiomers
B-83	 Mixture of enantiomers
B-84	 Mixture of enantiomers

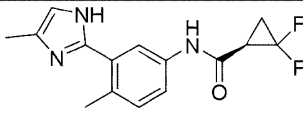
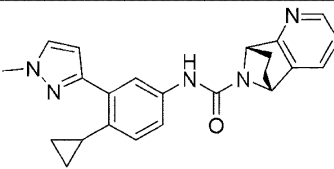
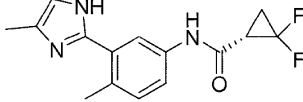
Ex.	Structure
B-85	
B-86	 Mixture of diastereomers
B-87	
B-88	
B-89	
B-90	
B-91	
B-92	
B-93	

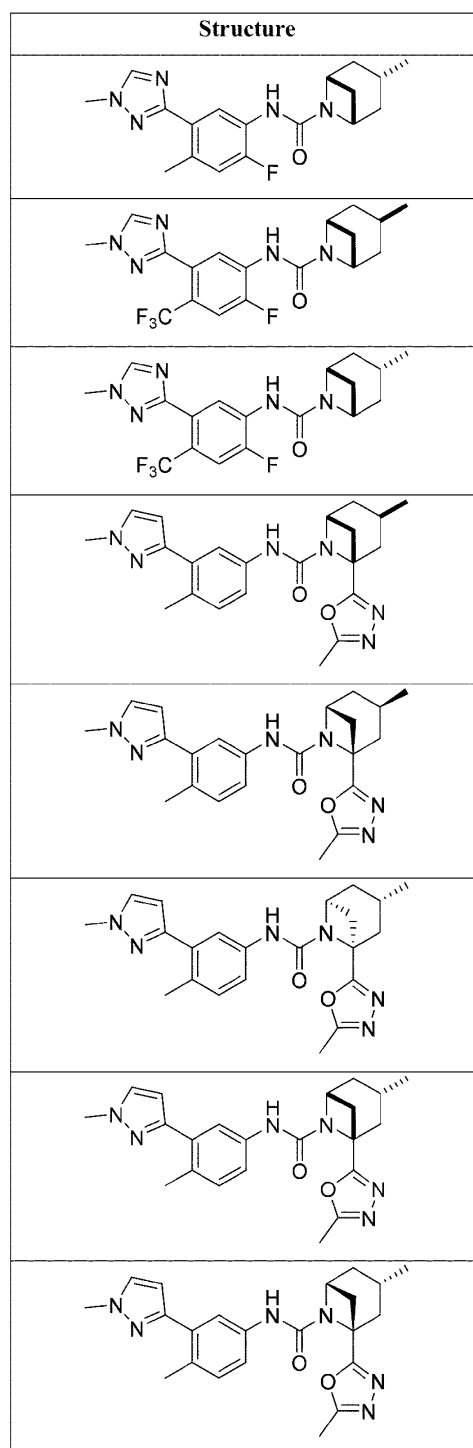
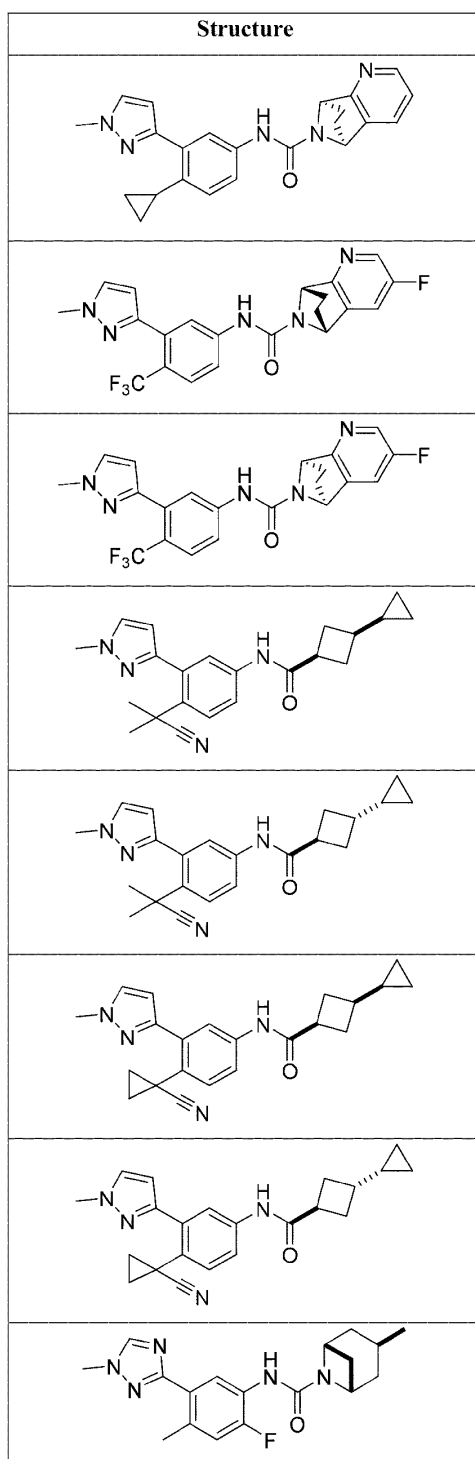
Ex.	Structure
B-94	
B-95	
B-96	
B-97	
B-98	
B-99	
B-100	
B-101	
B-102	
B-103	

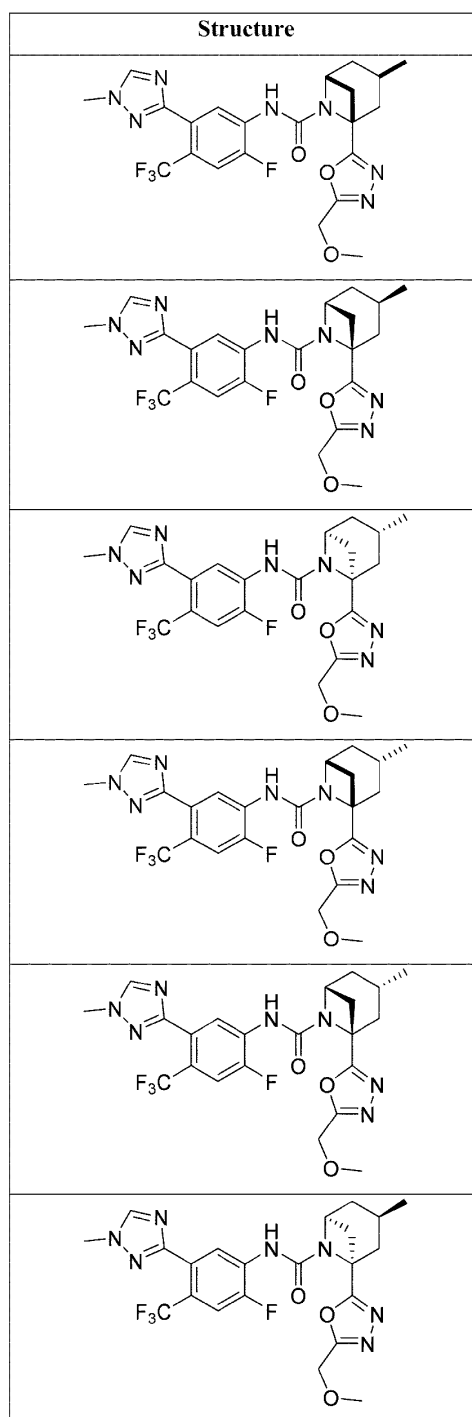
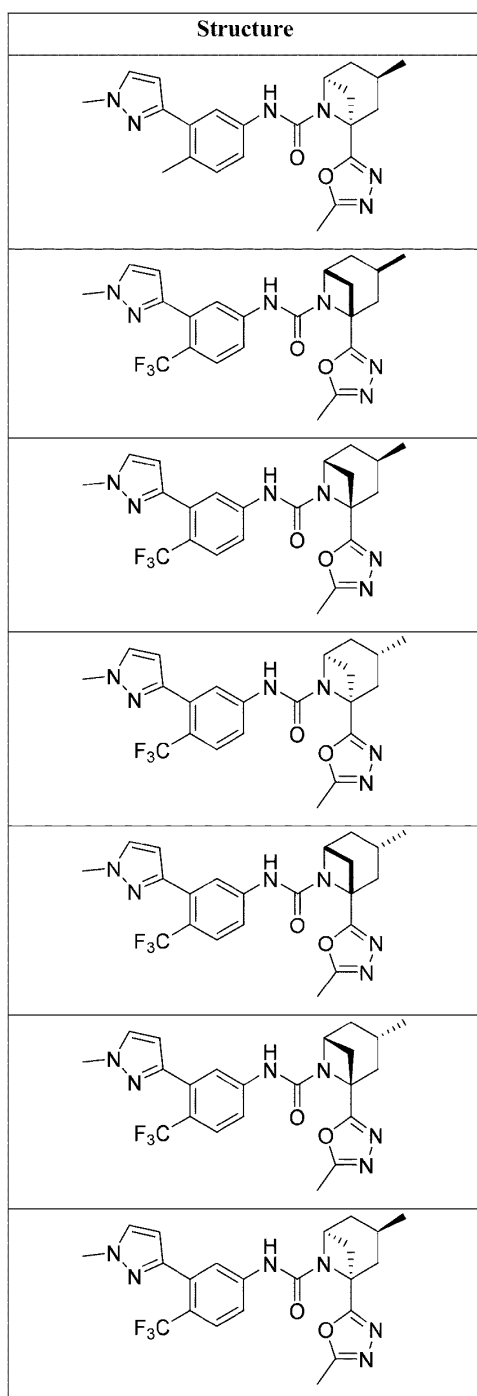
Ex.	Structure
B-104	
B-105	
B-106	
B-107	 Single unknown enantiomer prepared from Intermediate 31
B-108	 Single unknown enantiomer prepared from Intermediate 31

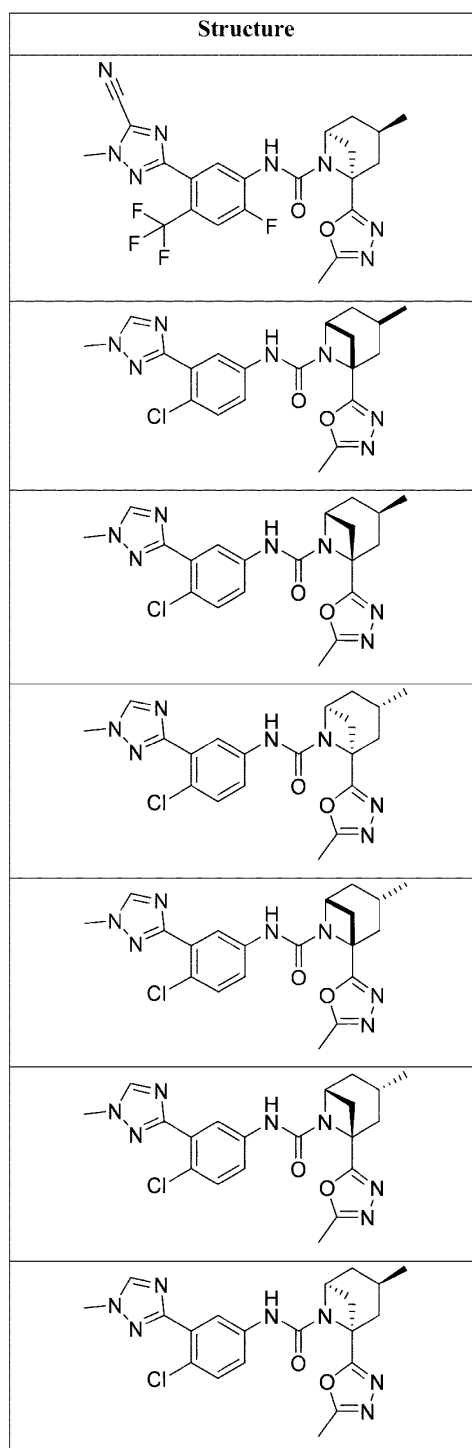
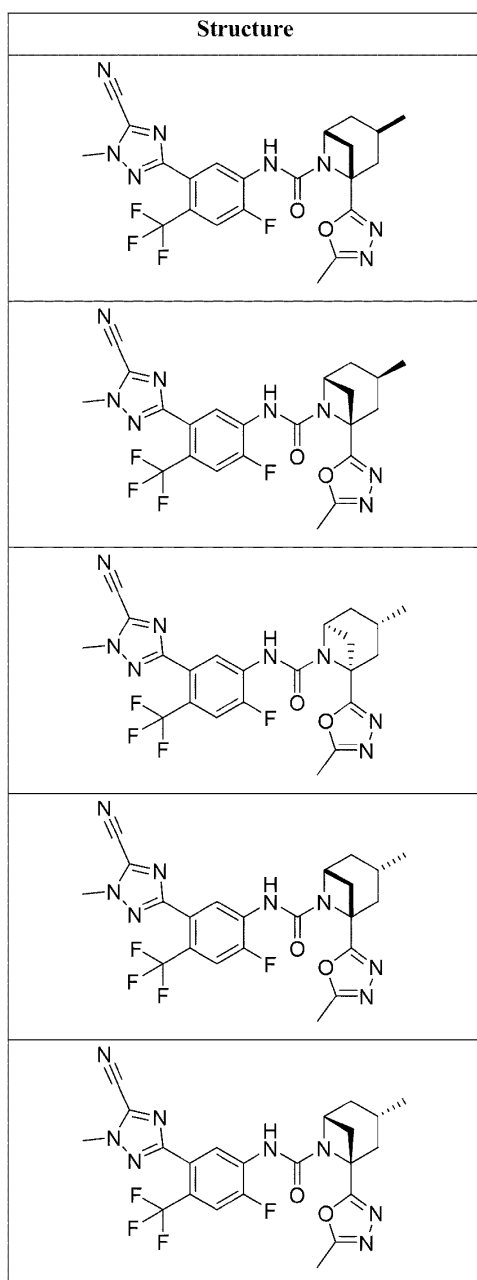
[0133] In certain embodiments, provided is a compound selected from Table 2 or a pharmaceutically acceptable salt thereof.

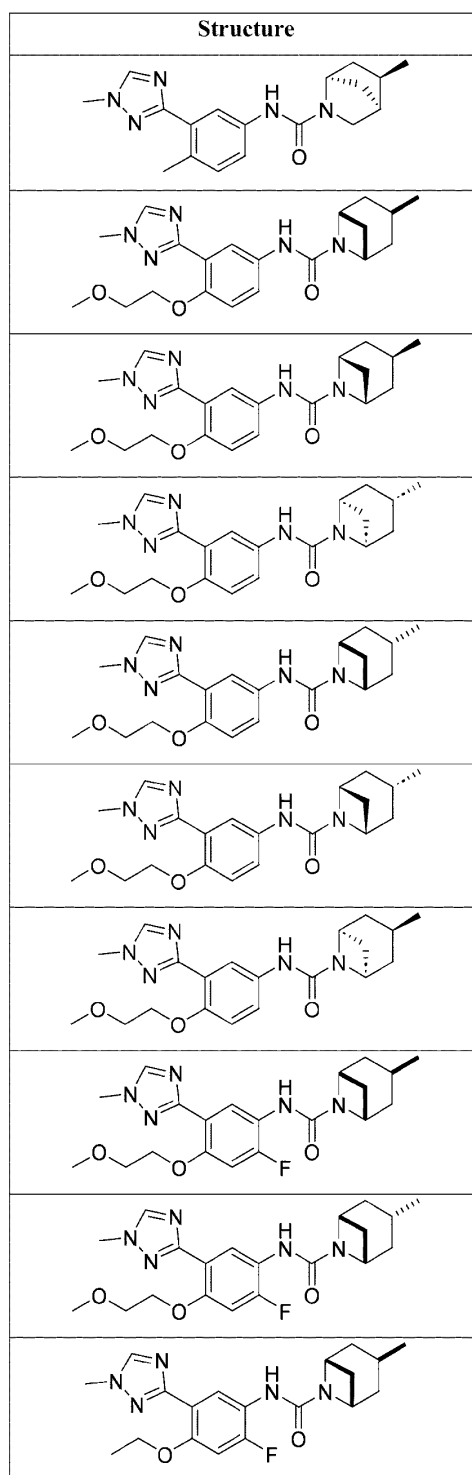
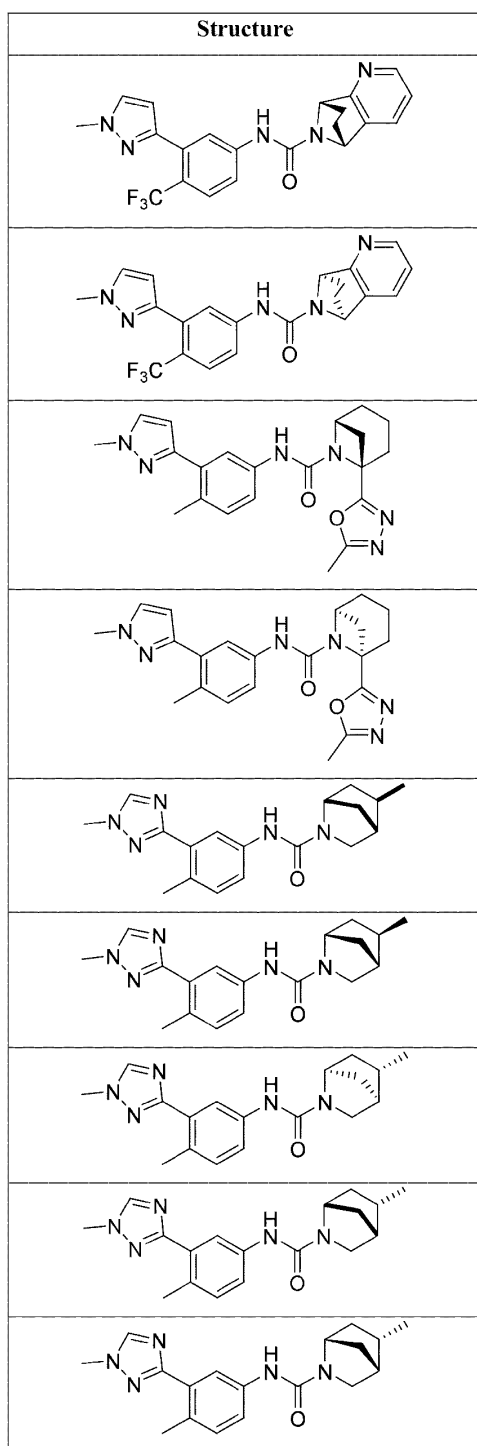
Table 2

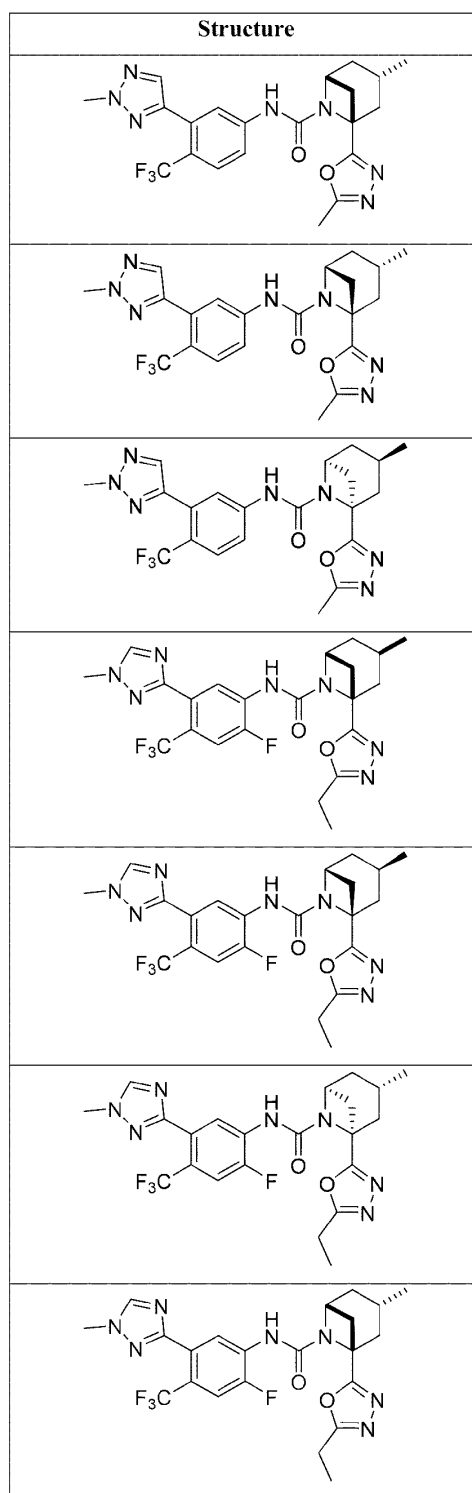
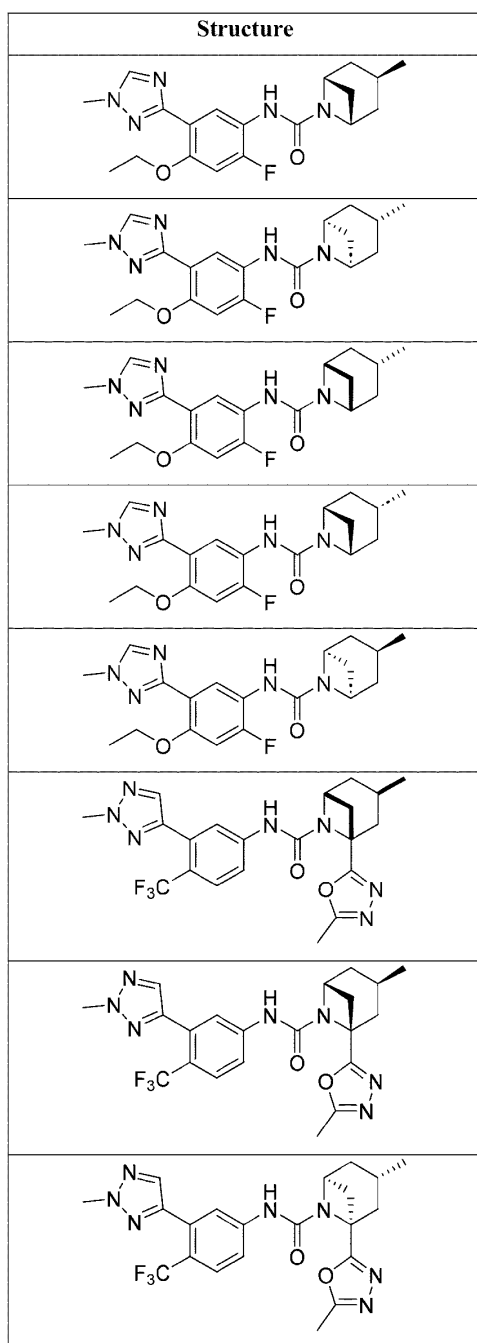
Structure	Structure
	
	





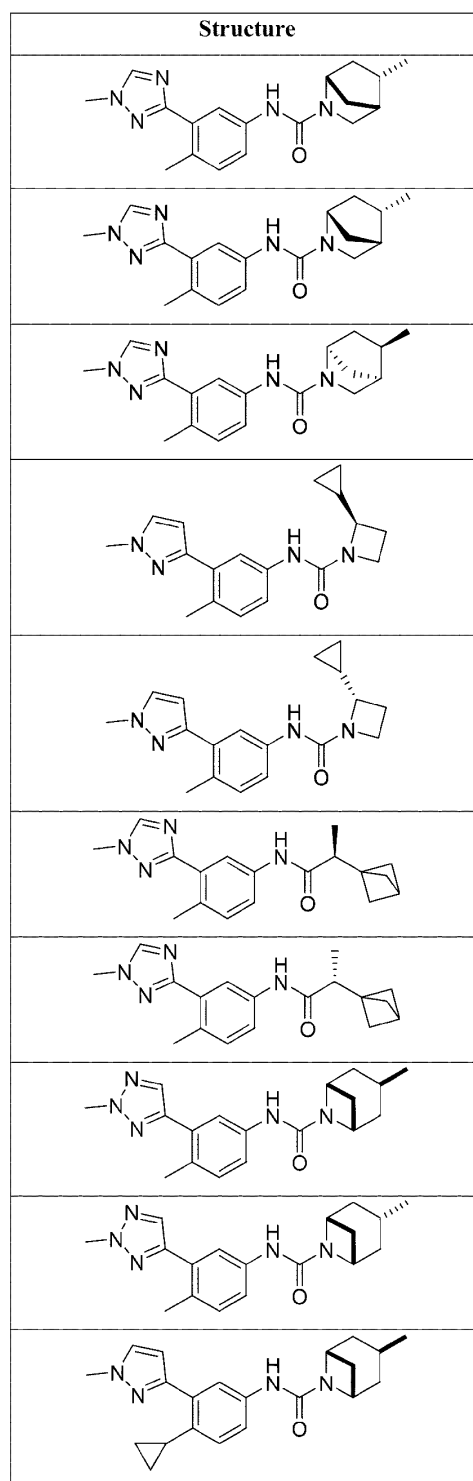
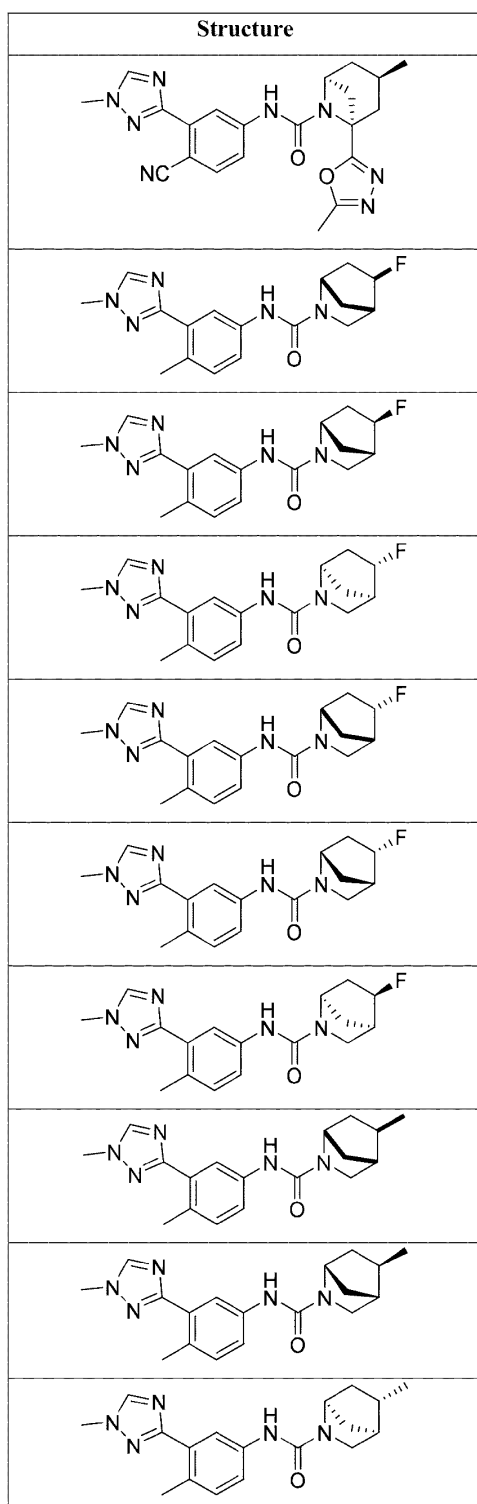


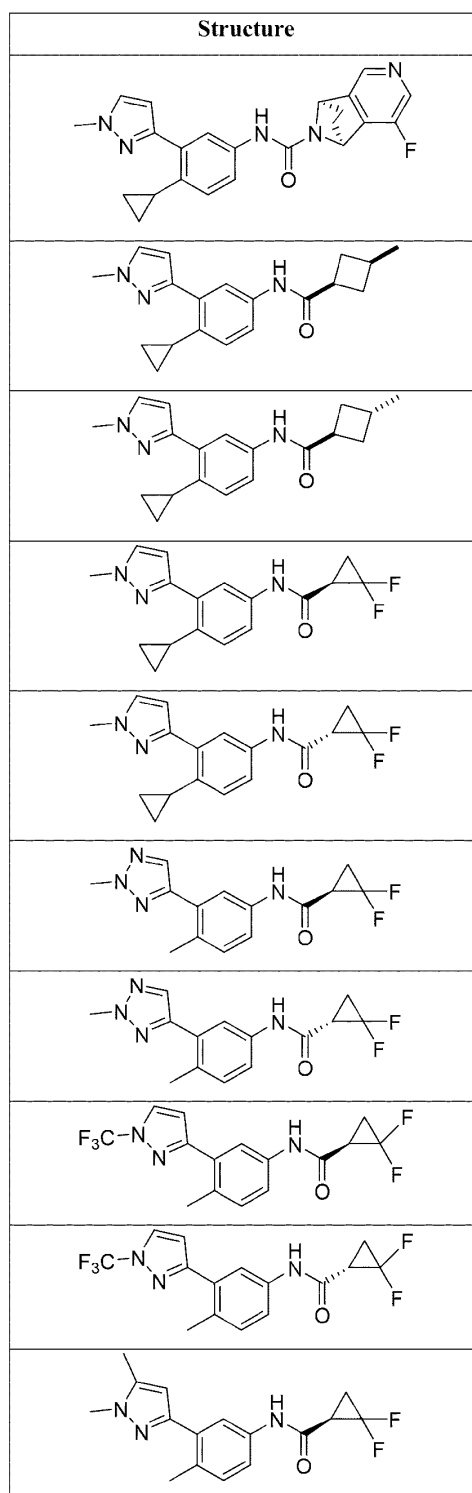
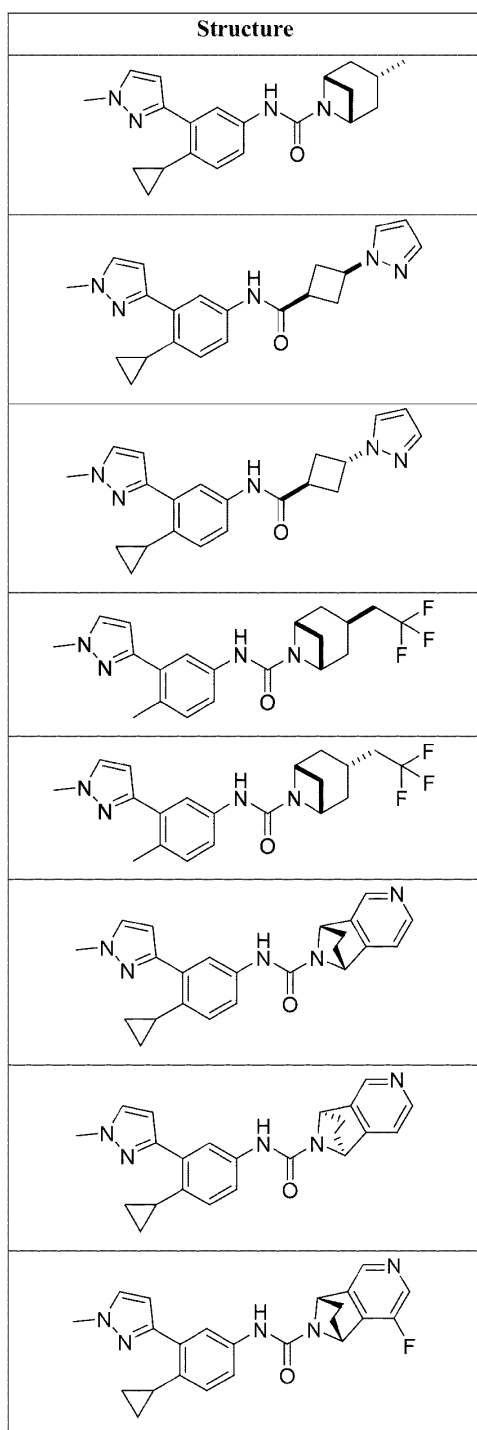


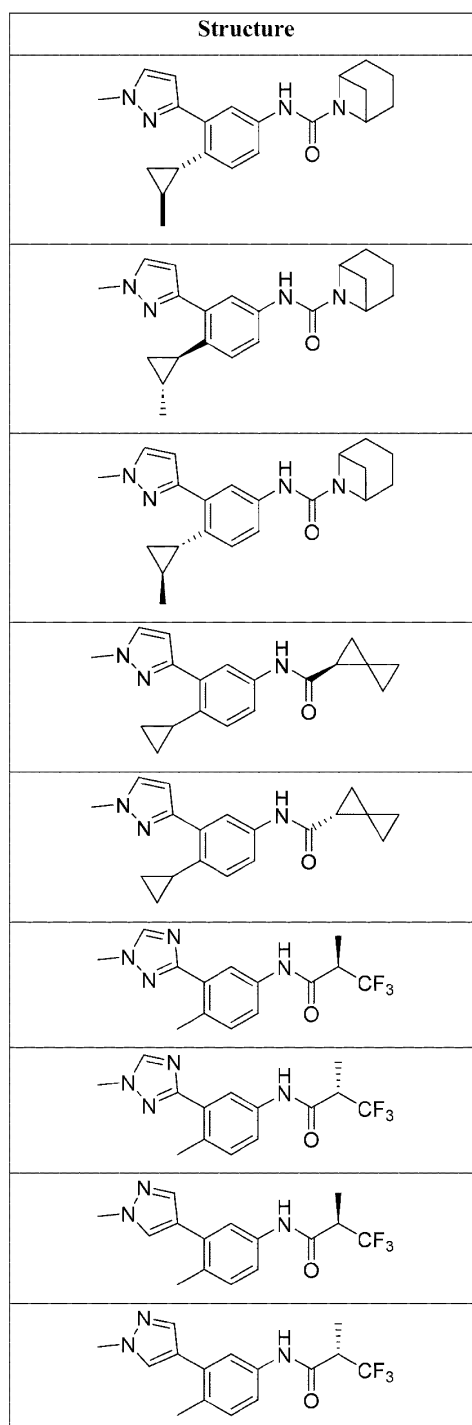
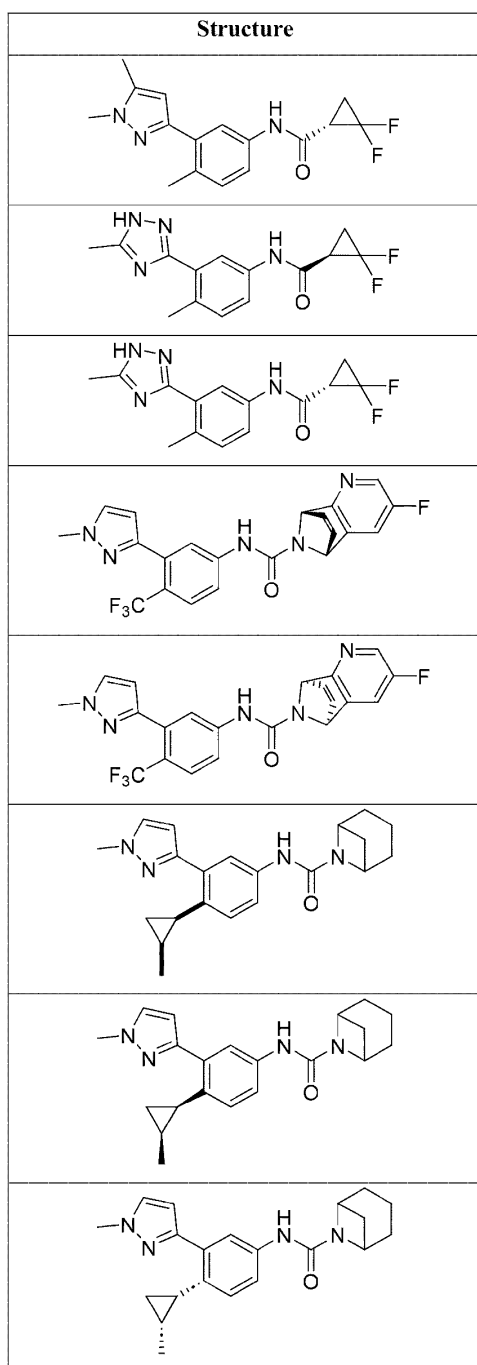


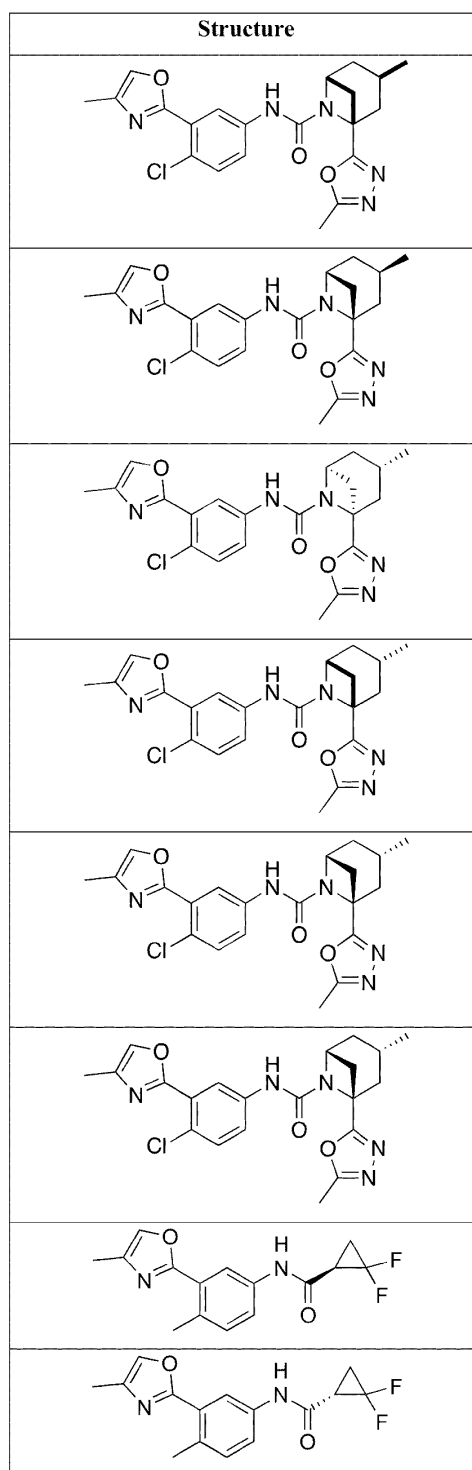
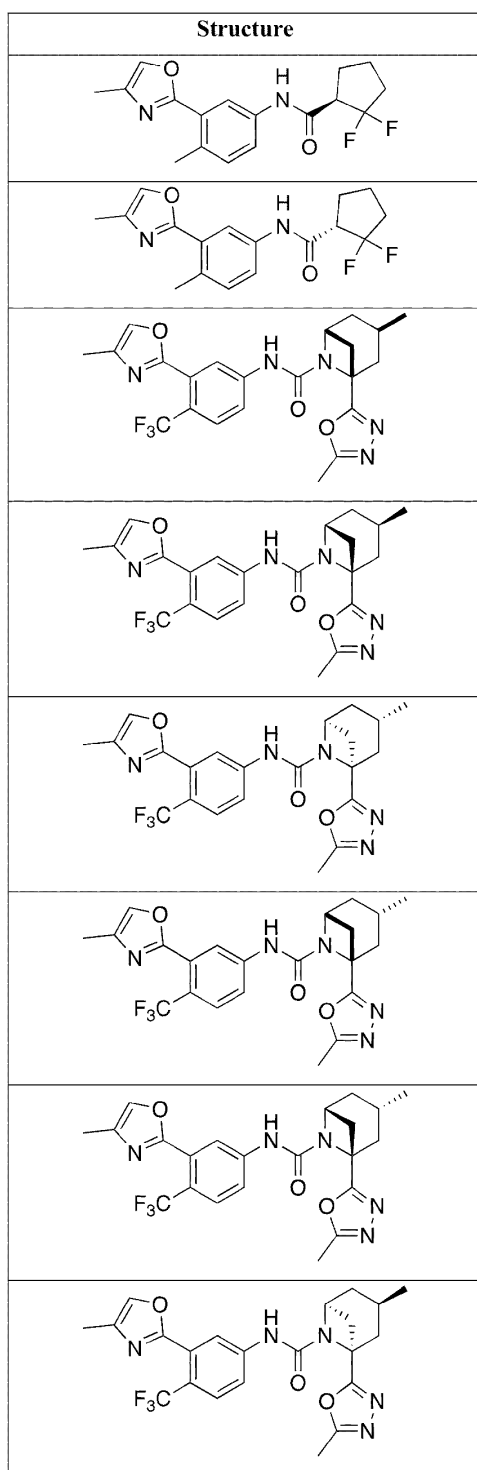
Structure

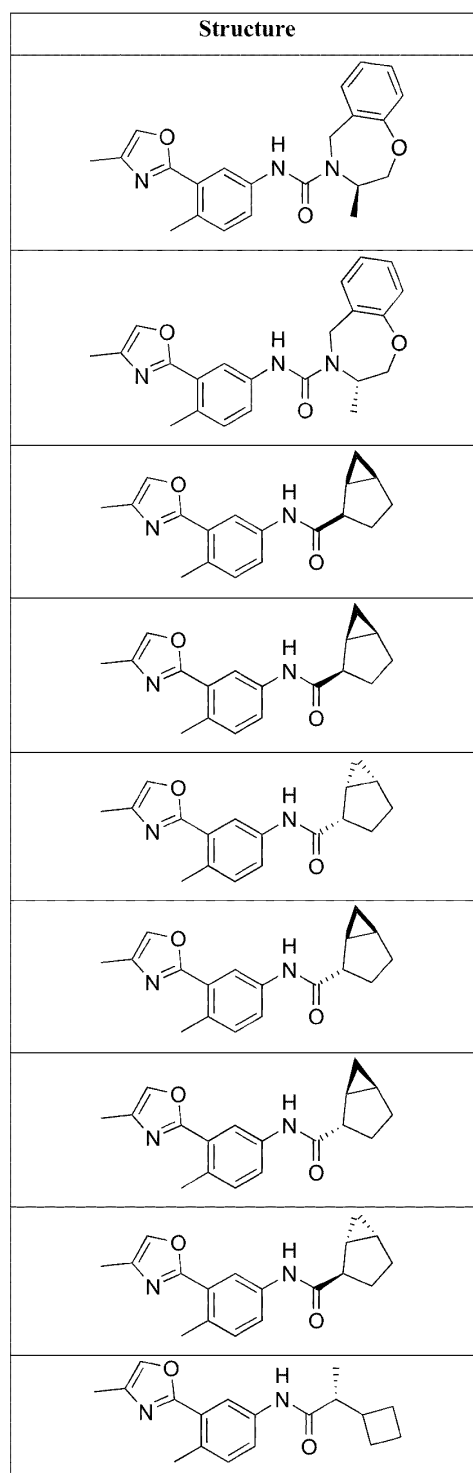
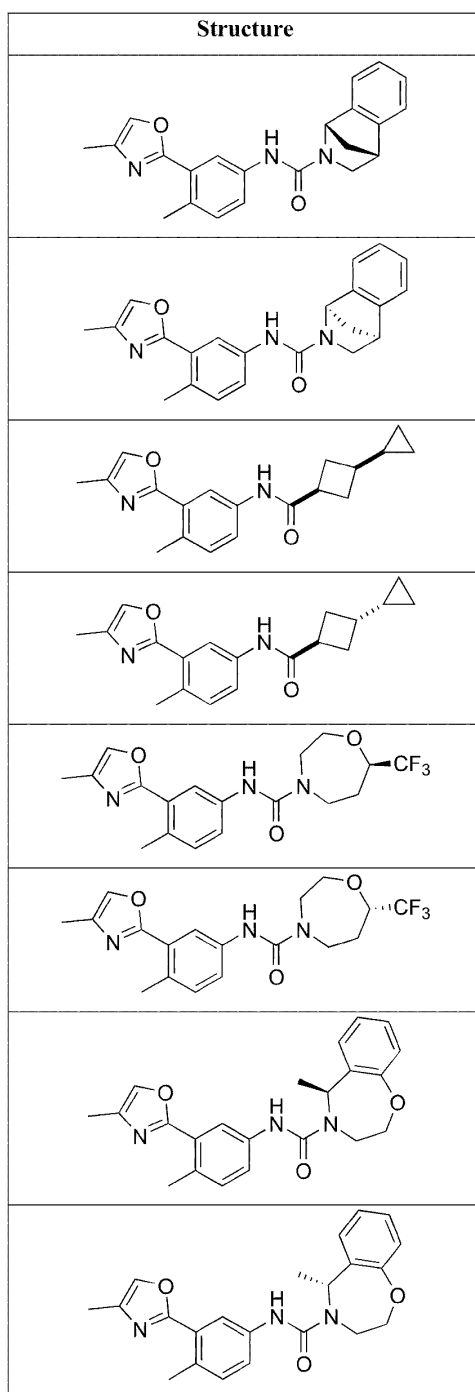
Structure

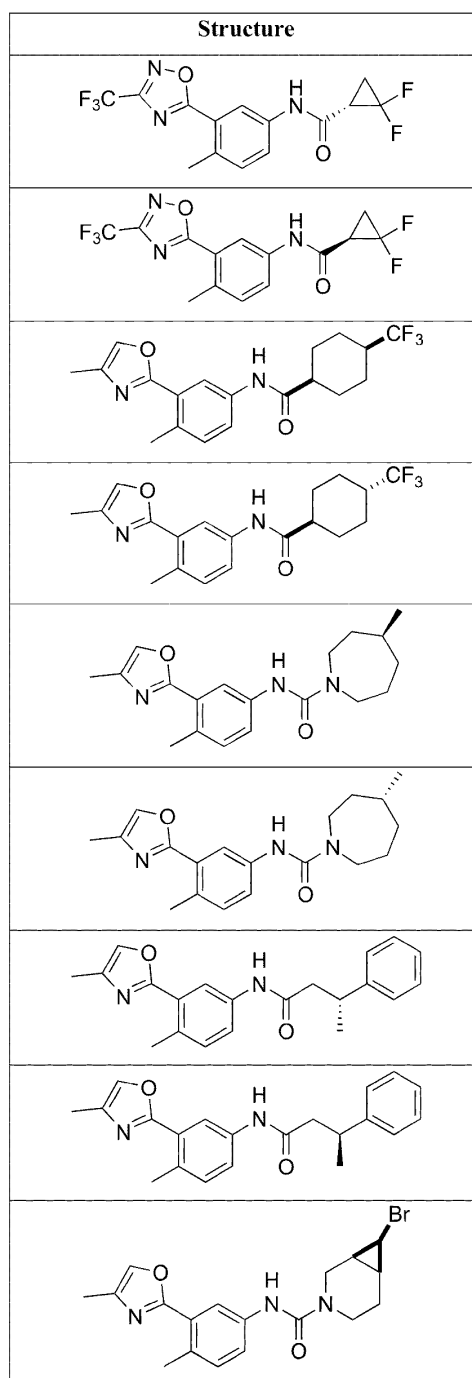
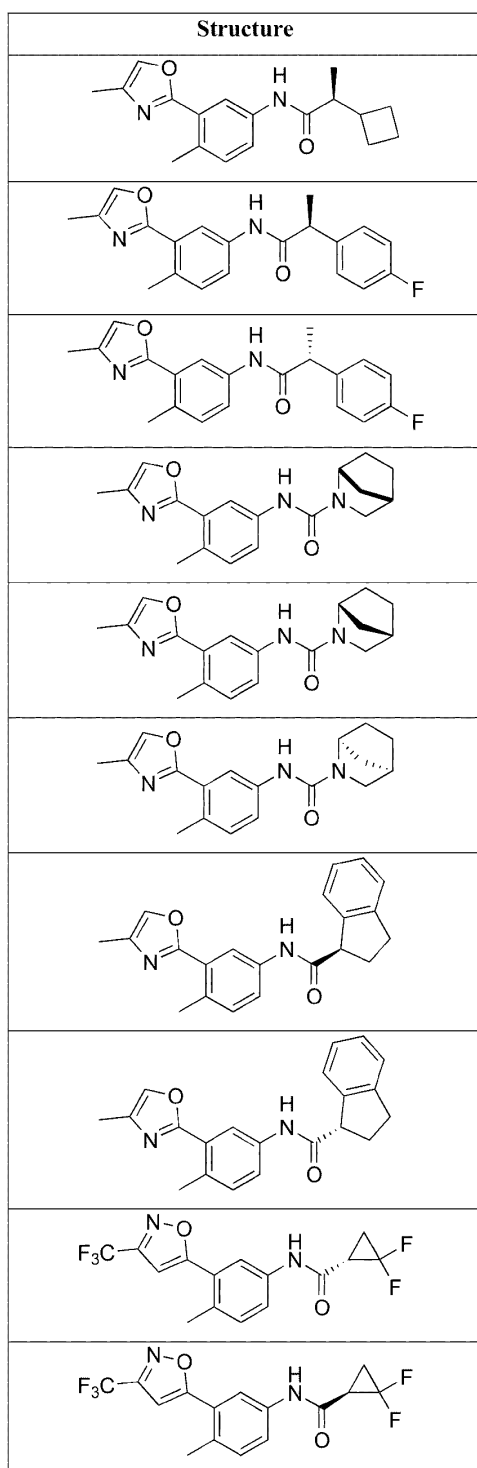


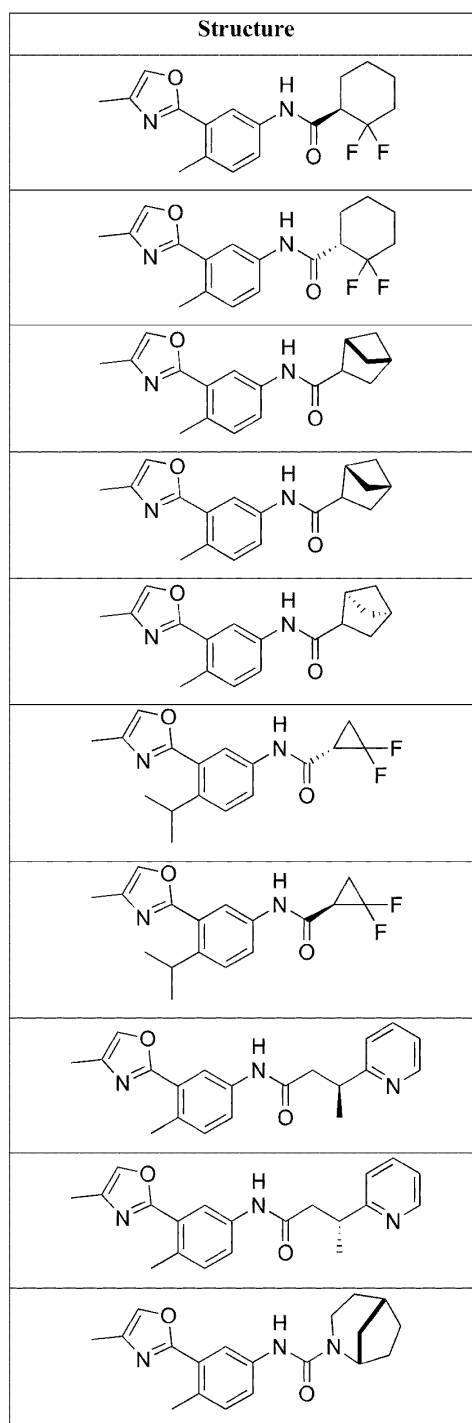
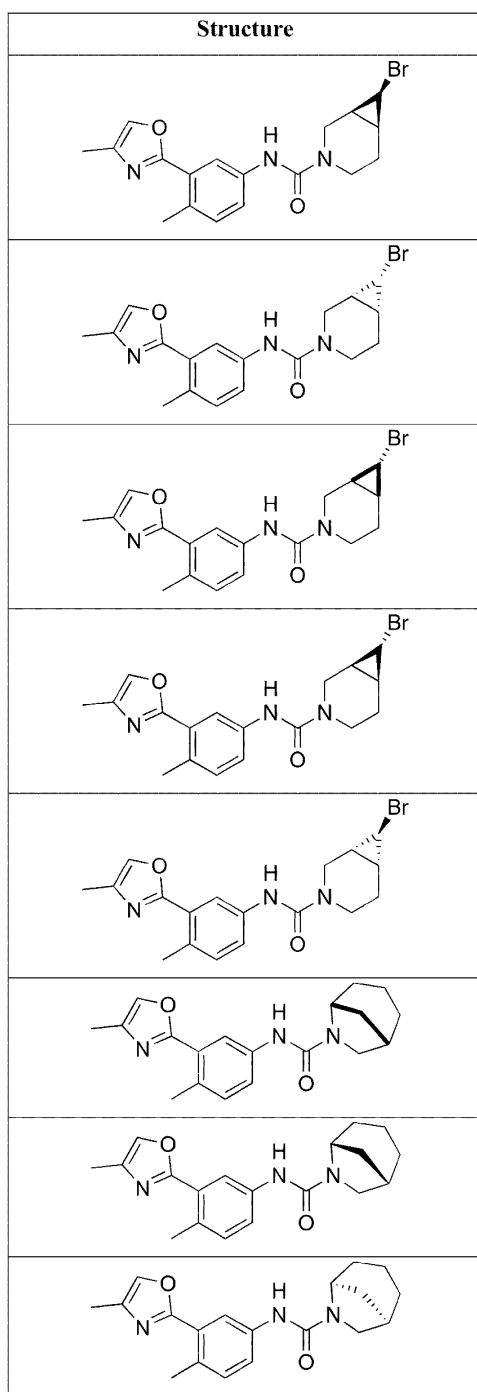


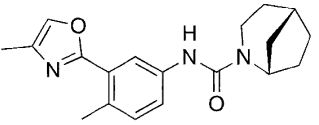
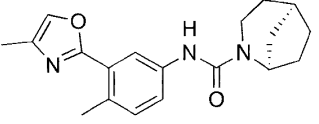
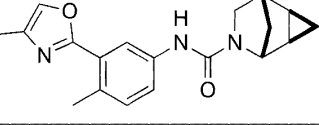
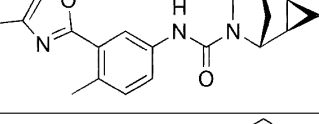
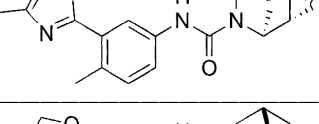
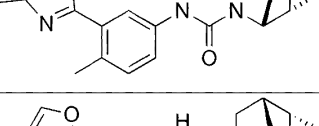
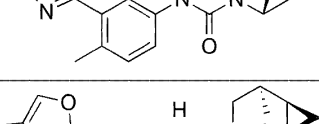
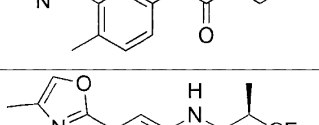
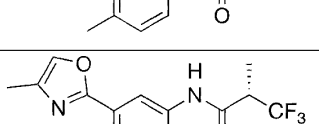
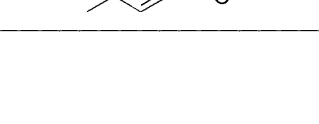




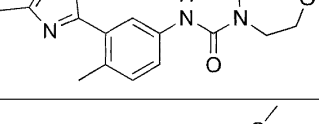
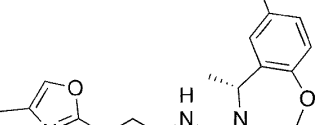
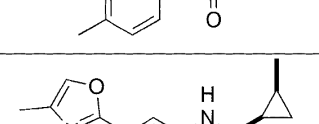
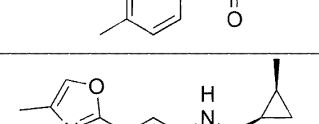
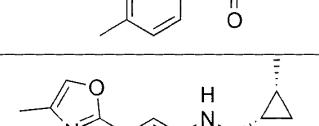
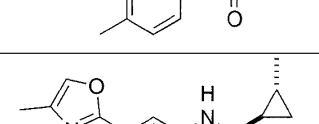
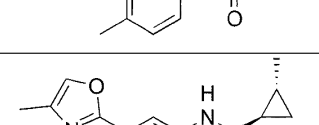
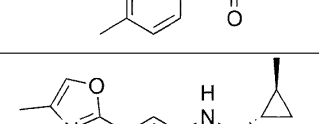
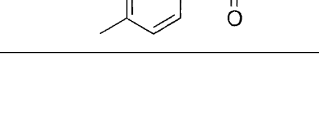


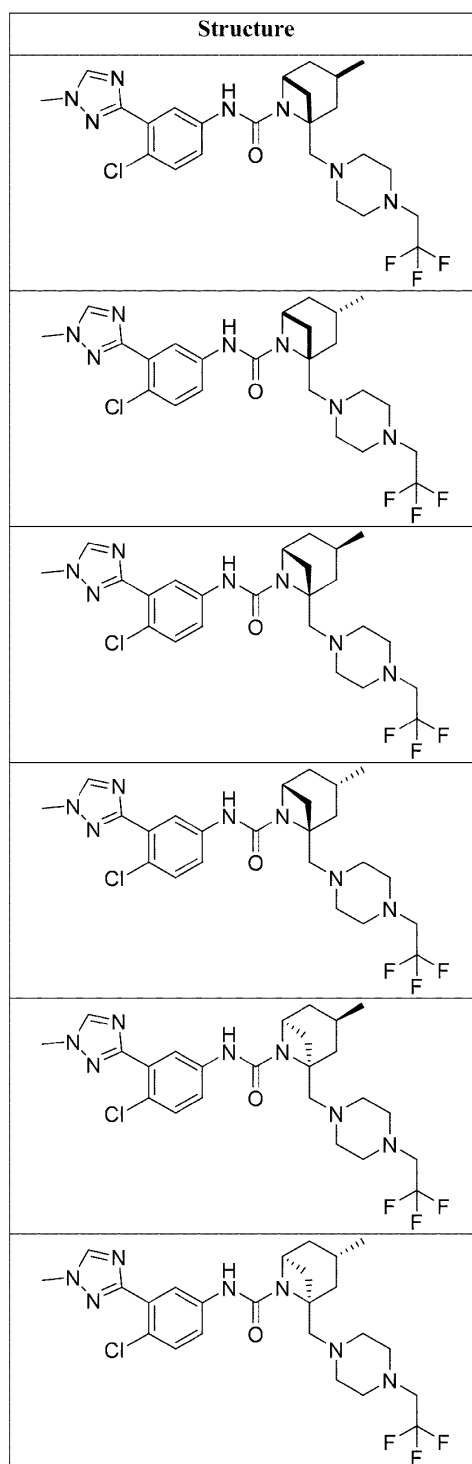
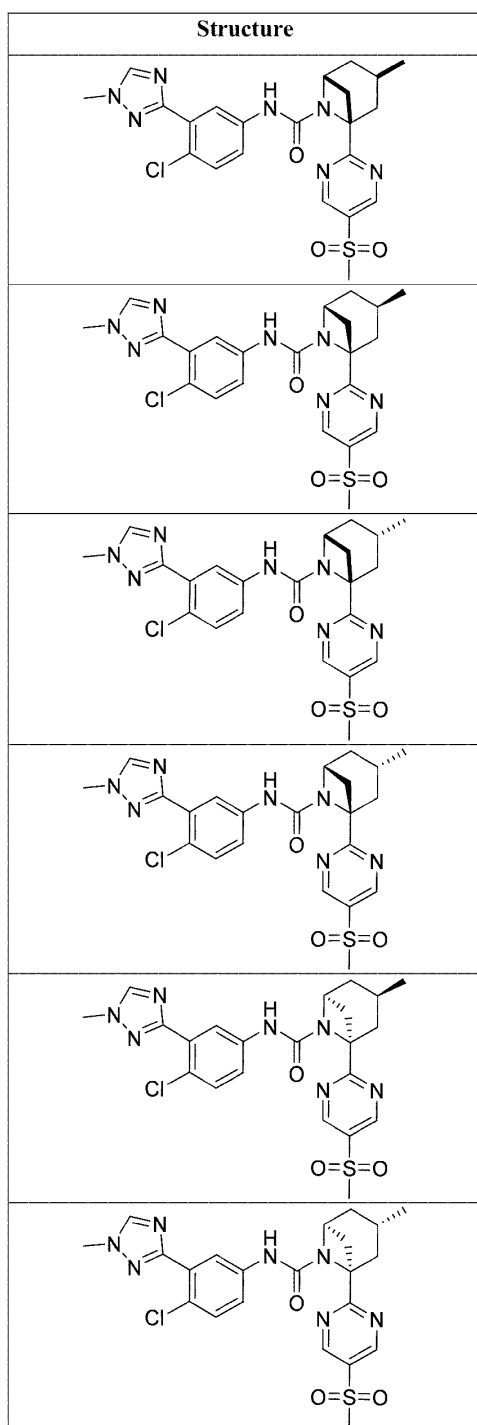


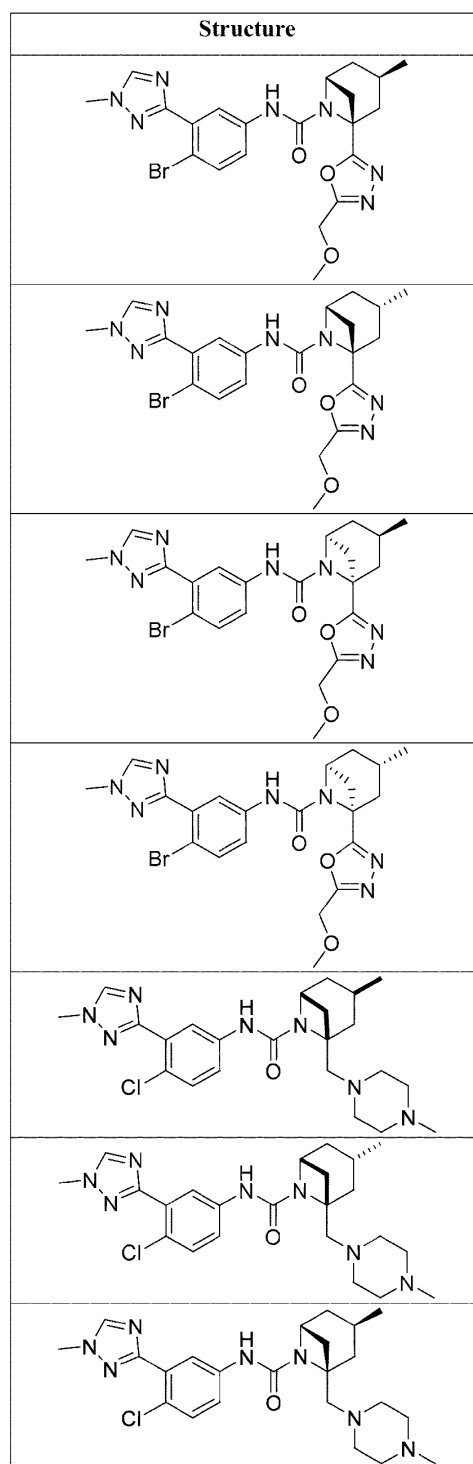
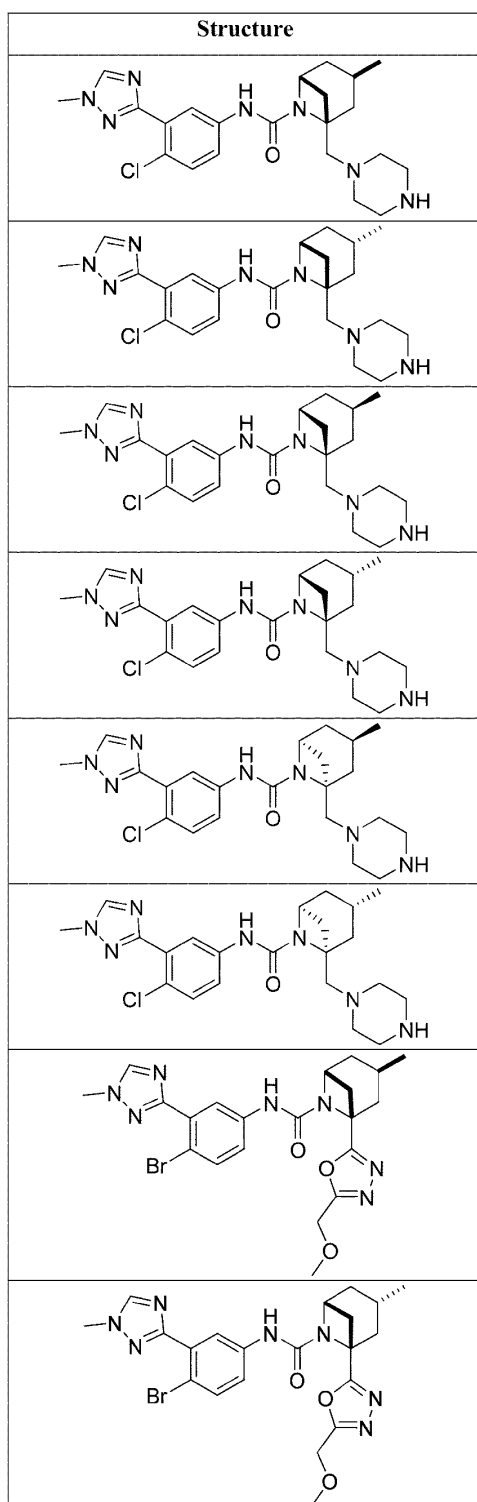


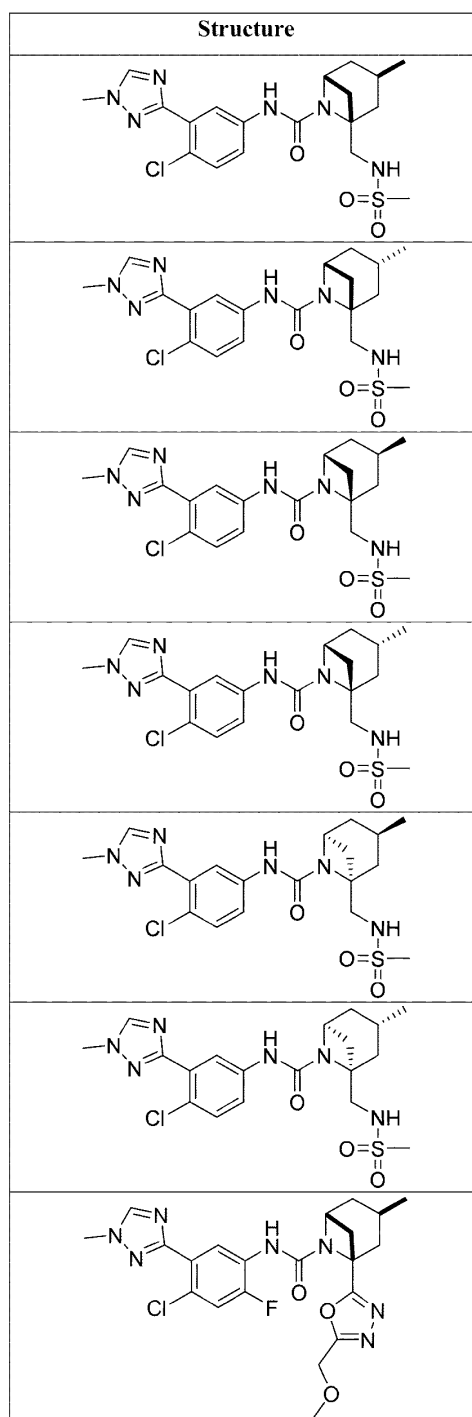
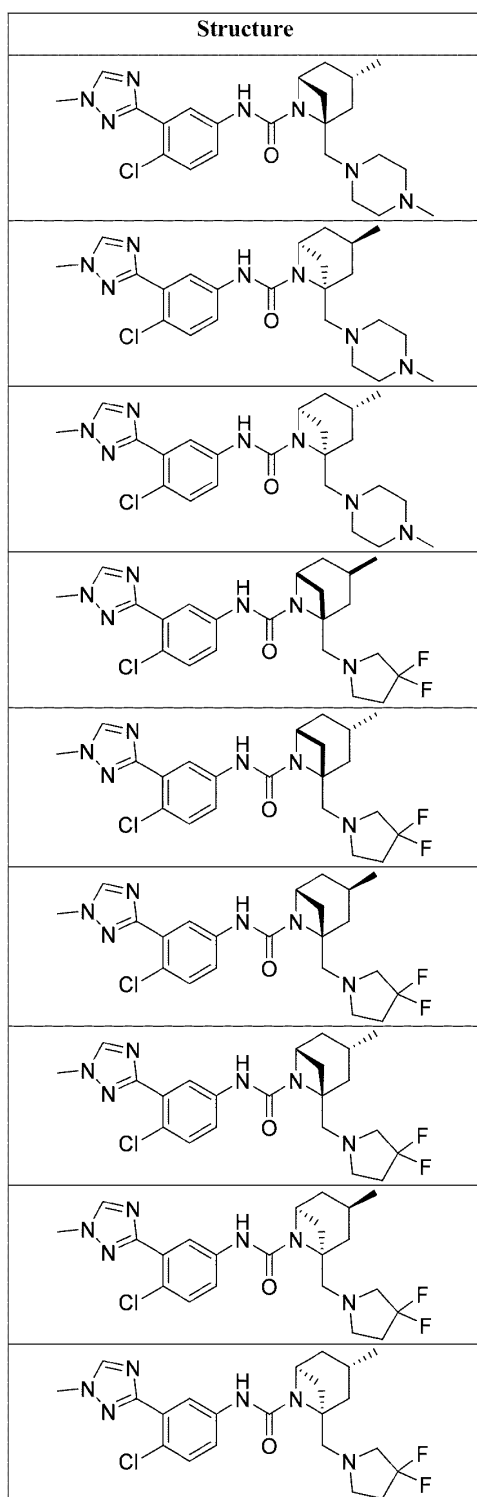
Structure











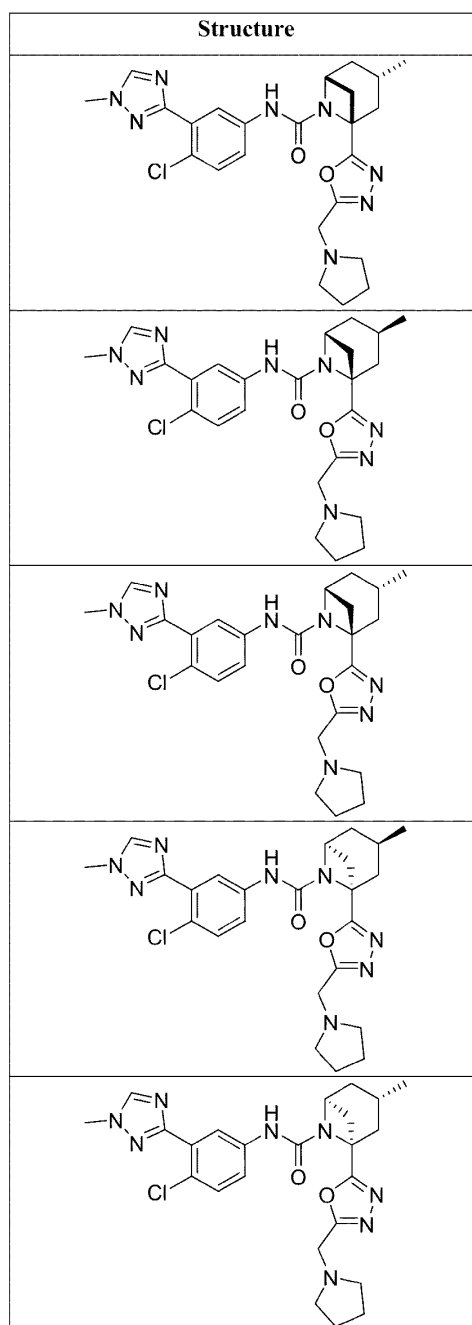
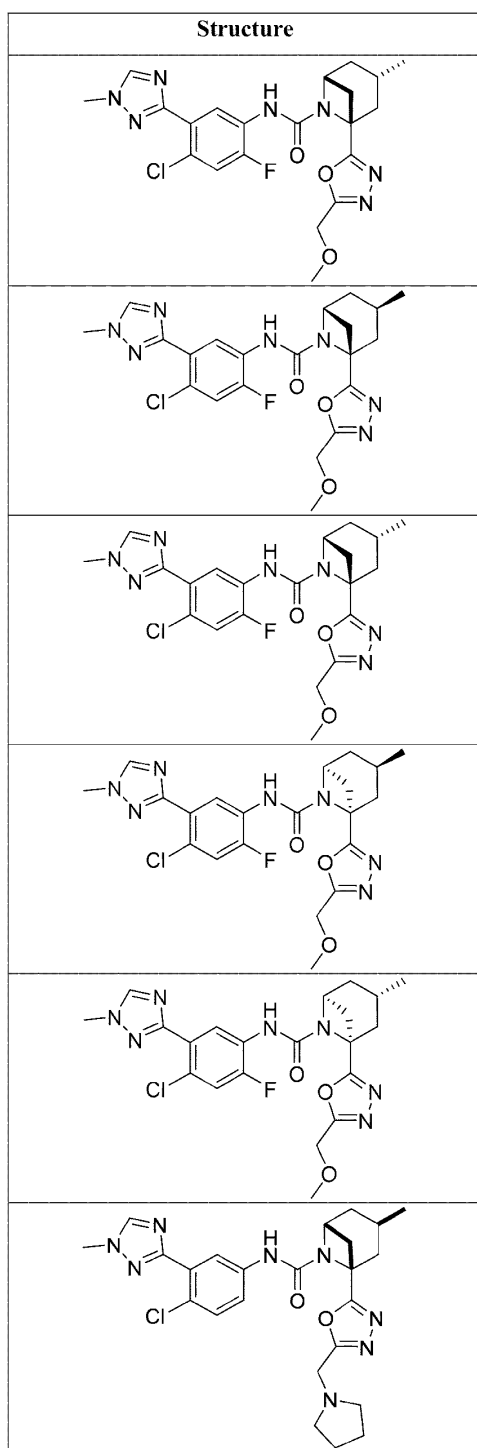
Structure

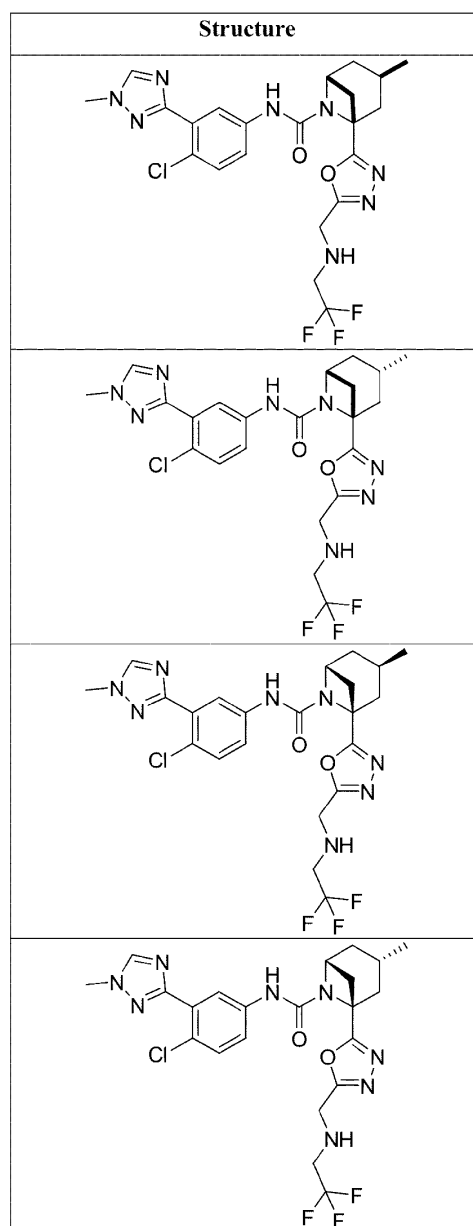
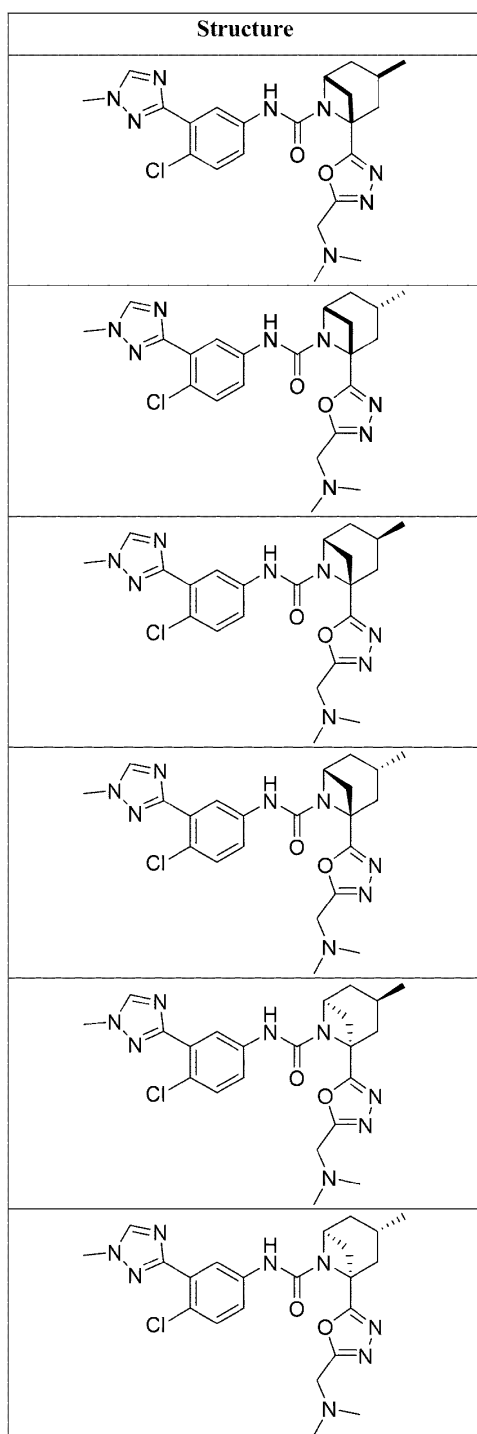










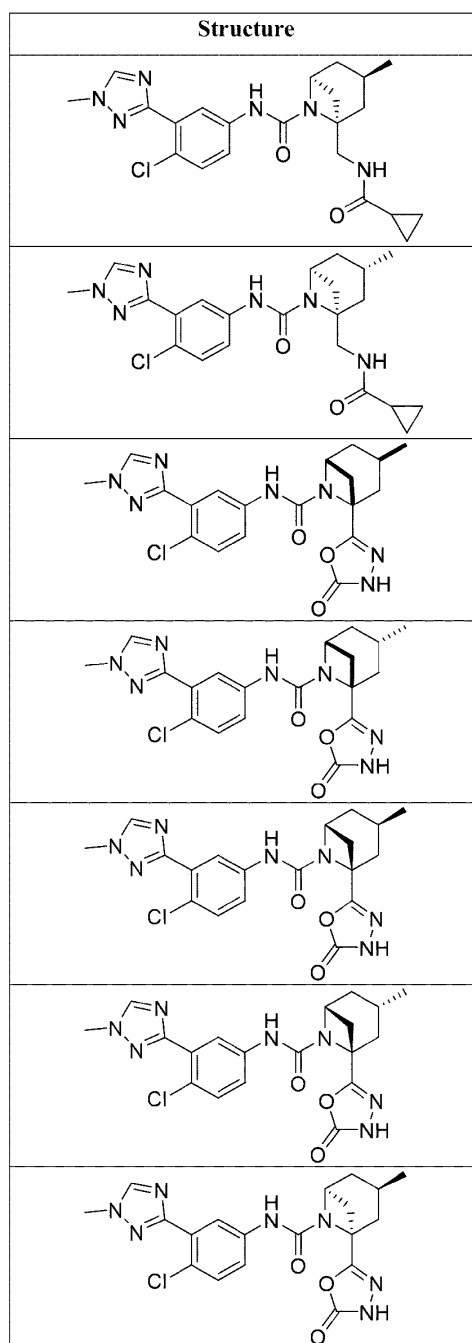
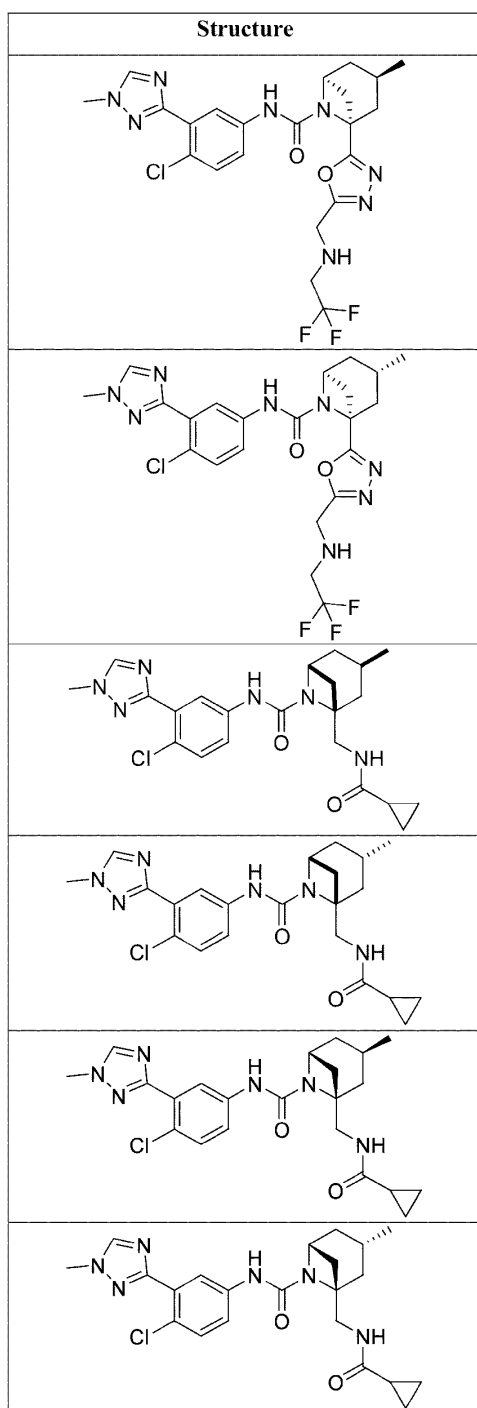


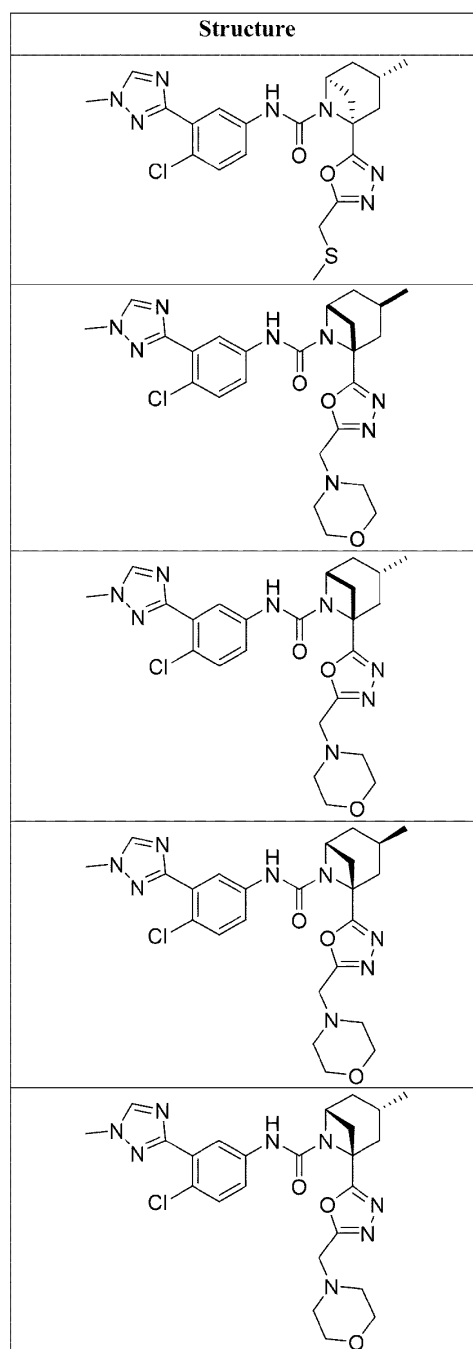
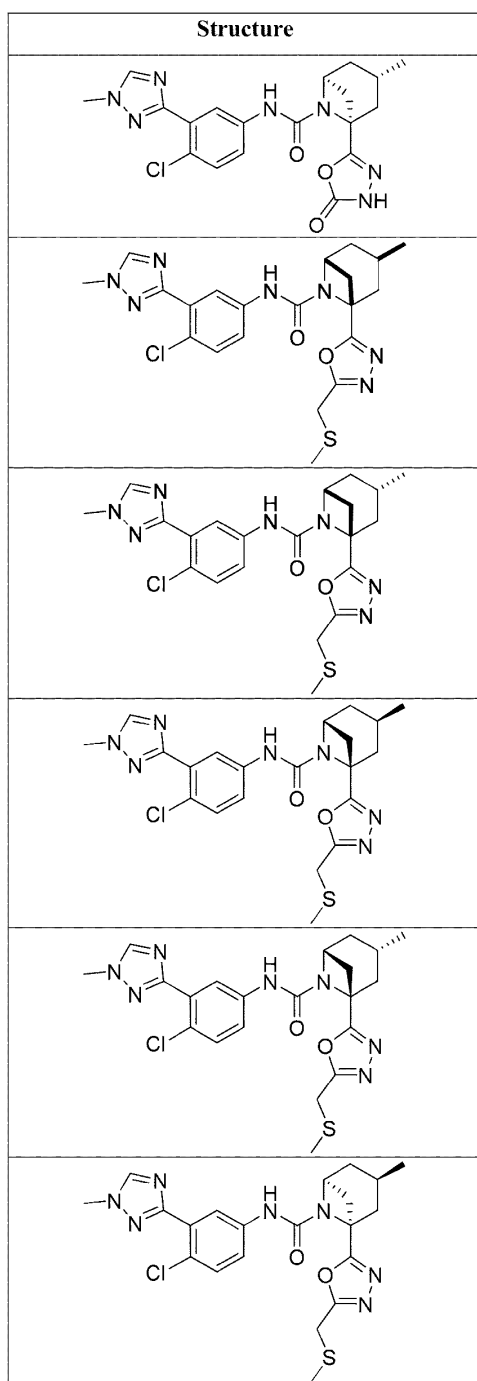


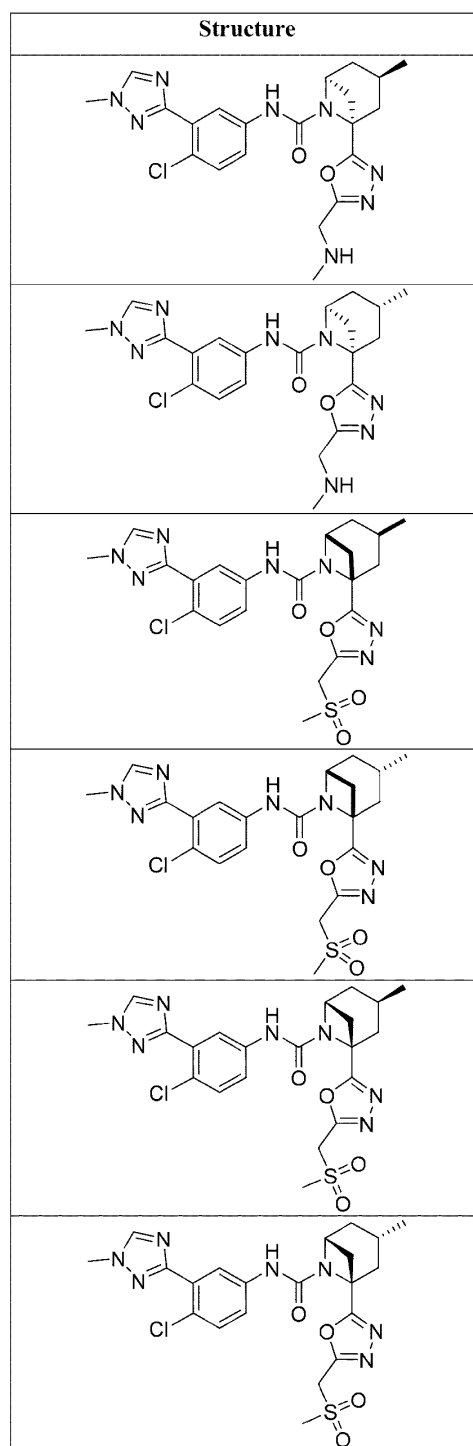
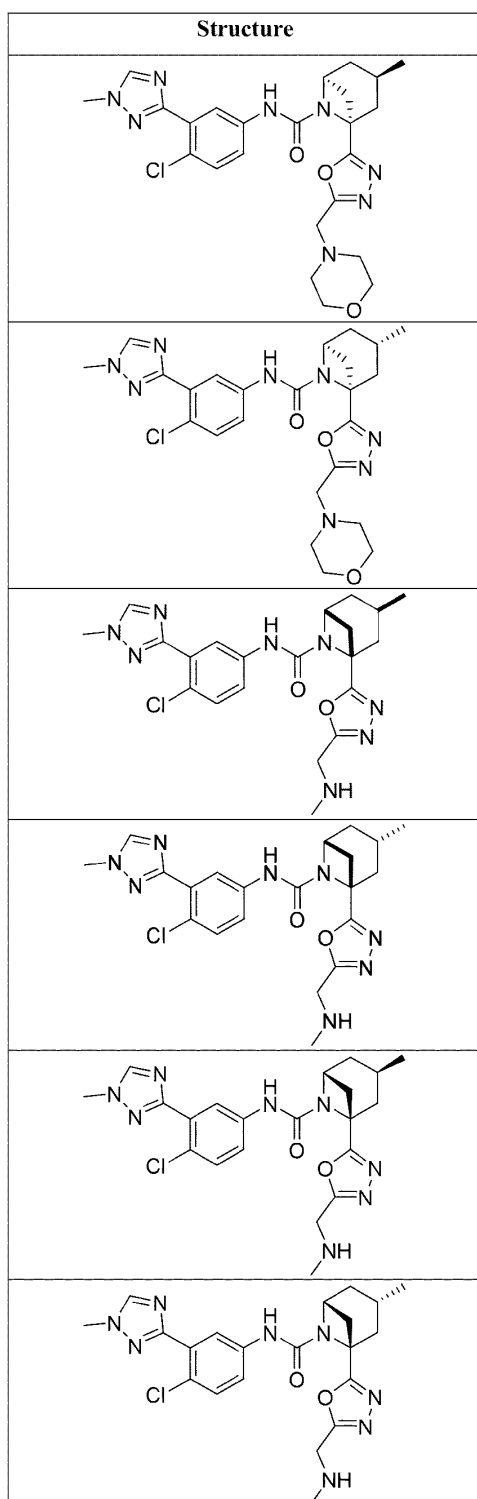


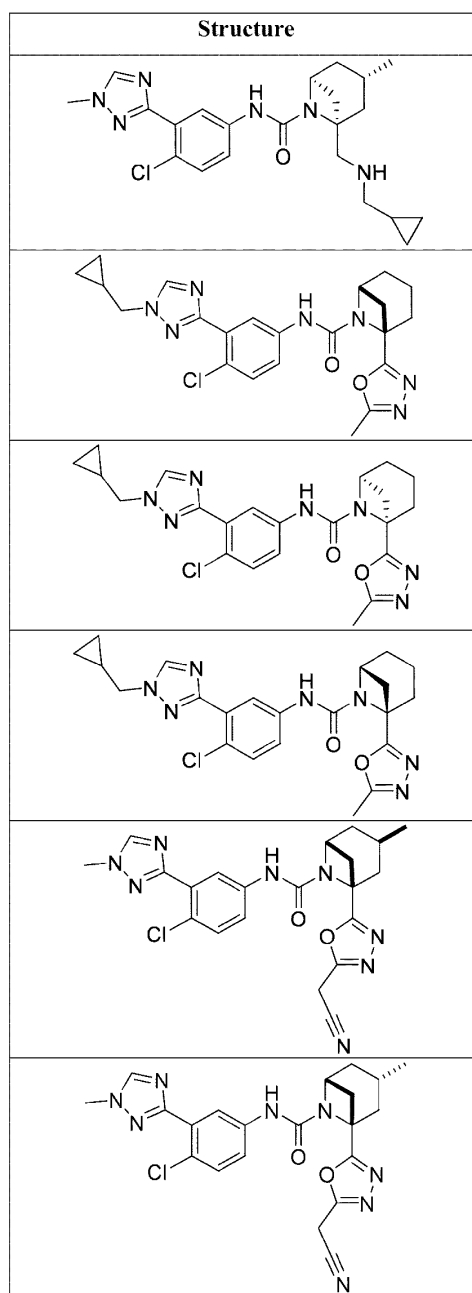
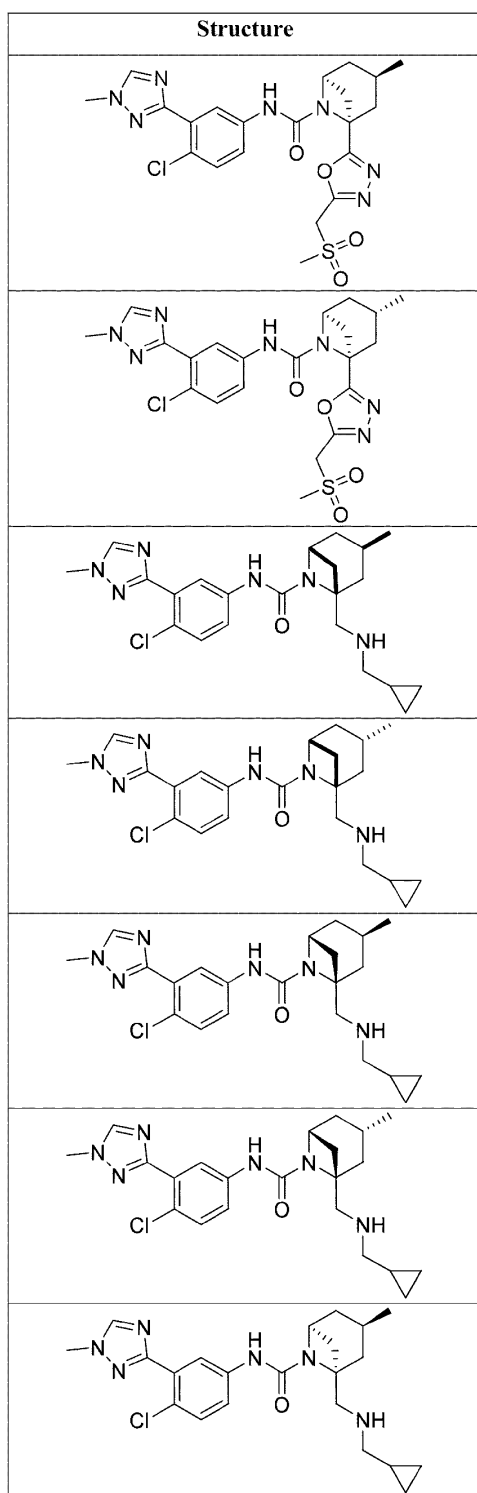


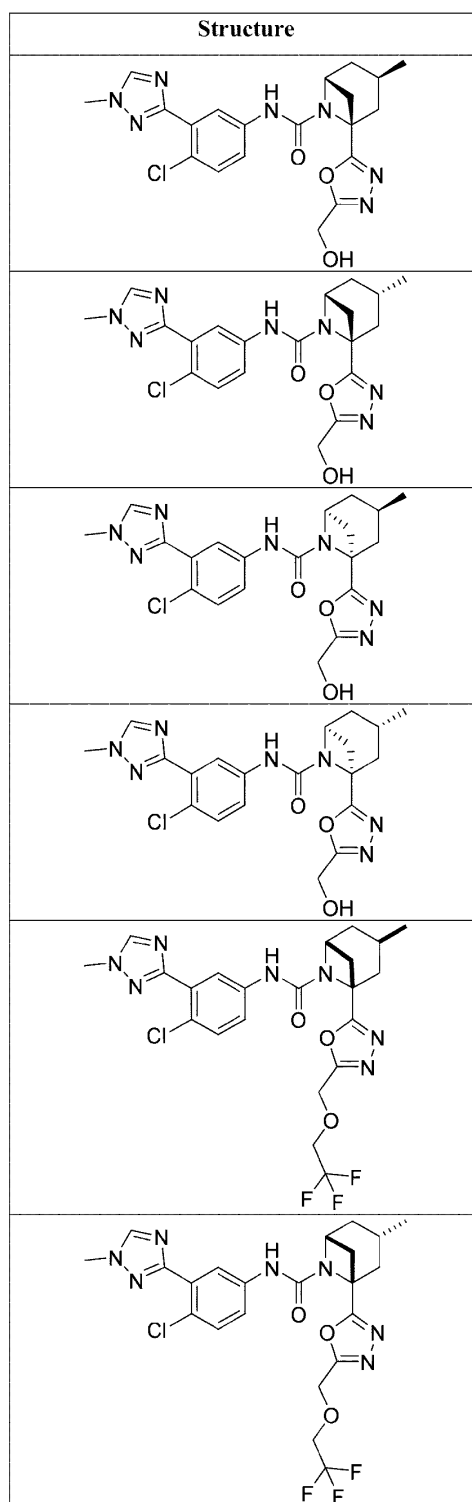
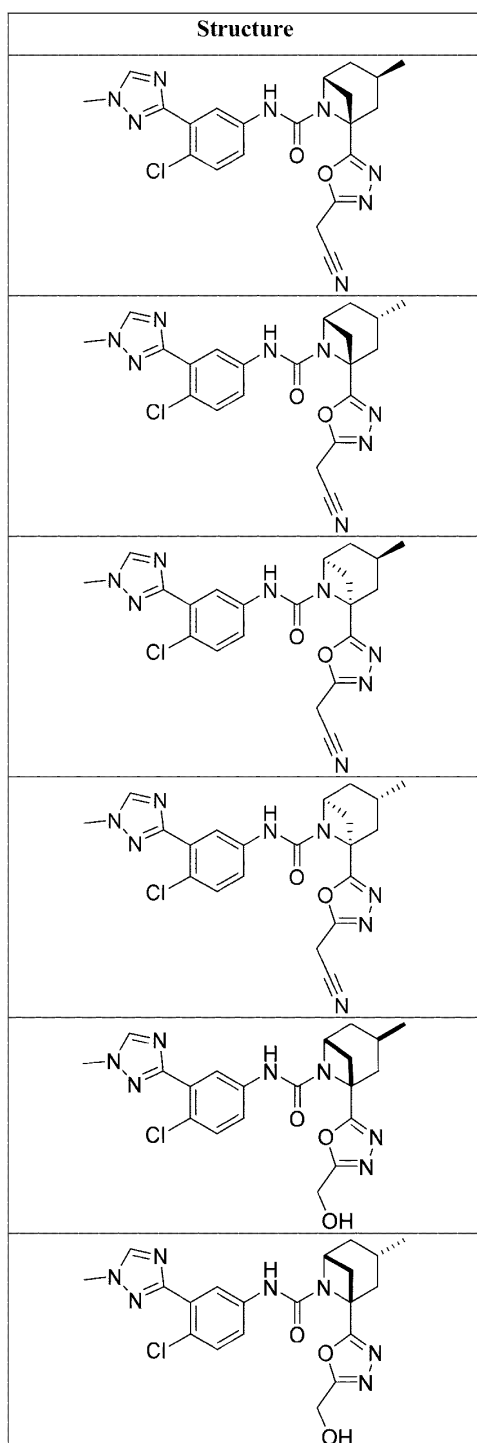


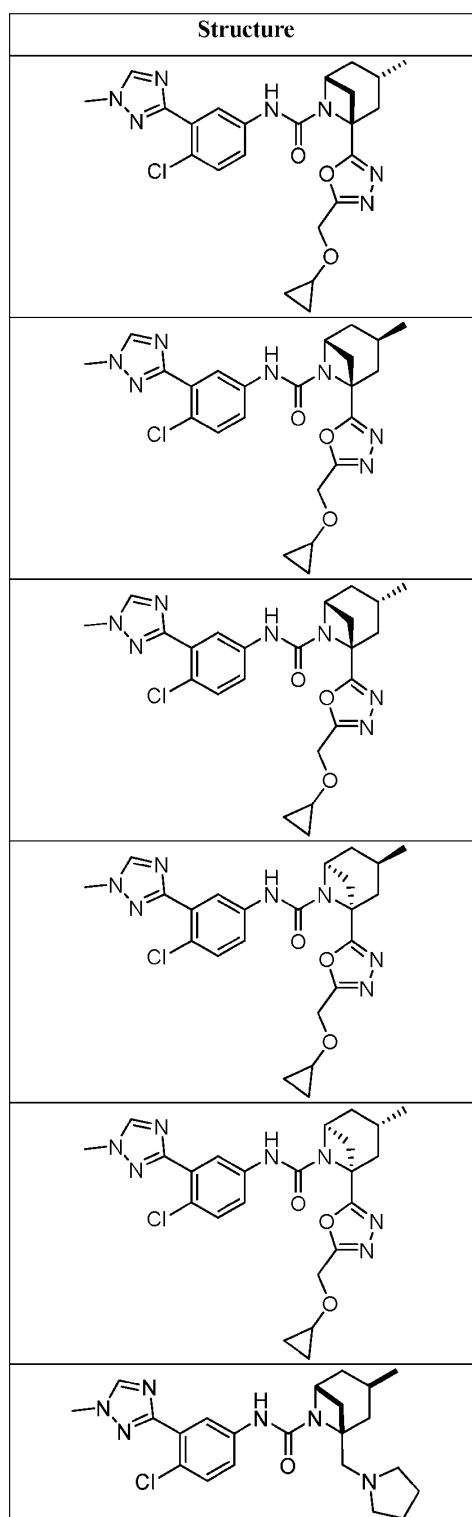
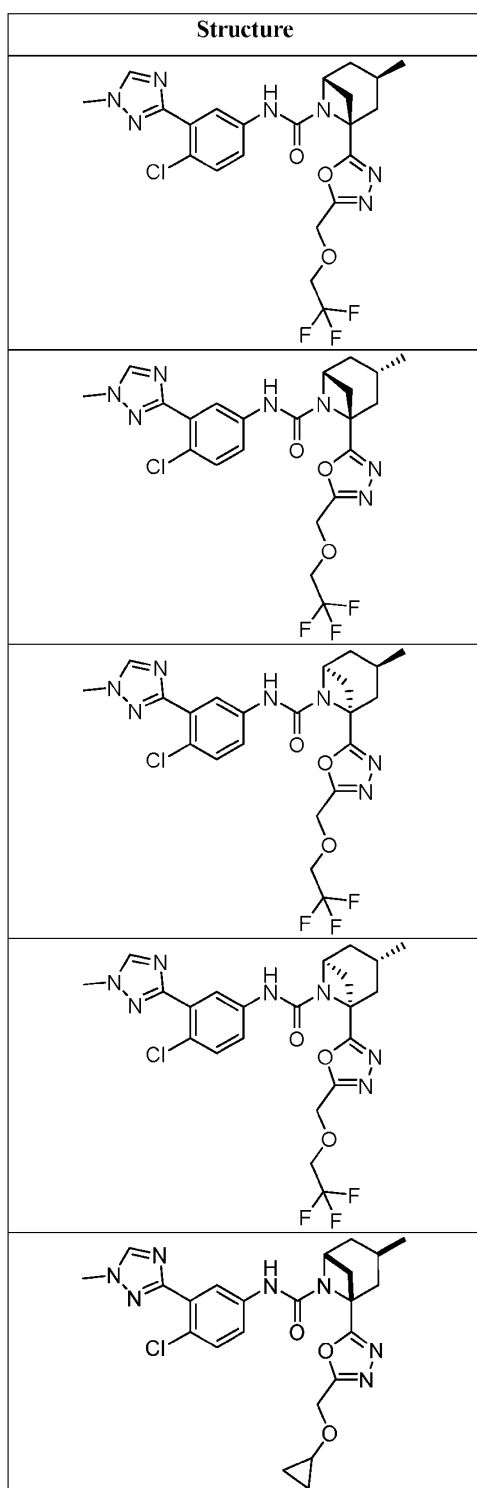


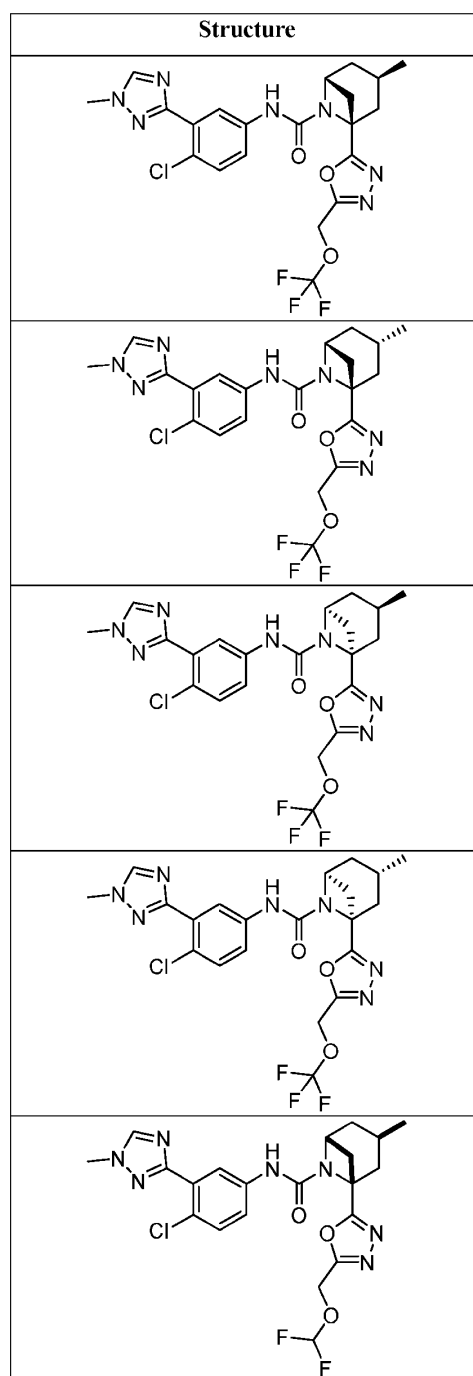
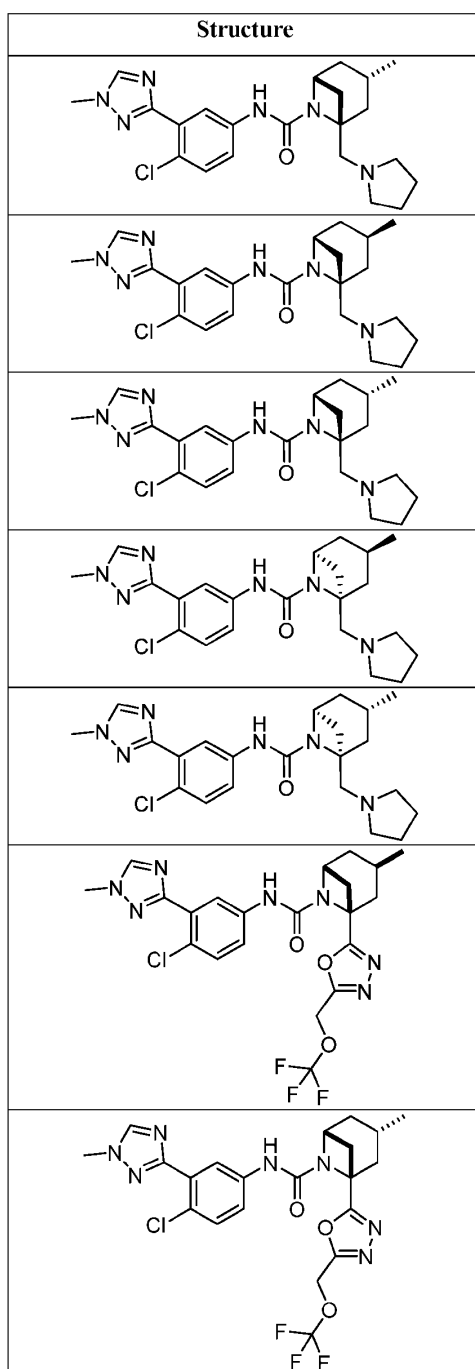


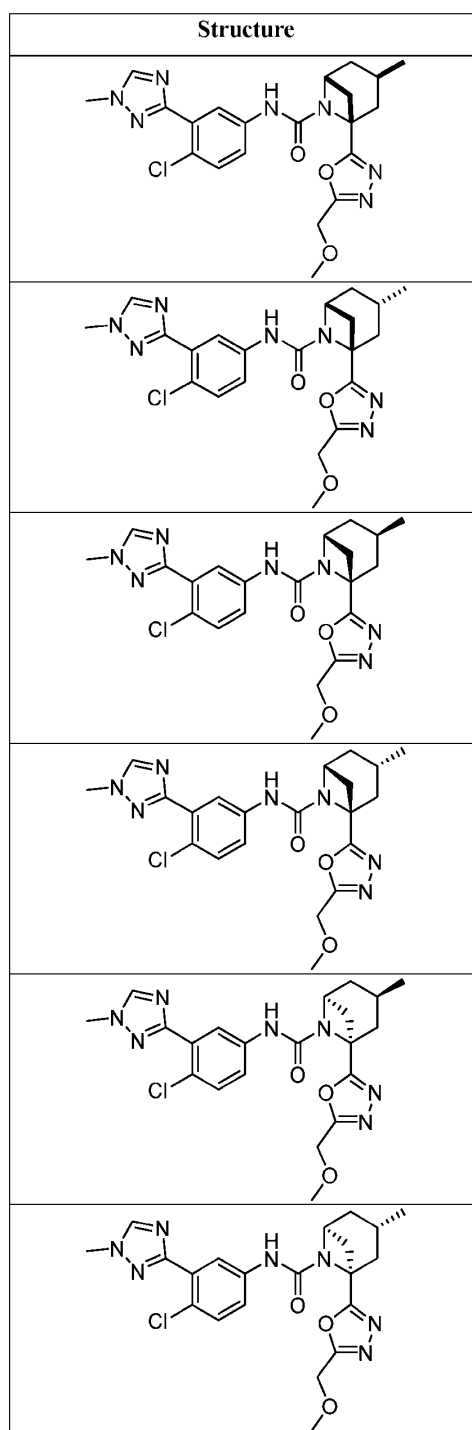
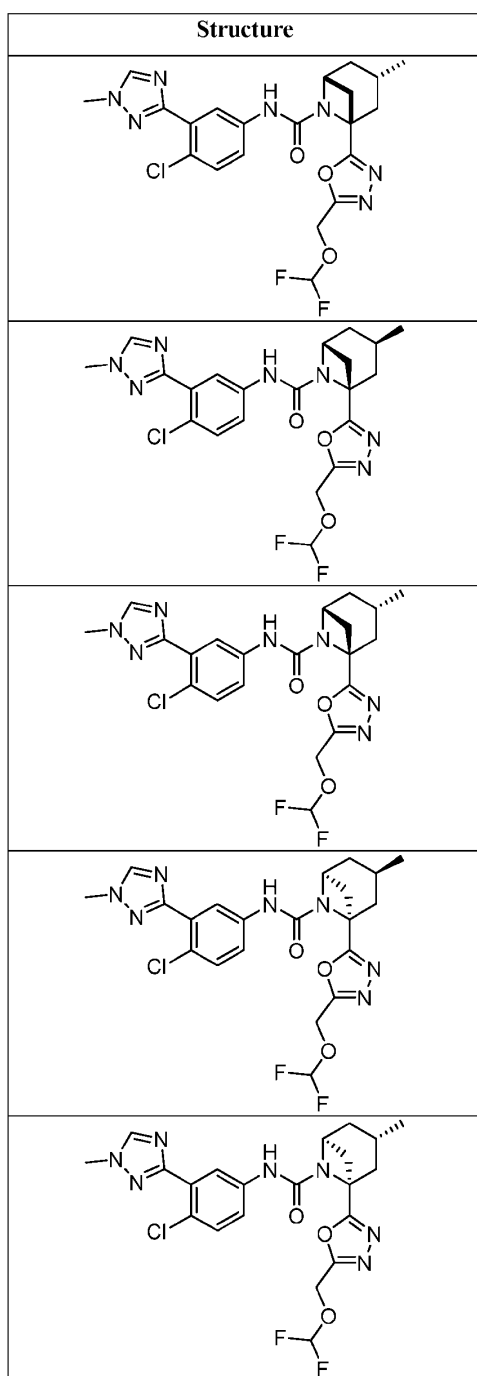


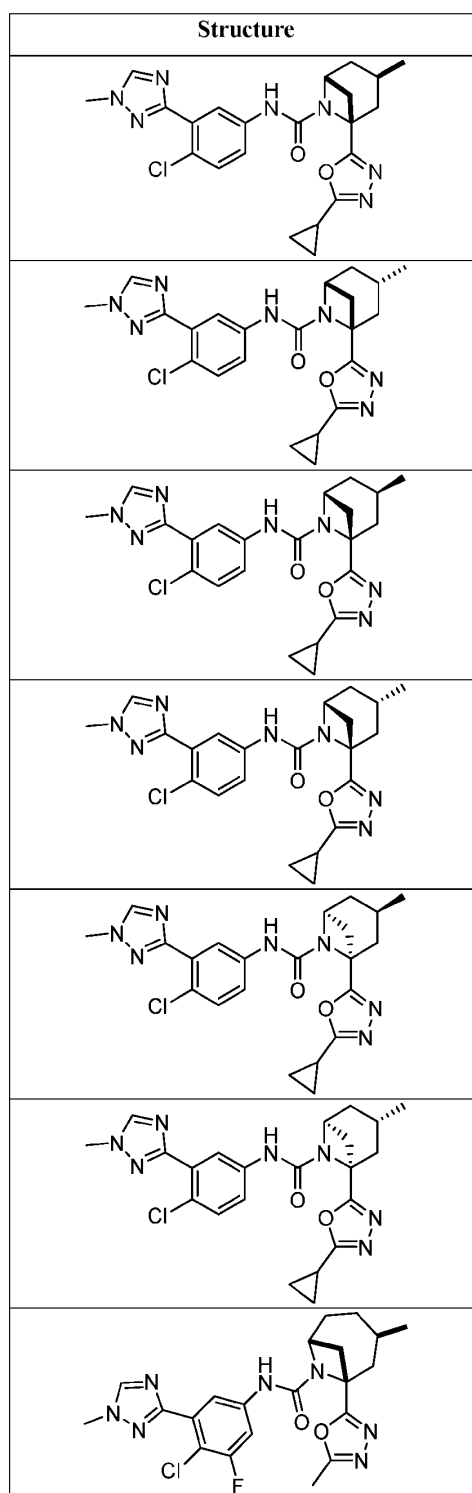
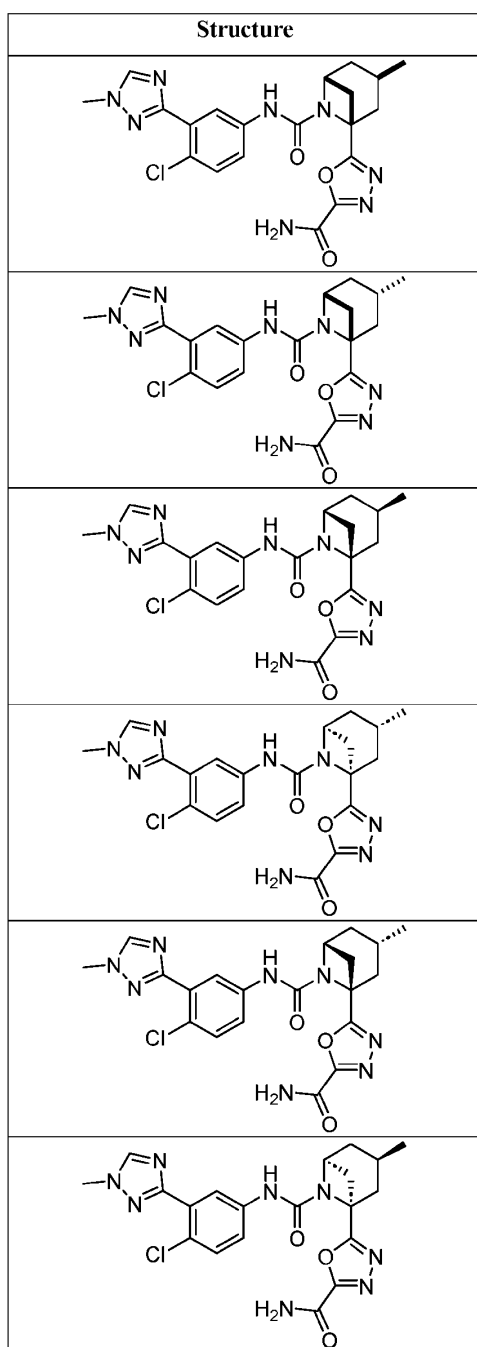


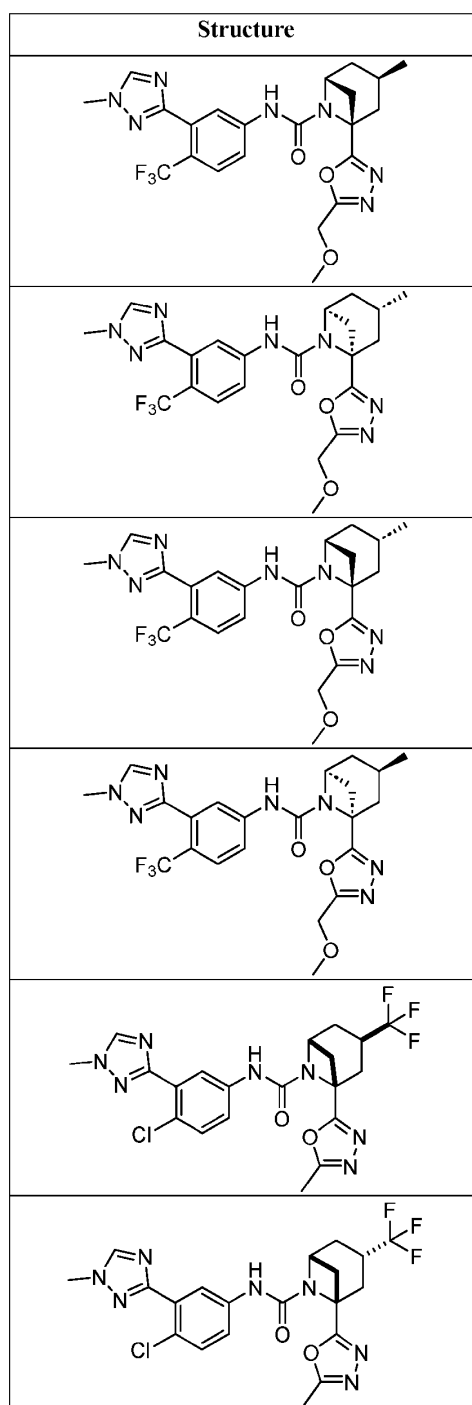
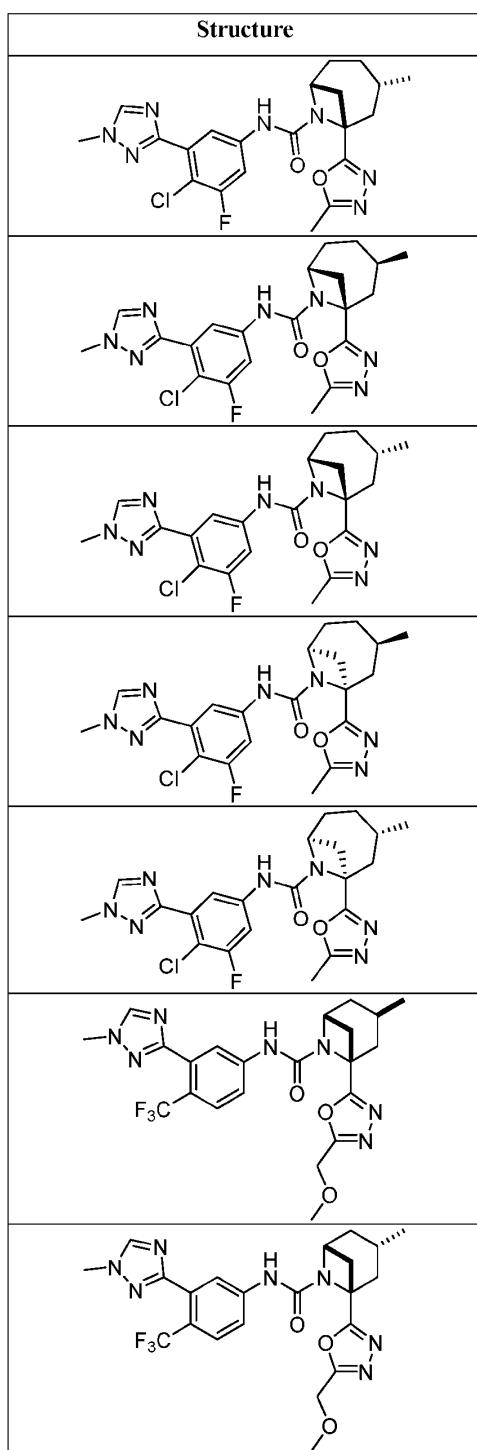


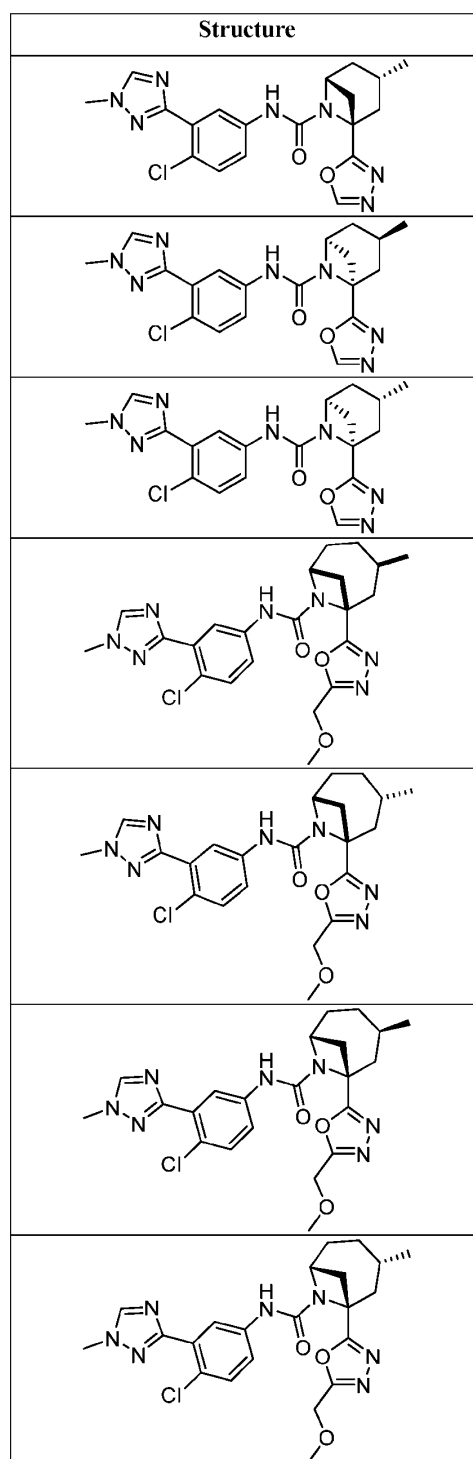
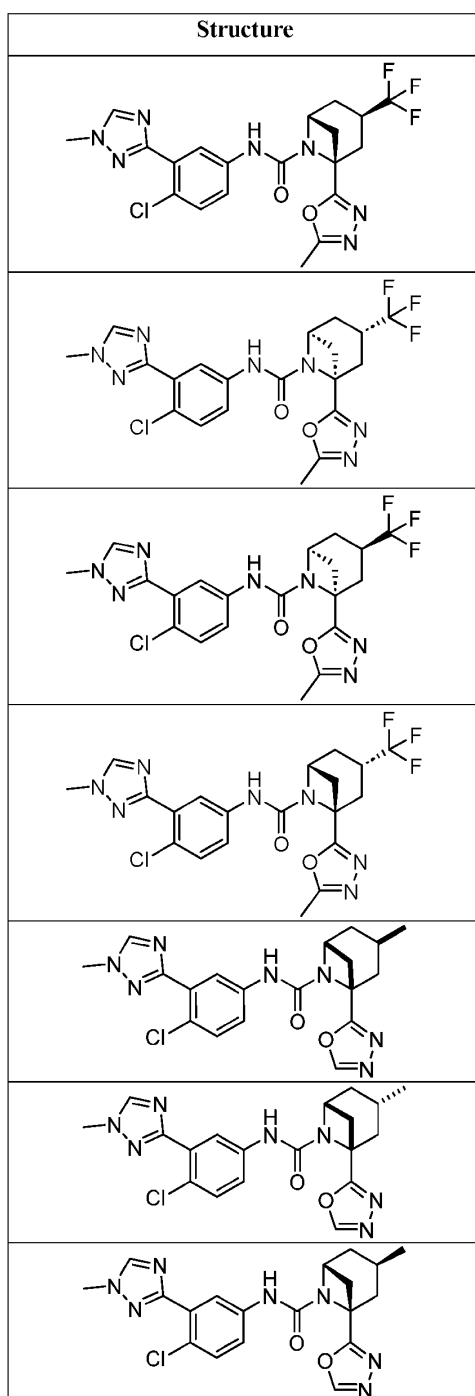


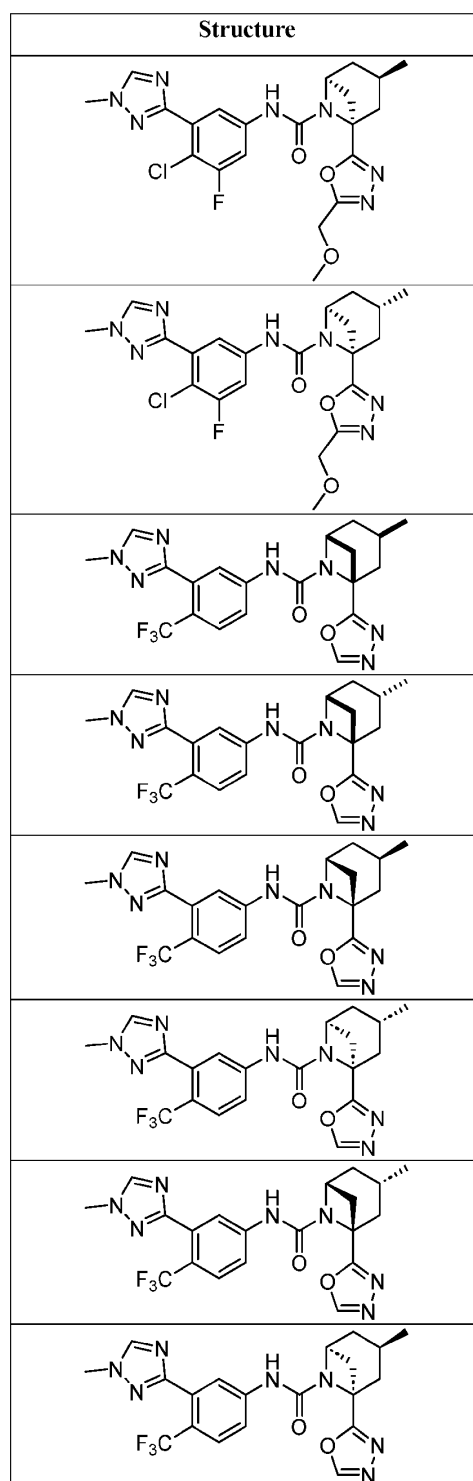
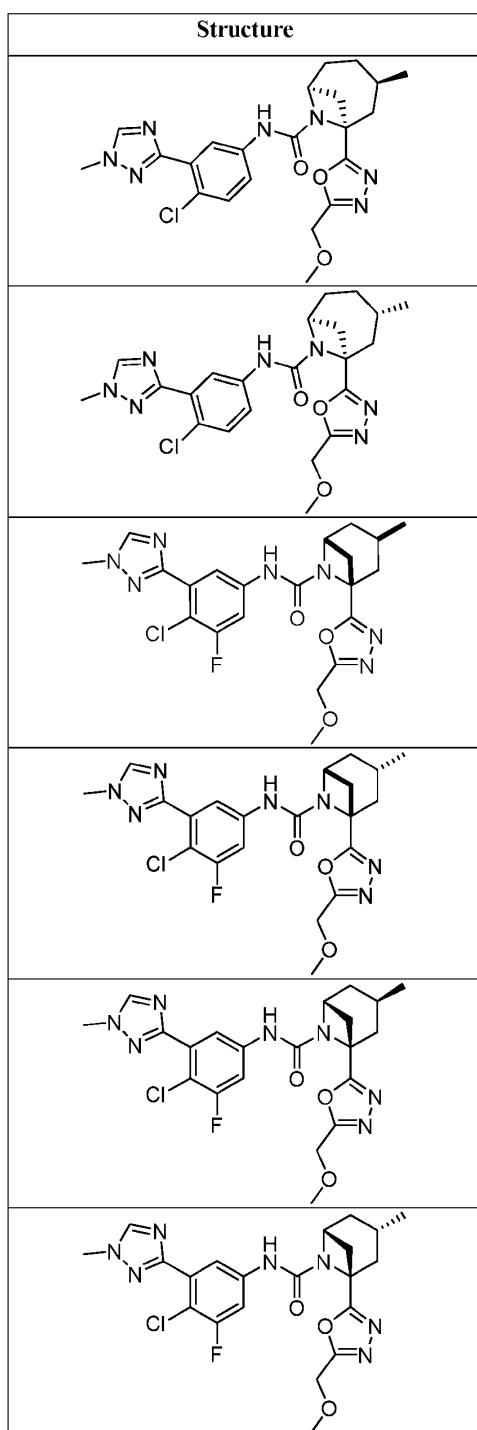


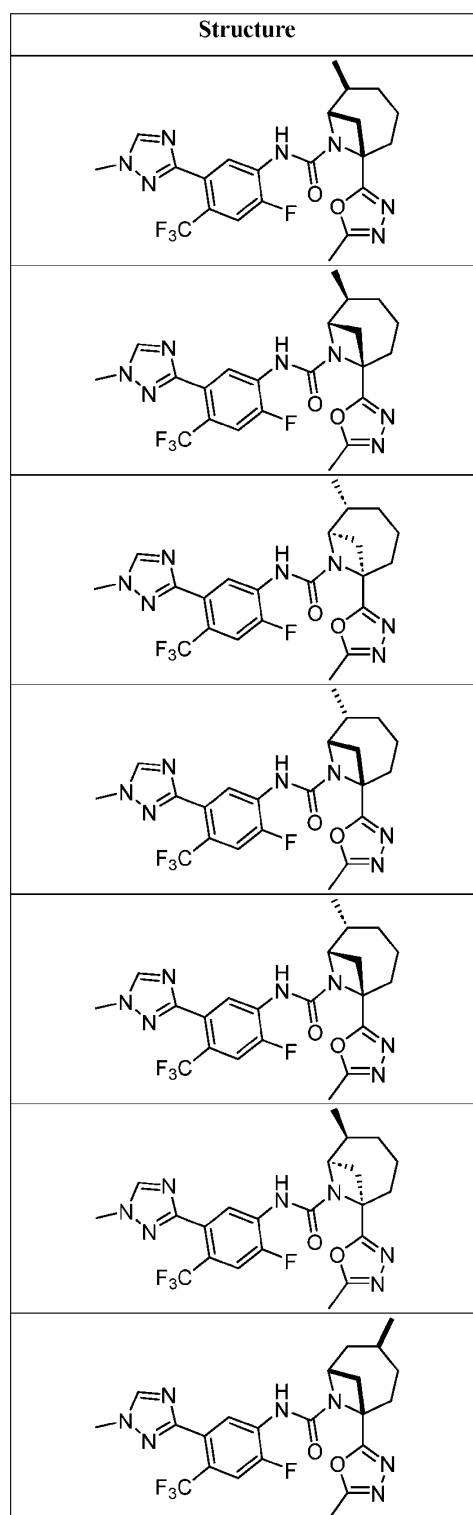
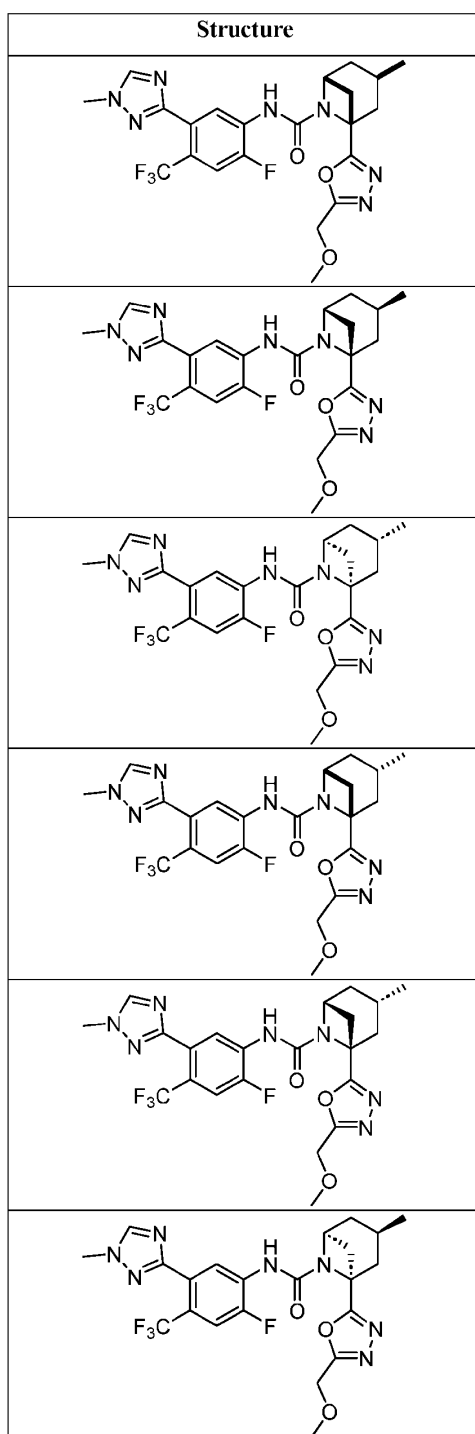


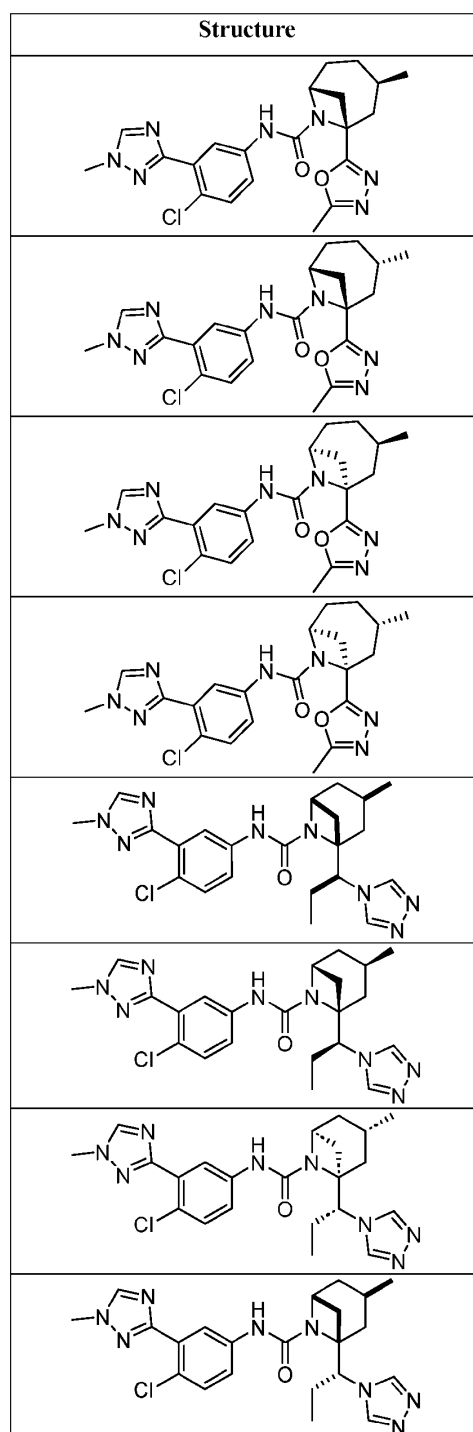
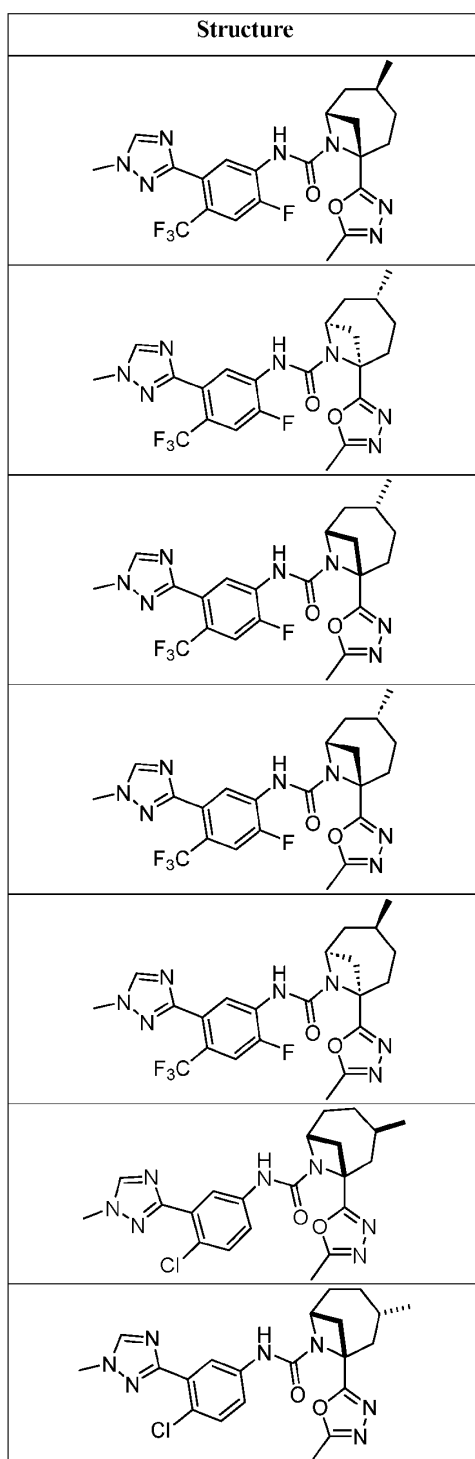


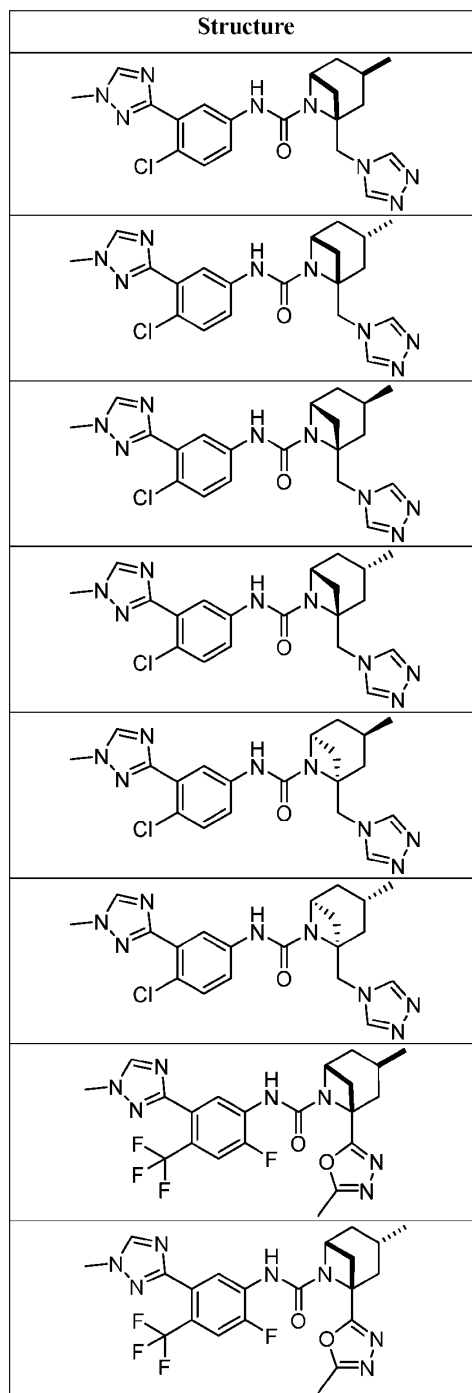
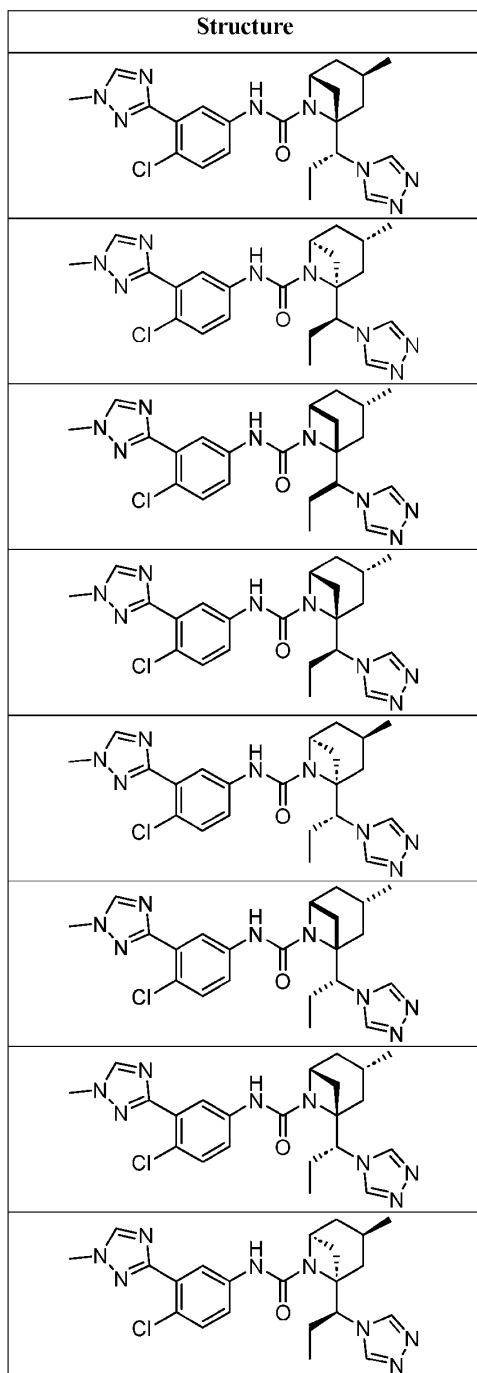


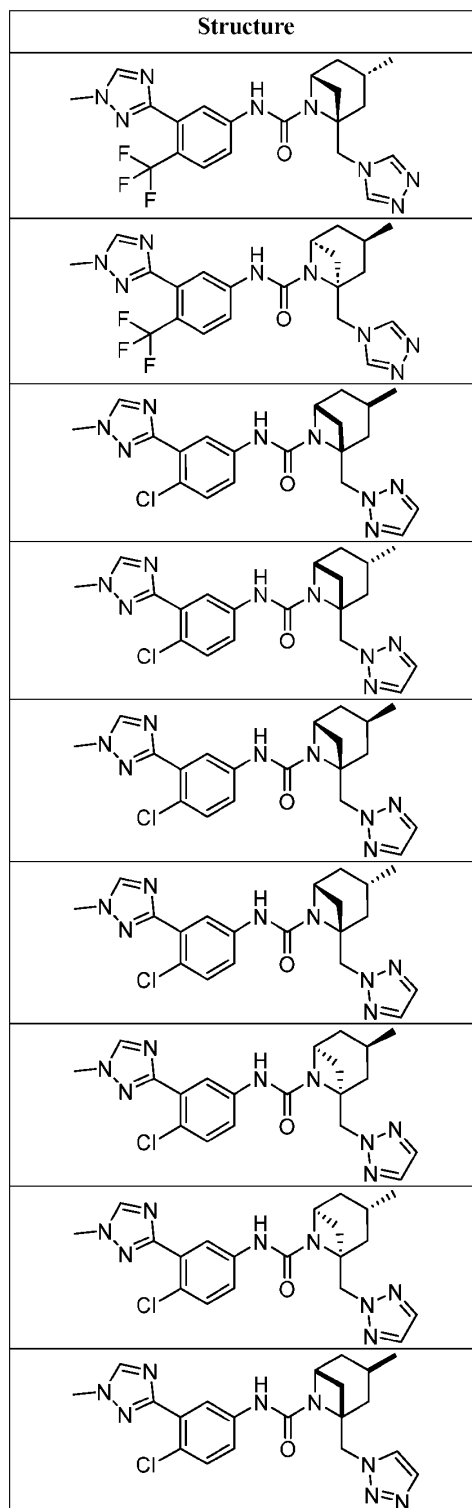
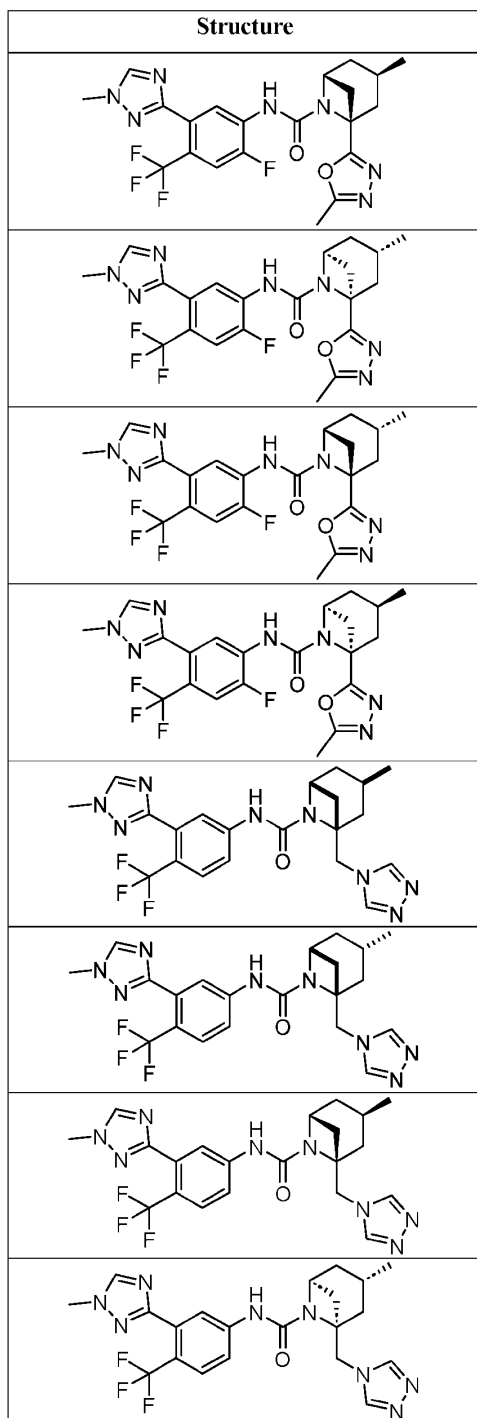


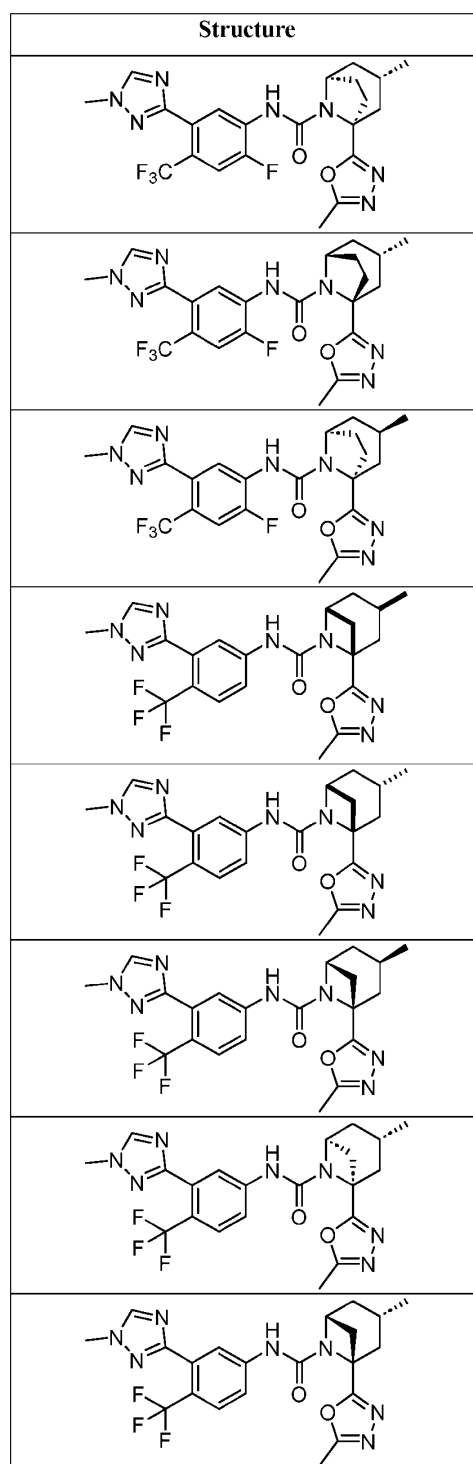
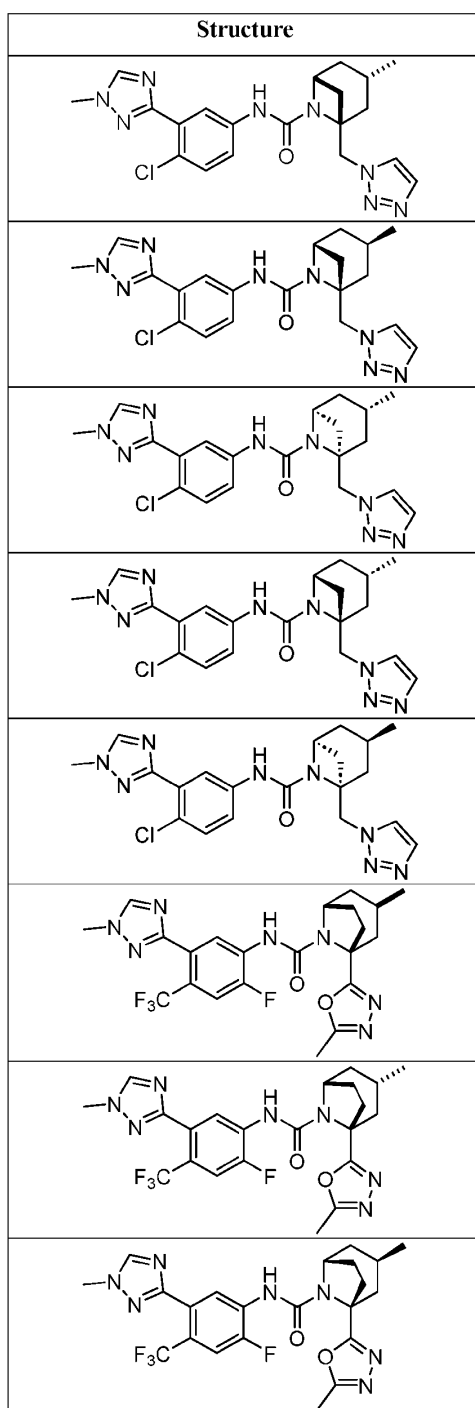


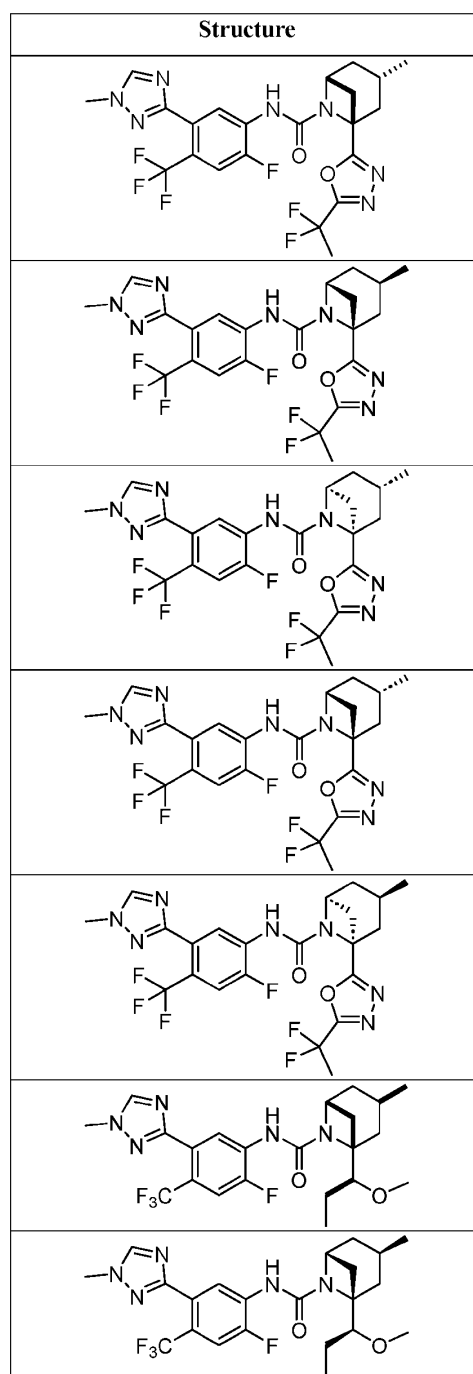
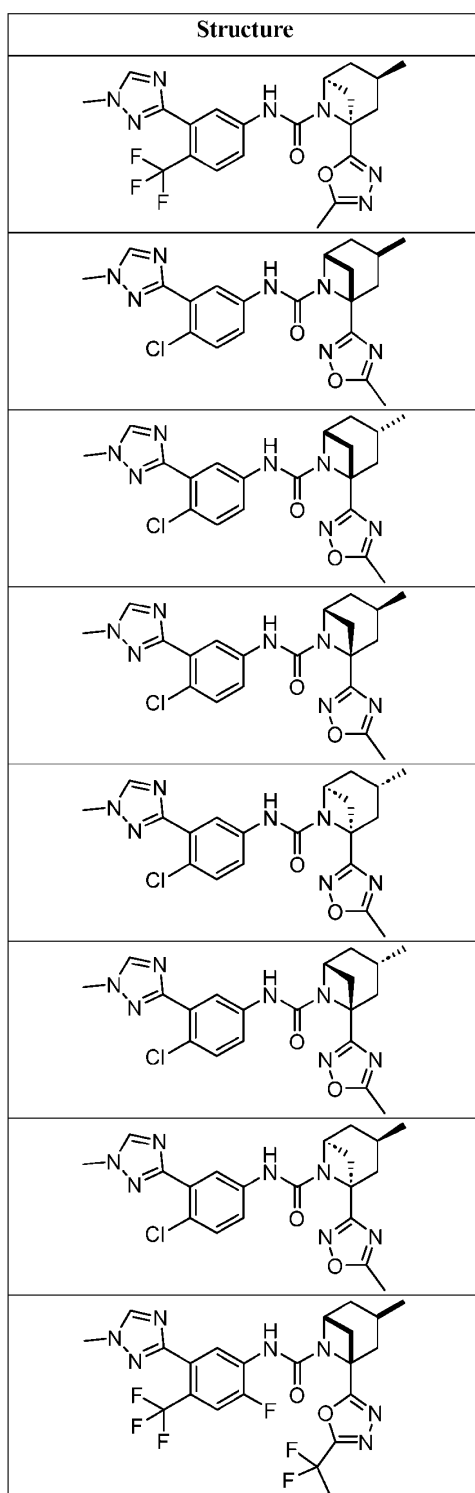


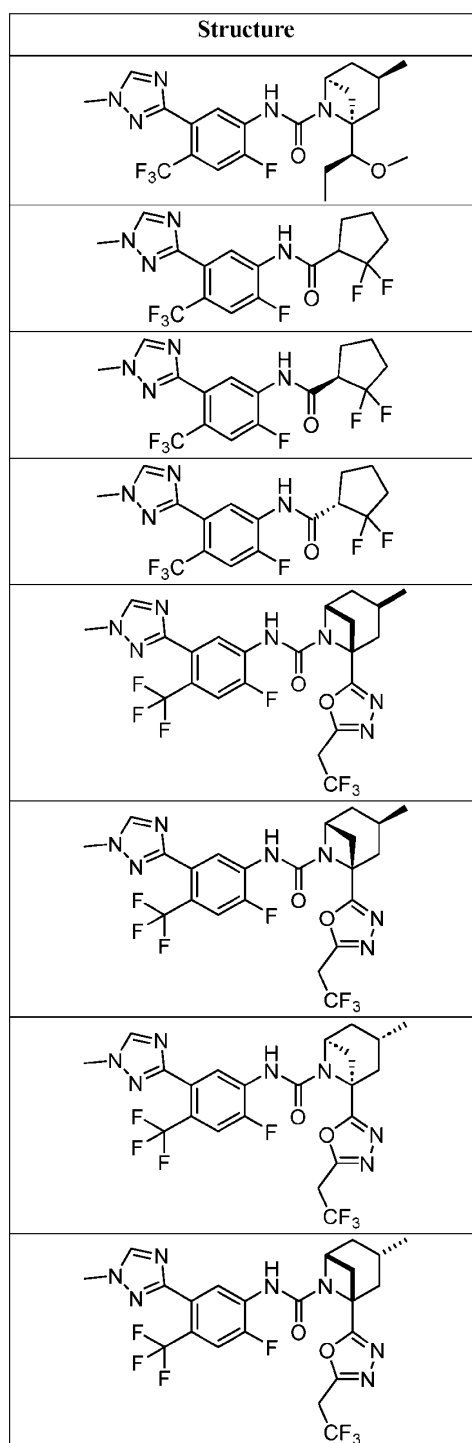
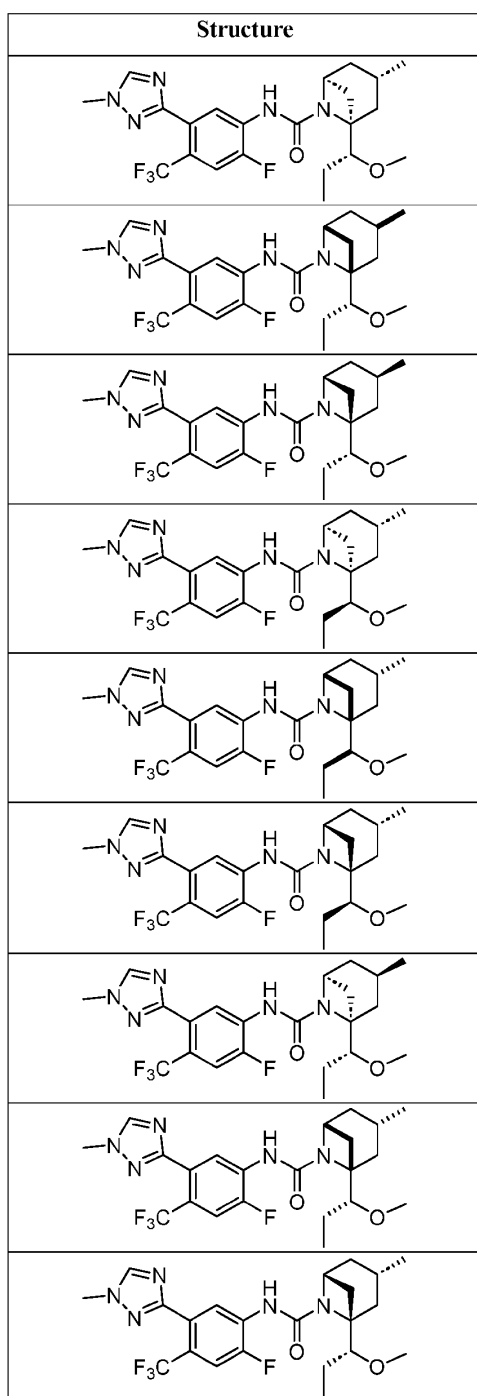


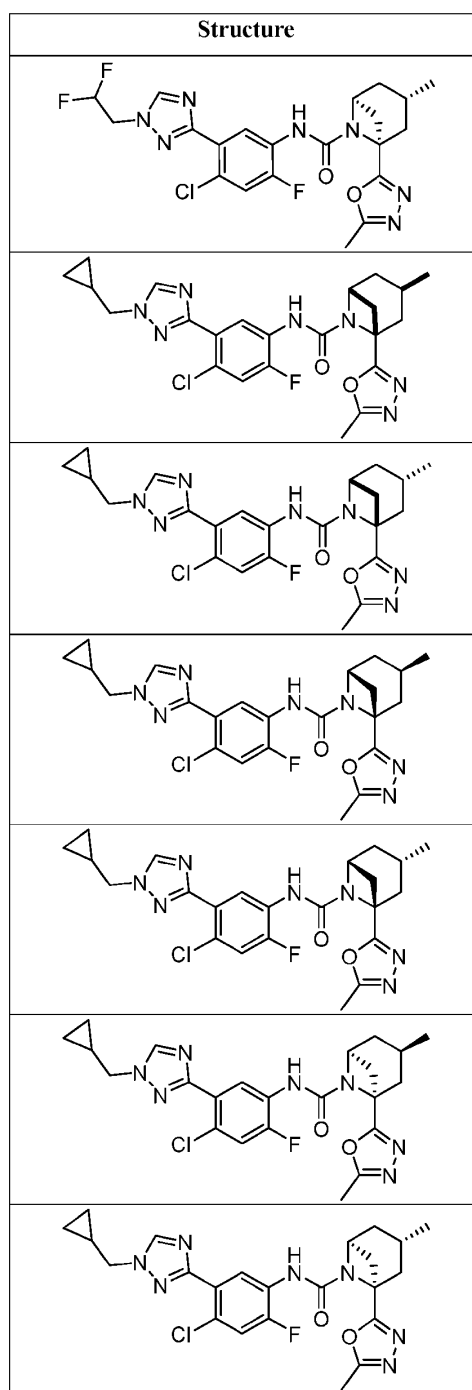
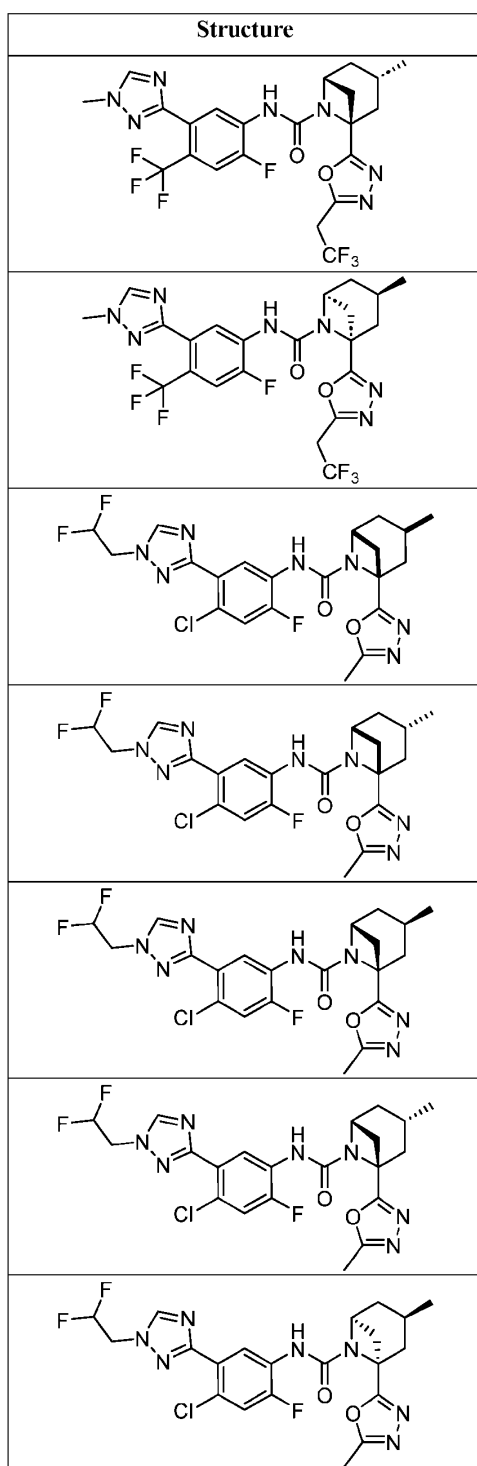


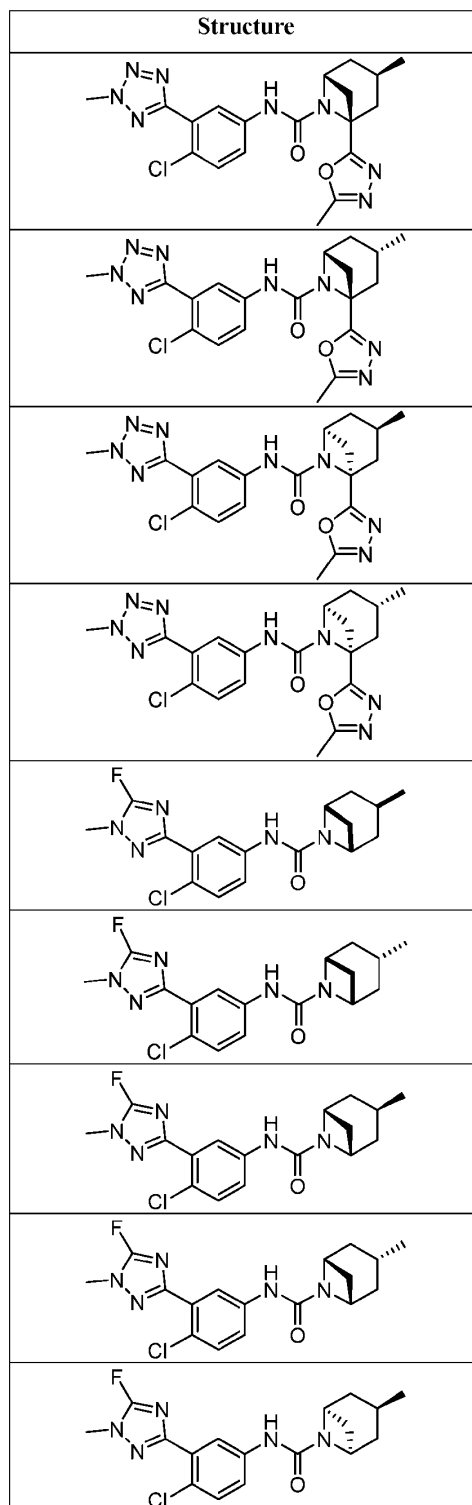
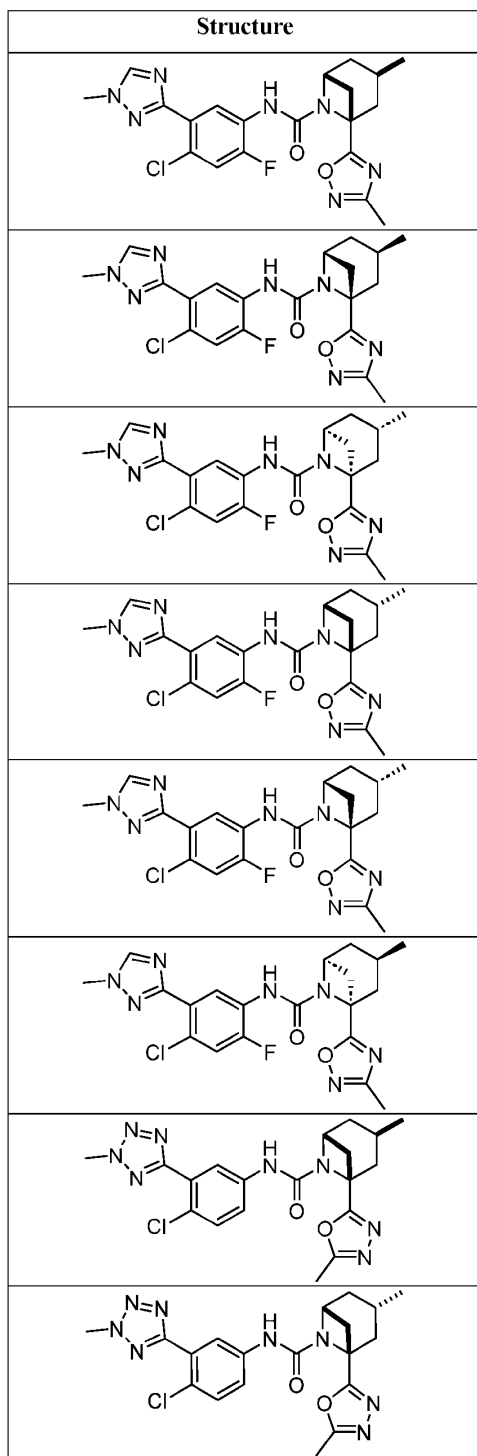


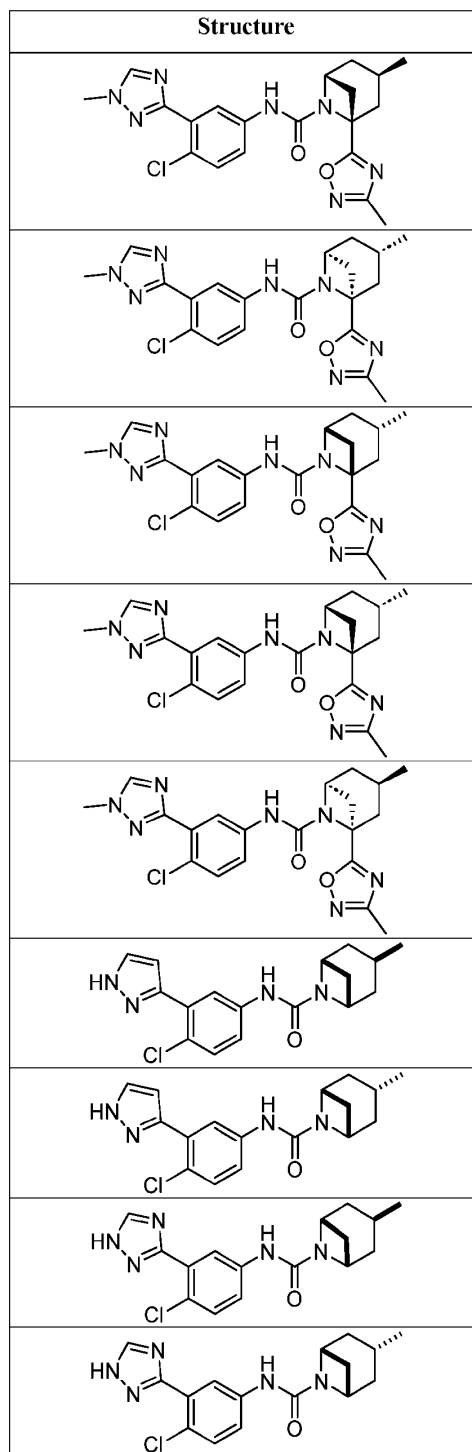
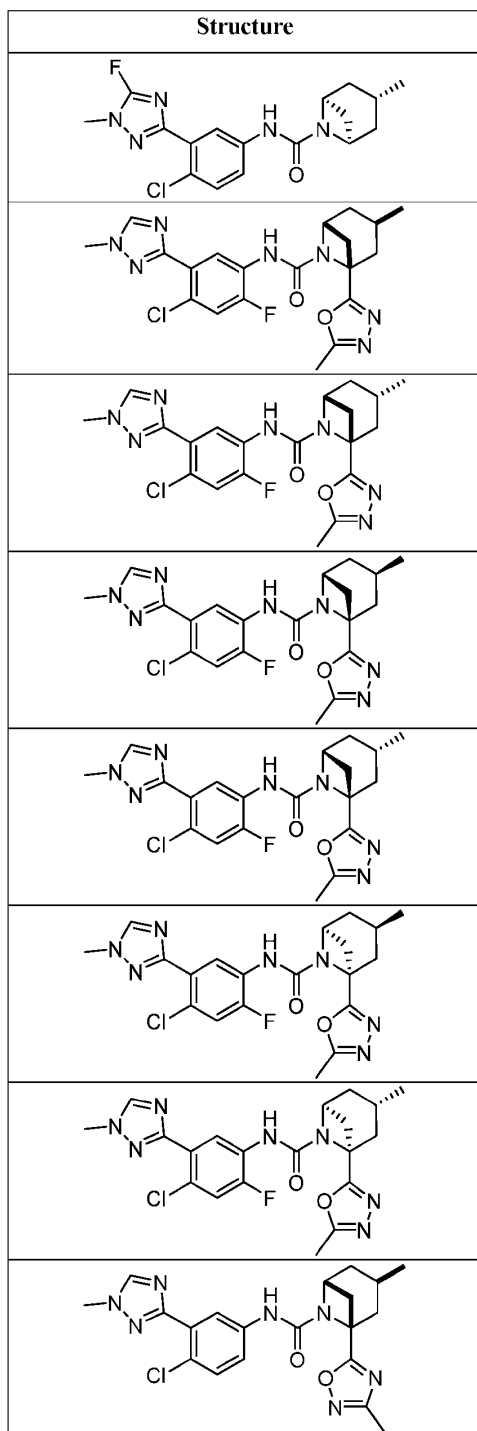


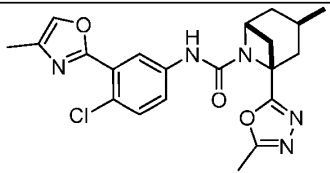
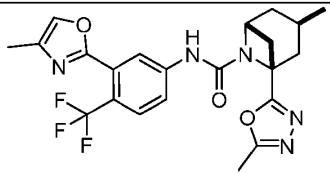
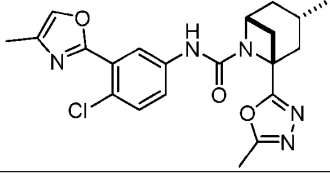
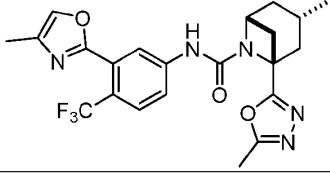
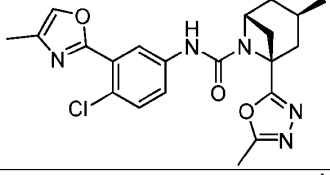
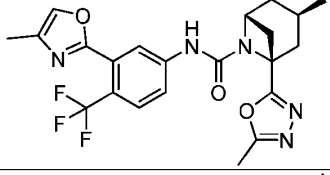
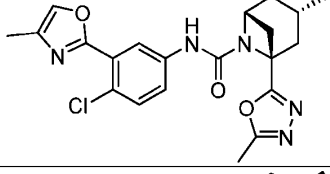
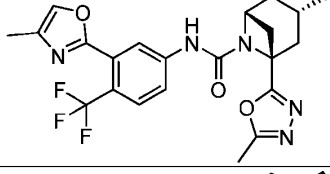
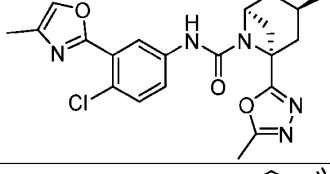
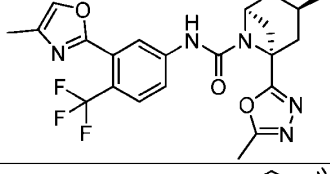
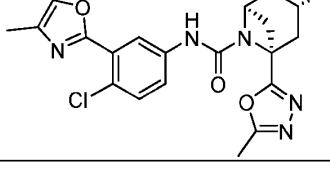
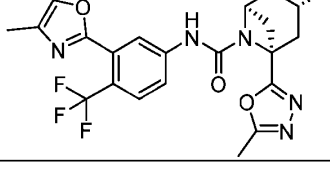










Structure	Structure
	
	
	
	
	
	

3. Methods

[0134] “Treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state,

providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0135] “Prevention” or “preventing” means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in certain embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0136] “Subject” refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy, and/or veterinary applications. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[0137] The term “therapeutically effective amount” or “effective amount” of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition of as described herein. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0138] The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. “*In vivo*” means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. “*Ex vivo*” means outside of a living individual. Examples of *ex vivo* cell populations include *in vitro* cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions described herein may be suited are described below or will become apparent to those skilled in the art. The compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0139] In certain embodiments, provided are compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, that inhibit the

activity of Sterile Alpha and TIR Motif containing 1 (SARM1) protein. In certain embodiments, the compounds provided herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, inhibits SARM1.

[0140] In certain embodiments, provided is a method of inhibiting SARM1 activity comprising contacting a cell with an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof. The inhibiting can be *in vitro* or *in vivo*.

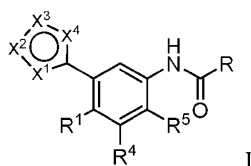
[0141] In certain embodiments, provided is a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in inhibiting SARM1 activity (e.g., *in vitro* or *in vivo*).

[0142] In certain embodiments, the present disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, in the manufacture of a medicament for inhibiting SARM1 activity (e.g., *in vitro* or *in vivo*).

[0143] In certain embodiments, provided is a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, for inhibiting NADase activity of SARM1. In certain embodiments, provided is a method of inhibiting SARM1 NADase activity and/or treating a neurodegenerative or neurological disease or disorder in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, to the subject.

[0144] In certain embodiments, provided is a method for treating a disease or condition mediated, at least in part, by SARM1, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof to a subject in need thereof.

[0145] In certain embodiments, provided is a method for treating a disease or condition mediated, at least in part, by SARM1, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N, NR^{8a}, O, S, or CR^{6a};

X² is N, NR^{8b}, O, S, or CR^{6b};

X^3 is N, NR^{8c} , or CR^{6c} ;

X^4 is N or CR^{6d} ;

provided that at least one of X^1 , X^2 , X^3 , and X^4 is N, and the ring containing X^1 , X^2 , X^3 , and X^4 is aromatic;

R is $-NR^2R^3$, $-OR^7$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl is optionally substituted with one to five Z^1 ;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-3} alkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

R^3 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^2 and R^3 together form a heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^7 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8a} and R^{6b} , or R^{8b} and R^{6c} , or R^{6b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{13})_2$, $-OR^{13}$, $-SR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{13}C(O)R^{13}$, $-NR^{13}S(O)R^{13}$, $-NR^{13}S(O)_2R^{13}$, $-S(O)N(R^{13})_2$, $-S(O)_2N(R^{13})_2$, $-NR^{13}C(O)N(R^{13})_2$, $-NR^{13}S(O)N(R^{13})_2$, $-NR^{13}S(O)_2N(R^{13})_2$, $-OC(O)N(R^{13})_2$, or $-NR^{13}C(O)OR^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-OH$, $-SH$, $-NH_2$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, $-L$ -heterocyclyl, $-L$ -aryl, or $-L$ -heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl.

[0146] In certain embodiments, provided is a method of treating axonal degeneration in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, to the subject. In certain embodiments, the compound, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, inhibits axonal degeneration, including axonal degeneration that results from reduction or depletion of NAD⁺. In certain embodiments, the compound, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, prevents an axon distal to an axonal injury from degenerating.

[0147] In certain embodiments, provided is a method for treating degradation of a peripheral nervous system neuron or a portion thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0148] In certain embodiments, provided is a method for treating degeneration of a central nervous system neuron or a portion thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0149] In certain embodiments, the treating comprises reducing one or more symptoms or features of neurodegeneration.

[0150] In certain embodiments, provided is a method for inhibiting axon degeneration, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0151] In certain embodiments, provided is a method for treating a neurodegenerative or neurological disease or disorder, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0152] In certain embodiments, provided is a method for treating a neurodegenerative or neurological disease or disorder associated with axonal degeneration, axonal damage, axonopathy, a demyelinating disease, a central pontine myelinolysis, a nerve injury disease or disorder, a metabolic disease, a mitochondrial disease, metabolic axonal degeneration, axonal damage resulting from traumatic axonal injury (TAI) (see Ziogas et al., J. Neuroscience, 2018, 38(16):4031-4032 and WO2020191257), a leukoencephalopathy or a leukodystrophy, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0153] In certain embodiments, provided is a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in treating a disease or condition mediated, at least in part, by SARM1 in a subject in need thereof.

[0154] In certain embodiments, provided is a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in inhibiting axon degeneration in a subject in need thereof.

[0155] In certain embodiments, the present disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof in the manufacture of a medicament for inhibiting axon degeneration in a subject in need thereof.

[0156] In certain embodiments, the present disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof in the manufacture of a medicament for treating a neurodegenerative or neurological disease or disorder, such as a disease or disorder associated with axonal degeneration, axonal damage, axonopathy, a demyelinating disease, a central pontine myelinolysis, a nerve injury disease or disorder, a metabolic disease, a mitochondrial disease, metabolic axonal degeneration, axonal damage resulting from traumatic axonal injury (TAI), a leukoencephalopathy or a leukodystrophy.

[0157] In certain embodiments, the disease or condition is an acute condition. In certain embodiments, the disease or condition is a chronic condition.

[0158] In certain embodiments, the disease or condition is characterized by axonal degeneration in the central nervous system, the peripheral nervous system, the optic nerve, the cranial nerves, or a combination thereof.

[0159] In certain embodiments, the disease or condition is or comprises acute injury to the central nervous system, such as, but not limited to, injury to the spinal cord and/or traumatic brain injury (TBI). In certain embodiments, the disease or condition is or comprises a chronic injury to the central nervous system, such as, but not limited to, injury to the spinal cord, traumatic brain injury (TBI), and/or traumatic axonal injury (TAI). In certain embodiments, the disease or condition is or comprises chronic traumatic encephalopathy (CTE).

[0160] In certain embodiments, the disease or condition is a chronic condition affecting the central nervous system, such as, but not limited to, Parkinson's disease (see, e.g., Sajadi, A., et al. *Curr. Biology*. **2004**, *14*, 326-330; and Hasbani, D.M., et al. *Exp. Neurology*. **2006**, *202*, 93-99), amyotrophic lateral sclerosis (see, e.g., White, M.A., et al. *Acta Neuropath. Comm*. 2019, *7*(1), 166), multiple sclerosis, Huntington disease, or Alzheimer's disease.

[0161] In certain embodiments, the disease or condition is an acute peripheral neuropathy. In certain embodiments, the disease or condition is chemotherapy-induced peripheral neuropathy (CIPN). See, e.g., Geisler, S., et al. *Brain*. **2016**, *139*, 3092-3108; Turkiew, E., et al. *J. Peripher. Nerv. Syst.* **2017**, *22*, 162-171; Geisler, S., et al. *JCI Insight*. **2019**, *4*(17), e129920; and Cetinkaya-Fisgin, A., et al. *Sci. Rep.* **2020**, 21889. Chemotherapy-induced peripheral neuropathy (CIPN), an example of an acute peripheral neuropathy, can be associated with various drugs, such as, but not limited to, thalidomide, epothilones (e.g., ixabepilone), taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids (e.g., vinblastine, vinorelbine, vincristine, and vindesine), proteasome inhibitors (e.g., bortezomib), or platinum-based drugs (e.g., cisplatin, oxaliplatin, and carboplatin).

[0162] In certain embodiments, the disease or condition is a chronic condition affecting the peripheral nervous system, such as, but not limited to, diabetic neuropathy, HIV neuropathy, Charcot Marie Tooth disease, or amyotrophic lateral sclerosis.

[0163] In certain embodiments, the disease or condition is glaucoma (see, e.g., Ko, K.W., et al. *J. Cell Bio.* **2020**, *219*(8), e201912047).

[0164] In certain embodiments, the disease or condition is an acute condition affecting the optic nerve, such as, but not limited to, diabetic optic neuropathy, acute optic neuropathy (AON) or acute angle closure glaucoma.

[0165] In certain embodiments, the disease or condition is a chronic condition affecting the optic nerve, such as, but not limited to, diabetic optic neuropathy, Leber's congenital amaurosis, Leber's hereditary optic neuropathy (LHON), primary open angle glaucoma, or autosomal dominant optic atrophy.

[0166] In certain embodiments, the disease or condition is associated with retinal degeneration. In certain embodiments, the disease or condition is Leber congenital amaurosis, such as Leber congenital amaurosis type 9 (LCA9) (see, e.g., Sasaki, Y., et al. *eLife*. **2020**, *9*, e62027.)

[0167] In certain embodiments, one or more compounds and/or compositions as described herein are useful, for example, to treat one or more neurodegenerative diseases, disorders or conditions selected from the group consisting of neuropathies or axonopathies. In certain embodiments, one or more compounds and/or compositions as described herein are useful, for example to treat a neuropathy or axonopathy associated with axonal degeneration. In certain embodiments, a neuropathy associated with axonal degeneration is a hereditary or congenital neuropathy or axonopathy. In certain embodiments, a neuropathy associated with axonal degeneration results from a *de novo* or somatic mutation. In certain embodiments, a neuropathy associated with axonal degeneration is selected from a list contained herein. In certain embodiments, a neuropathy or axonopathy is associated with axonal degeneration, including,

but not limited to Parkinson's disease, Alzheimer's disease, herpes infection, diabetes, amyotrophic lateral sclerosis, a demyelinating disease, ischemia, stroke, chemical injury, thermal injury, or AIDS.

[0168] In certain embodiments, one or more compounds or compositions as described herein is characterized that, when administered to a population of subjects, reduces one or more symptoms or features of neurodegeneration. For example, in certain embodiments, a relevant symptom or feature may be selected from the group consisting of extent, rate, and/or timing of neuronal disruption. In certain embodiments, neuronal disruption may be or comprise axonal degradation, loss of synapses, loss of dendrites, loss of synaptic density, loss of dendritic arborization, loss of axonal branching, loss of neuronal density, loss of myelination, loss of neuronal cell bodies, loss of synaptic potentiation, loss of action-potential potentiation, loss of cytoskeletal stability, loss of axonal transport, loss of ion channel synthesis and turnover, loss of neurotransmitter synthesis, loss of neurotransmitter release and reuptake capabilities, loss of axon-potential propagation, neuronal hyperexcitability, and/or neuronal hypoexcitability. In certain embodiments, neuronal disruption is characterized by an inability to maintain an appropriate resting neuronal membrane potential. In certain embodiments, neuronal disruption is characterized by the appearance of inclusion bodies, plaques, and/or neurofibrillary tangles. In certain embodiments, neuronal disruption is characterized by the appearance of stress granules. In certain embodiments, neuronal disruption is characterized by the intracellular activation of one or more members of the cysteine-aspartic protease (Caspase) family. In certain embodiments, neuronal disruption is characterized by a neuron undergoing programmed cell death (e.g. apoptosis, pyroptosis, ferroptosis, and/or necrosis) and/or inflammation.

[0169] In certain embodiments, the neurodegenerative or neurological disease or disorder is associated with axonal degeneration, axonal damage, axonopathy, a demyelinating disease, a central pontine myelinolysis, a nerve injury disease or disorder, a metabolic disease, a mitochondrial disease, metabolic axonal degeneration, axonal damage resulting from a leukoencephalopathy or a leukodystrophy. In certain embodiments, the neurodegenerative or neurological disease or disorder is spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, osmotic hyponatremia, hypoxic demyelination, ischemic demyelination, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury (TBI), traumatic axonal injury (TAI), post radiation injury, neurologic complications of chemotherapy (e.g., chemotherapy induced peripheral neuropathy, CIPN), neuropathy, acute ischemic optic neuropathy, vitamin B12 deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, retinal degeneration, glaucoma, retinitis pigmentosa, traumatic optic injury, Leber's hereditary optic atrophy (neuropathy), Leber congenital amaurosis (e.g., Leber congenital amaurosis type 9 (LCA9)),

neuromyelitis optica, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, west Nile virus encephalopathy, La Crosse virus encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, essential tremor, Charcot-Marie-Tooth disease, motor neuron disease, spinal muscular atrophy (SMA), hereditary sensory and autonomic neuropathy (HSAN), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, hereditary ataxias, noise induced hearing loss, congenital hearing loss, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, HIV neuropathy, enteric neuropathies and axonopathies, Guillain-Barre syndrome, severe acute motor axonal neuropathy (AMAN), Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, spinocerebellar ataxias, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, or non-alcoholic steatohepatitis (NASH).

[0170] In certain embodiments, the present disclosure provides inhibitors of SARM1 activity for treatment of neurodegenerative or neurological diseases or disorders that involve axon degeneration or axonopathy. The present disclosure also provides methods of using inhibitors of SARM1 activity to treat, prevent or ameliorate axonal degeneration, axonopathies and neurodegenerative or neurological diseases or disorders that involve axonal degeneration. In certain embodiments, the present disclosure provides a method for inhibiting axon degeneration, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0171] In certain embodiments, the present disclosure provides methods of treating neurodegenerative or neurological diseases or disorders related to axonal degeneration, axonal damage, axonopathies, demyelinating diseases, central pontine myelinolysis, nerve injury diseases or disorders, metabolic diseases, mitochondrial diseases, metabolic axonal degeneration, axonal damage resulting from a leukoencephalopathy or a leukodystrophy.

[0172] In certain embodiments, neuropathies and axonopathies include any disease or condition involving neurons and/or supporting cells, such as for example, glia, muscle cells or fibroblasts, and, in particular, those diseases or conditions involving axonal damage. Axonal damage can be caused by traumatic injury or by non-mechanical injury due to diseases, conditions, or exposure to toxic molecules or drugs. The result of such damage can be degeneration or dysfunction of the axon and loss of functional neuronal activity. Disease and conditions producing or associated with such axonal damage are among a large number of neuropathic diseases and conditions. Such neuropathies can include peripheral neuropathies, central neuropathies, or combination thereof. Furthermore, peripheral neuropathic manifestations can be produced by diseases focused primarily in the central nervous systems and central nervous system manifestations can be produced by essentially peripheral or systemic diseases.

[0173] In certain embodiments, a peripheral neuropathy may involve damage to the peripheral nerves, and/or can be caused by diseases of the nerves or as the result of systemic illnesses. Some such diseases

include diabetes, uremia, infectious diseases such as AIDS or leprosy, nutritional deficiencies, vascular or collagen disorders such as atherosclerosis, or autoimmune diseases such as systemic lupus erythematosus, scleroderma, sarcoidosis, rheumatoid arthritis, and polyarteritis nodosa. In certain embodiments, peripheral nerve degeneration results from traumatic (mechanical) damage to nerves as well as chemical or thermal damage to nerves. Such conditions that injure peripheral nerves include compression or entrapment injuries such as glaucoma, carpal tunnel syndrome, direct trauma, penetrating injuries, contusions, fracture or dislocated bones; pressure involving superficial nerves (ulna, radial, or peroneal) which can result from prolonged use of crutches or staying in one position for too long, or from a tumor; intraneural hemorrhage; ischemia; exposure to cold or radiation or certain medicines or toxic substances such as herbicides or pesticides. In particular, the nerve damage can result from chemical injury due to a cytotoxic anticancer agent such as, for example, taxol, cisplatin, a proteasome inhibitor, or a vinca alkaloid such as vincristine. Typical symptoms of such peripheral neuropathies include weakness, numbness, paresthesia (abnormal sensations such as burning, tickling, pricking or tingling) and pain in the arms, hands, legs and/or feet. In certain embodiments, a neuropathy is associated with mitochondrial dysfunction. Such neuropathies can exhibit decreased energy levels, i.e., decreased levels of NAD and ATP.

[0174] In certain embodiments, peripheral neuropathy is a metabolic and endocrine neuropathy which includes a wide spectrum of peripheral nerve disorders associated with systemic diseases of metabolic origin. These diseases include, for example, diabetes mellitus, hypoglycemia, uremia, hypothyroidism, hepatic failure, polycythemia, amyloidosis, acromegaly, porphyria, a disorder of lipid/glycolipid metabolism, a nutritional/vitamin deficiency, or a mitochondrial disorder. The common hallmark of these diseases is involvement of peripheral nerves by alteration of the structure or function of myelin and axons due to metabolic pathway dysregulation.

[0175] In certain embodiments, neuropathies include optic neuropathies such as glaucoma, retinal ganglion degeneration such as those associated with retinitis pigmentosa and outer retinal neuropathies, optic nerve neuritis and/or degeneration including that associated with multiple sclerosis, traumatic injury to the optic nerve which can include, for example, injury during tumor removal, hereditary optic neuropathies such as Kjer's disease and Leber's hereditary optic neuropathy (LHON), ischemic optic neuropathies, such as those secondary to giant cell arteritis, metabolic optic neuropathies such as neurodegenerative diseases including Leber's neuropathy, nutritional deficiencies such as deficiencies in vitamins B12 or folic acid, and toxicities such as due to ethambutol or cyanide, neuropathies caused by adverse drug reactions and neuropathies caused by vitamin deficiency. Ischemic optic neuropathies also include non-arteritic anterior ischemic optic neuropathy.

[0176] In certain embodiments, neurodegenerative diseases that are associated with neuropathy or axonopathy in the central nervous system include a variety of diseases. Such diseases include those involving progressive dementia such as, for example, Alzheimer's disease, senile dementia, Pick's disease, and Huntington's disease, central nervous system diseases affecting muscle function such as, for

example, Parkinson's disease, motor neuron diseases and progressive ataxias such as amyotrophic lateral sclerosis, demyelinating diseases such as, for example multiple sclerosis, viral encephalitis such as, for example, those caused by enteroviruses, arboviruses, and herpes simplex virus, and prion diseases. Mechanical injuries such as glaucoma or traumatic injuries to the head and spine can also cause nerve injury and degeneration in the brain and spinal cord. In addition, ischemia and stroke as well as conditions such as nutritional deficiency and chemical toxicity such as with chemotherapeutic agents can cause central nervous system neuropathies.

[0177] In certain embodiments, the present disclosure provides a method of treating a neuropathy or axonopathy associated with axonal degeneration. In certain embodiments, a neuropathy or axonopathy associated with axonal degeneration can be any of a number of neuropathies or axonopathies such as, for example, those that are hereditary or congenital or associated with Parkinson's disease, Alzheimer's disease, Herpes infection, diabetes, amyotrophic lateral sclerosis, a demyelinating disease, ischemia or stroke, chemical injury, thermal injury, and AIDS. In addition, neurodegenerative diseases not mentioned above as well as a subset of the above mentioned diseases can also be treated with the methods of the present disclosure. Such subsets of diseases can include Parkinson's disease or Alzheimer's disease.

[0178] In certain embodiments, the present methods comprise administering an effective amount of a compound and/or composition as described herein (e.g., a compound of Formula I) to a subject in need thereof. In some such embodiments, the subject is at risk of developing a condition characterized by axonal degeneration. In certain embodiments, the subject has a condition characterized by axonal degeneration. In certain embodiments, the subject has been diagnosed with a condition characterized by axonal degeneration. In certain embodiments, the subject is at risk of developing a condition characterized by axonal degeneration. In certain embodiments, the subject is identified as being at risk of axonal degeneration, e.g., based on the subject's genotype, a diagnosis of a condition associated with axonal degeneration, and/or exposure to an agent and/or a condition that induces axonal degeneration.

[0179] In certain embodiments, the subject is at risk of developing a neurodegenerative disorder. In certain embodiments, the subject is elderly. In certain embodiments, the subject is known to have a genetic risk factor for neurodegeneration. In certain embodiments, the subject has a family history of neurodegenerative disease. In certain embodiments, the subject expresses one or more copies of a known genetic risk factor for neurodegeneration. In certain embodiments, the subject is drawn from a population with a high incidence of neurodegeneration. In certain embodiments, the subject has a hexanucleotide repeat expansion in chromosome 9 open reading frame 72. In certain embodiments, the subject has one or more copies of the ApoE4 allele.

[0180] In certain embodiments, a neurodegenerative disease, disorder or condition may be or comprise a traumatic neuronal injury. In certain embodiments, a traumatic neuronal injury is blunt force trauma, a closed-head injury, an open head injury, exposure to a concussive and/or explosive force, a penetrating injury in to the brain cavity or innervated region of the body. In certain embodiments, a traumatic

neuronal injury is a force which causes the axons to deform, stretch, crush or sheer. In certain embodiments, the disease or disorder is a traumatic brain injury (TBI).

[0181] In certain embodiments, the subject has engaged, or engages, in an activity identified as a risk factor for neuronal degradation, e.g., a contact sport or occupations with a high chance for traumatic neuronal injury or TBI.

[0182] In certain embodiments, provided is a method of treating a neurodegenerative disease, disorder or condition comprising administering to a patient in need thereof, a compound as described herein, and one or more of a DLK inhibitor or a NAMPT inhibitor. In certain embodiments, provided is a combination therapy comprising a compound as described herein and a DLK inhibitor and/or a NAMPT inhibitor. In certain embodiments, provided is a combination therapy comprising a compound as described herein, a DLK inhibitor, and one or more additional therapeutic agents. In certain embodiments, provided is a combination therapy comprising a compound as described herein, a NAMPT inhibitor, and one or more additional therapeutic agents. In certain embodiments, provided is a combination therapy comprising a compound as described herein, a DLK inhibitor, a NAMPT inhibitor and one or more additional therapeutic agents.

[0183] In certain embodiments, the DLK inhibitor is a small molecule, a polypeptide, a peptide fragment, a nucleic acid (e.g., a siRNA, an antisense oligonucleotide, a micro-RNA, or an aptamer), an antibody, a dominant-negative inhibitor, or a ribozyme. In certain embodiments, the DLK inhibitor is a small molecule. In certain embodiments, the DLK inhibitor is a siRNA. In certain embodiments, the DLK inhibitor is an antisense oligonucleotide. In certain embodiments, the DLK inhibitor is a polypeptide. In certain embodiments, a DLK inhibitor is a peptide fragment. In certain embodiments, a DLK inhibitor is a nucleic acid. In certain embodiments, a DLK inhibitor is an antisense oligonucleotide.

[0184] Exemplary DLK inhibitors are provided in WO2013174780, WO2014111496, WO2014177524, WO2014177060, WO2015091889, WO2016142310, US20180057507, WO2018107072, WO2019241244, WO2020168111, and CN104387391A, which are hereby incorporated by reference in their entirety.

[0185] In certain embodiments, the NAMPT inhibitor is a small molecule, a polypeptide, a peptide fragment, a nucleic acid (e.g., a siRNA, an antisense oligonucleotide, a micro-RNA, or an aptamer), an antibody, a dominant-negative inhibitor, or a ribozyme. In certain embodiments, the NAMPT inhibitor is a small molecule. In some embodiments, the NAMPT inhibitor is a siRNA. In some embodiments, the NAMPT inhibitor is an antisense oligonucleotide. In certain embodiments, the NAMPT inhibitor is a polypeptide. In some embodiments, a NAMPT inhibitor is a peptide fragment. In certain embodiments, a NAMPT inhibitor is a nucleic acid. In some embodiments, a NAMPT inhibitor is an antisense oligonucleotide.

[0186] In certain embodiments, a NAMPT inhibitor prevents the formation of nicotinamide mononucleotide (NMN). In certain embodiments, inhibition of NAMPT inhibits the mammalian NAD⁺ salvage pathway.

[0187] In certain embodiments, the provided is a composition comprising a compound as described herein, formulated for use in administering to a subject in combination with a DLK inhibitor and/or a NAMPT inhibitor.

[0188] In certain embodiments, the provided is a composition comprising a compound as described herein, for use in combination with a DLK inhibitor and/or a NAMPT inhibitor. In certain embodiments, such compositions are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, diluent or excipient.

[0189] In certain embodiments, the subject may be a subject who has received, is receiving, or has been prescribed, a chemotherapy associated with peripheral neuropathy. Examples of chemotherapeutic agents include, but not limited to, thalidomide, epothilones (e.g., ixabepilone), taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids (e.g., vinblastine, vinorelbine, vincristine, and vindesine), proteasome inhibitors (e.g., bortezomib), platinum-based drugs (e.g., cisplatin, oxaliplatin, and carboplatin).

[0190] In certain embodiments, SARM1 inhibition as described herein may be utilized in combination with one or more other therapies to treat a relevant disease, disorder, or condition. In certain embodiments, dosing of a SARM1 inhibitor is altered when utilized in combination therapy as compared with when administered as monotherapy; alternatively or additionally, a therapy that is administered in combination with SARM1 inhibition as described herein is administered according to a regimen or protocol that differs from its regimen or protocol when administered alone or in combination with one or more therapies other than SARM1 inhibition. In certain embodiments, compositions which comprise an additional therapeutic agent, that additional therapeutic agent and a provided compound may act synergistically. In certain embodiments, one or both therapies utilized in a combination regimen is administered at a lower level or less frequently than when it is utilized as monotherapy.

[0191] In certain embodiments, a compound, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, or composition provided herein is administered in combination with a NAD⁺ or a NAD⁺ precursor (e.g., nicotinamide riboside (NR), nicotinic acid (NA), nicotinic acid riboside (NaR), nicotinamide (NAM), nicotinamide mononucleotide (NMN), nicotinic acid mononucleotide (NaMN), tryptophan (TRP), nicotinic acid adenine dinucleotide (NAAD), or vitamin B₃).

[0192] In certain embodiments, provided is a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in inhibiting sterile alpha and TIR motif-containing protein 1 (SARM1) activity (e.g., *in vitro* or *in vivo*).

[0193] In certain embodiments, the present disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, in the manufacture of a medicament for inhibiting sterile alpha and TIR motif-containing protein 1 (SARM1) activity (e.g., *in vitro* or *in vivo*) and supplementing axonal NAD⁺ levels.

[0194] Axonal degeneration has been associated with various types of neurodegenerative diseases, being recognized as an important indicator of disease progression, and an interesting target for the therapeutic treatment of these diseases. Similarly, axonal degeneration is also observed in those with traumatic brain injuries and peripheral neuropathies.

[0195] In certain embodiments, provided is a method for treating a disease or condition mediated, at least in part, by SARM1, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, in combination with NAD⁺ or a NAD⁺ precursor (e.g., NR, NA, NaR, NAM, NMN, NaMN, TRP, NAAD, or vitamin B₃).

[0196] In certain embodiments, the present disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, in combination with NAD⁺ or a NAD⁺ precursor (e.g., NR, NA, NaR, NAM, NMN, NaMN, TRP, NAAD, or vitamin B₃), in the manufacture of a medicament for treating or preventing a neurodegenerative disease in a subject in need thereof.

[0197] In certain embodiments, provided is a method for treating any disease caused by SARM1 activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, in combination with NAD⁺ or a NAD⁺ precursor (e.g., NR, NA, NaR, NAM, NMN, NaMN, TRP, NAAD, or vitamin B₃).

[0198] In certain embodiments, the disease or condition may be a disease or condition of the central nervous system, and/or may be caused by or associated with a pathogen or traumatic injury. It will be appreciated that these general embodiments defined according to broad categories of diseases, disorders and conditions are not mutually exclusive.

[0199] In certain embodiments, provided is a method for treating a neurodegenerative disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, in combination with NAD⁺ or a NAD⁺ precursor (e.g., NR, NA, NaR, NAM, NMN, NaMN, TRP, NAAD, or vitamin B₃).

[0200] Other embodiments include use of the presently disclosed compounds in therapy.

4. Kits

[0201] Provided herein are also kits that include a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and suitable packaging. In certain embodiments, a kit further includes instructions for use. In one aspect, a kit includes a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0202] Provided herein are also articles of manufacture that include a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, or intravenous bag.

5. Pharmaceutical Compositions and Modes of Administration

[0203] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that contain one or more of the compounds described herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants, and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers, and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0204] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0205] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0206] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0207] Some examples of suitable excipients include, e.g., lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxybenzoates; sweetening agents; and flavoring agents.

[0208] The compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0209] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[0210] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0211] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In certain embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be

nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, in one embodiment, orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0212] The amount of the compound in a pharmaceutical composition or formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of this disclosure based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. In one embodiment, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations are described below.

Formulation Example 1 - Tablet formulation

[0213] The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this disclosure	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Formulation Example 2 - Capsule formulation

[0214] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule

Ingredient	Quantity per capsule, mg
compound of this disclosure	200
lactose, spray-dried	148
magnesium stearate	2

Formulation Example 3 - Suspension formulation

[0215] The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this disclosure	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.0 g
sorbitol (70% solution)	13.00 g

Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
coloring	0.5 mg
distilled water	q.s. to 100 mL

Formulation Example 4 - Injectable formulation

[0216] The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this disclosure	0.2 mg-20 mg
sodium acetate buffer solution, 0.4 M	2.0 mL
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 mL

Formulation Example 5 - Suppository Formulation

[0217] A suppository of total weight 2.5 g is prepared by mixing the compound of this disclosure with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Ingredient	Amount
compound of this disclosure	500 mg
Witepsol® H-15	balance

6. Dosing

[0218] The specific dose level of a compound of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In certain embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. In certain embodiments, a dosage of from about 0.0001 to about 100 mg per kg of body weight per day, from about 0.001 to about 50 mg of compound per kg of body weight, or from about 0.01 to about 10 mg of compound per kg of body weight may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

7. Synthesis of the Compounds

[0219] The compounds may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds described herein may be accomplished as described in the following examples. If available, reagents and starting materials may be purchased commercially, e.g., from Sigma Aldrich or other chemical suppliers.

[0220] It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0221] Additionally, conventional protecting groups ("PG") may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in Wuts, P. G. M., Greene, T. W., & Greene, T. W. (2006). *Greene's protective groups in organic synthesis*. Hoboken, N.J., Wiley-Interscience, and references cited therein. For example, protecting groups for alcohols, such as hydroxy, include silyl ethers (including trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS), tri-isopropylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS) ethers), which can be removed by acid or fluoride ion, such as NaF, TBAF (tetra-n-butylammonium fluoride), HF-Py, or HF-NEt₃. Other protecting groups for alcohols include acetyl, removed by acid or base, benzoyl, removed by acid or base, benzyl, removed by hydrogenation, methoxyethoxymethyl ether, removed by acid, dimethoxytrityl, removed by acid, methoxymethyl ether, removed by acid, tetrahydropyranyl or tetrahydrofuranyl, removed by acid, and trityl, removed by acid. Examples of protecting groups for amines include carbobenzyloxy, removed by hydrogenolysis p-methoxybenzyl carbonyl, removed by hydrogenolysis, tert-butyloxycarbonyl, removed by concentrated strong acid (such as HCl or CF₃COOH), or by heating to greater than about 80 °C, 9-fluorenylmethyloxycarbonyl, removed by base, such as piperidine, acetyl, removed by treatment with a base, benzoyl, removed by treatment with a base, benzyl, removed by hydrogenolysis, carbamate group, removed by acid and mild heating, p-methoxybenzyl, removed by hydrogenolysis, 3,4-dimethoxybenzyl, removed by hydrogenolysis, p-methoxyphenyl, removed by ammonium cerium(IV) nitrate, tosyl, removed by concentrated acid (such as HBr or H₂SO₄) and strong reducing agents (sodium in liquid ammonia or sodium naphthalenide), troc (trichloroethyl chloroformate), removed by Zn insertion in the presence of acetic acid, and sulfonamides (Nosyl & Nps), removed by samarium iodide or tributyltin hydride.

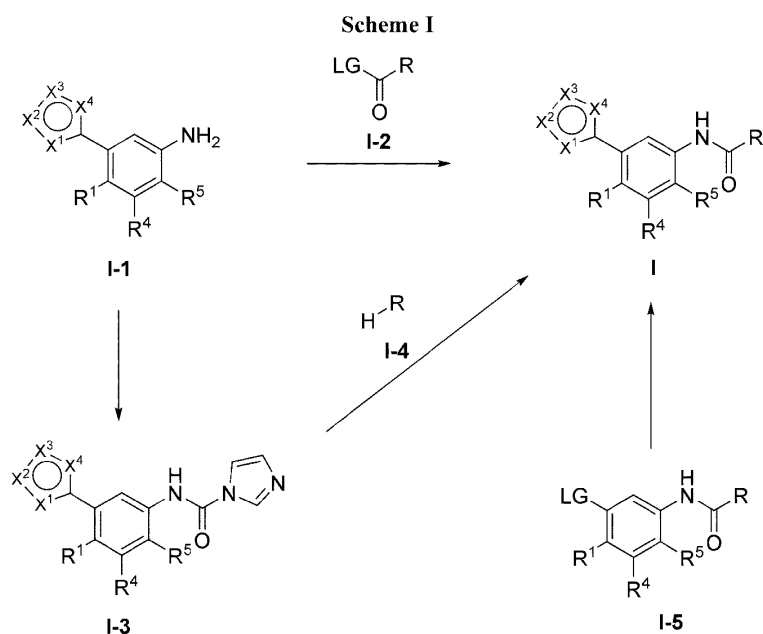
[0222] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as

individual enantiomers or diastereomers or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

[0223] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

General Synthesis

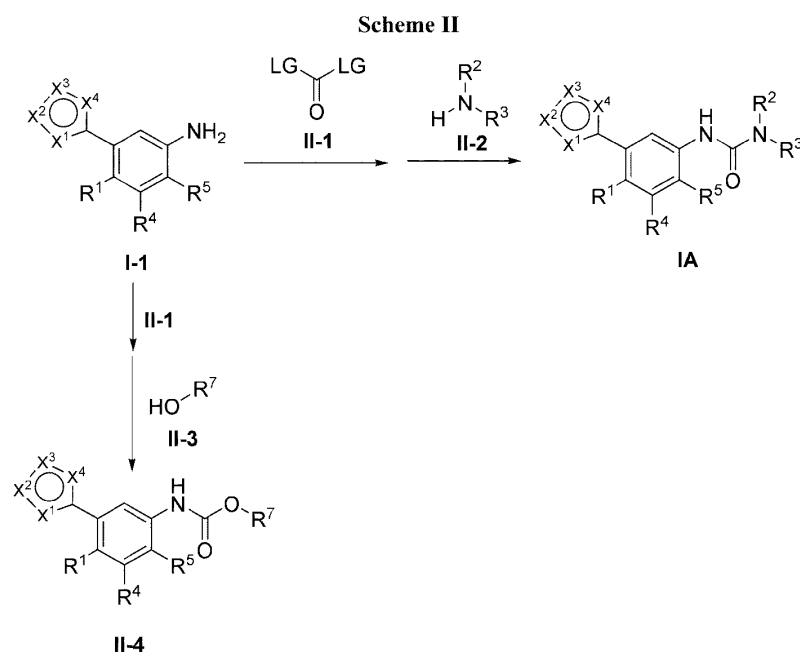
[0224] Scheme I illustrates general methods which can be employed for the synthesis of compounds described herein (e.g., Formula I), where X^1 , X^2 , X^3 , X^4 , R, R^1 , R^4 , and R^5 are each independently as defined herein, and each LG is independently a leaving group (e.g., halo, alkoxy, etc.).



[0225] In Scheme I, compounds of Formula I can be prepared by contacting compound I-1 with compound I-2 under suitable coupling reaction conditions, followed by optional functionalization or deprotection when required. Alternatively, compounds of Formula I can be prepared by contacting compound I-3 with compound I-4 under suitable coupling reaction conditions, followed by optional functionalization or deprotection when required. Alternatively, compounds of Formula I can be prepared by contacting compound I-5 with a suitable functionalized precursor to the moiety A, under suitable coupling reaction conditions, followed by optional functionalization or deprotection when required. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration and the like.

[0226] Further derivatization of the compound provided by the steps outlined in Scheme I, or any intermediate, provides additional compounds of Formula I. It should be understood that any of the compounds or intermediates shown in Scheme I may be prepared using traditional methods or purchased from commercial sources. In addition, any of the intermediates or any product obtained by the process outlined in Scheme I can be derivatized at any step to provide various compounds of Formula I. In certain embodiments, the various substituents of the compounds or intermediates as used in Scheme I are as defined for Formula I.

[0227] In certain embodiments, compounds of Formula I wherein R is $-\text{OR}^7$, or compounds of Formula IA or IB, can be prepared according to Scheme II, where X^1 , X^2 , X^3 , X^4 , R^1 , R^2 , R^3 , R^4 , R^5 , and R^7 are each independently as defined herein, and each LG is independently a leaving group (e.g., halo, alkoxy, etc.).



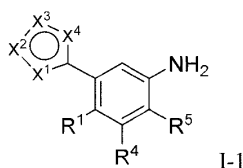
[0228] In Scheme II, compounds of Formula IA can be prepared by contacting compound I-1 with compound II-1 under suitable coupling reaction conditions to provide an acylated intermediate, followed by contacting the acylated intermediate with compound II-2, or a salt thereof. Compounds of Formula I wherein R is -OR⁷, i.e., compound II-4, can be prepared by contacting compound I-1 with compound II-1 under suitable coupling reaction conditions to provide the acylated intermediate, followed by contacting the acylated intermediate with compound II-3. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration and the like.

[0229] It should be understood that any of the compounds or intermediates shown in Scheme II may be prepared using traditional methods or purchased from commercial sources. In addition, any of the intermediates or any product obtained by the process outlined in Scheme II can be derivatized at any step to provide various compounds of Formula I or IA. In certain embodiments, the various substituents of the compounds or intermediates as used in Scheme II are as defined for Formula I or IA.

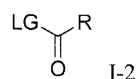
[0230] Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration and the like.

[0231] In certain embodiments, provided is a process for providing a compound of Formula I, comprising:

- 1) contacting a compound of Formula I-1:



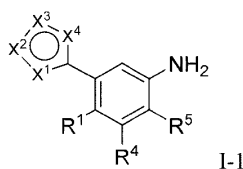
with a compound of Formula I-2:



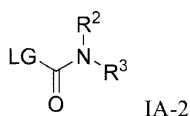
under conditions sufficient to provide the compound of Formula I; wherein X^1 , X^2 , X^3 , X^4 , R, R^1 , R^4 , and R^5 are each independently as defined herein.

[0232] In certain embodiments, provided is a process for providing a compound of Formula IA, comprising:

- 1) contacting a compound of Formula I-1:



with a compound of Formula IA-2:



under conditions sufficient to provide the compound of Formula IA; wherein X^1 , X^2 , X^3 , X^4 , R^1 , R^2 , R^3 , R^4 , and R^5 are each independently as defined herein. In certain embodiments, the conditions comprise a phosgene reagent, e.g., triphosgene.

EXAMPLES

[0233] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those skilled in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes of its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

General Experimental Methods

[0234] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

[0235] NMR Spectroscopy: ^1H Nuclear magnetic resonance (NMR) spectroscopy was carried out using a Bruker Avance III equipped with a BBFO 300 MHz probe operating at 300 MHz or one of the following instruments: a Bruker Avance 400 instrument equipped with probe DUAL 400 MHz S1, a Bruker Avance 400 instrument equipped with probe 6 S1 400 MHz 5mm ^1H - ^{13}C ID, a Bruker Avance III 400 instrument with nanobay equipped with probe Broadband BBFO 5 mm direct, a Bruker Mercury Plus 400 NMR spectrometer equipped with a Bruker 400 BBO probe operating at 400 MHz. All deuterated solvents contained typically 0.03% to 0.05% v/v tetramethylsilane, which was used as the reference signal (set at δ 0.00 for both ^1H and ^{13}C). In certain cases, ^1H Nuclear magnetic resonance (NMR) spectroscopy was carried out using a Bruker Advance 400 instrument operating at 400 MHz using the stated solvent at around room temperature unless otherwise stated. In all cases, NMR data were consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; br, broad.

[0236] Thin Layer Chromatography: Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel F254 (Merck) plates, R_f is the distance travelled by the compound divided by the distance travelled by the solvent on a TLC plate. Column chromatography was performed using an automatic flash chromatography system over silica gel cartridges or in the case of reverse phase chromatography over C18 cartridges. Alternatively, thin layer chromatography (TLC) was performed on Alugram® (Silica gel 60 F254) from Mancherey-Nagel and UV was typically used to visualize the spots. Additional visualization methods were also employed in some cases. In these cases the TLC plate was developed with iodine (generated by adding approximately 1 g of I_2 to 10 g silica gel and thoroughly mixing), ninhydrin (available commercially from Aldrich), or Magic Stain (generated by thoroughly mixing 25 g $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$, 5 g $(\text{NH}_4)_2\text{Ce}(\text{IV})(\text{NO}_3)_6$ in 450 mL water and 50 mL concentrated H_2SO_4) to visualize the compound.

[0237] Liquid Chromatography-Mass Spectrometry and HPLC Analysis: HPLC analysis was performed on Shimadzu 20AB HPLC system with a photodiode array detector and Luna-C18(2) 2.0×50 mm, 5 μm column at a flow rate of 1.2 mL/min with a gradient solvent Mobile phase A (MPA, H_2O +0.037 % (v/v) TFA): Mobile phase B (MPB, ACN+0.018 % (v/v) TFA) (0.01 min, 10% MPB; 4 min, 80% MPB; 4.9 min, 80% MPB; 4.92 min, 10% MPB; 5.5 min, 10% MPB). LCMS was detected under 220 and 254 nm or used evaporative light scattering (ELSD) detection as well as positive electrospray ionization (MS). Semi-preparative HPLC was performed by either acidic or neutral conditions. Acidic: Luna C18 100 × 30 mm, 5 μm ; MPA: $\text{HCl}/\text{H}_2\text{O}$ =0.04%, or formic acid/ H_2O =0.2% (v/v); MPB: ACN. Neutral: Waters Xbridge 150 × 25, 5 μm ; MPA: 10 mM NH_4HCO_3 in H_2O ; MPB: ACN. Gradient for both conditions: 10% of MPB to 80% of MPB over 12 min at a flow rate of 20 mL/min, then 100% MPB over 2 min, 10% MPB over 2 min, UV detector. SFC analysis was performed on Thar analytical SFC system with a UV/Vis detector and series of chiral columns including AD, AS-H, OJ, OD, AY and IC, 4.6 × 100 mm, 3 μm column at a flow rate of 4 mL/min with a gradient solvent

Mobile phase A (MPA, CO₂): Mobile phase B (MPB, MeOH+0.05 % (v/v) IPA) (0.01 min, 10% MPB; 3 min, 40% MPB; 3.5 min, 40% MPB; 3.56-5 min, 10% MPB). SFC preparative was performed on Thar 80 preparative SFC system with a UV/Vis detector and series of chiral preparative columns including AD-H, AS-H, OJ-H, OD-H, AY-H and IC-H, 30×250 mm, 5 µm column at a flow rate of 65 mL/min with a gradient solvent Mobile phase A (MPA, CO₂): Mobile phase B (MPB, MeOH+0.1 % (v/v) NH₃H₂O) (0.01 min, 10% MPB; 5 min, 40% MPB; 6 min, 40% MPB; 6.1-10 min, 10% MPB). LC-MS data were also collected using an UPLC-MS AcuityTM system equipped with PDA detector and coupled to a Waters single quadrupole mass spectrometer operating in alternated positive and negative electrospray ionization mode. The column used was a Cortecs UPLC C18, 1.6 µm, 2.1 × 50 mm. A linear gradient was applied, starting at 95% A (A: 0.1% formic acid in water) and ending at 95% B (B: 0.1% formic acid in MeCN) over 2.0 min with a total run time of 2.5 min. The column temperature was at 40 °C with the flow rate of 0.8 mL/min.

EXAMPLES

[0238] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those skilled in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes of its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

General Experimental Methods

[0239] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those skilled in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes of its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

General Experimental Methods

[0240] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

[0241] **NMR Spectroscopy:** ¹H Nuclear magnetic resonance (NMR) spectroscopy was carried out using a Bruker Avance III equipped with a BBFO 300 MHz probe operating at 300 MHz or one of the following instruments: a Bruker Avance 400 instrument equipped with probe DUAL 400 MHz S1, a Bruker Avance 400 instrument equipped with probe 6 S1 400 MHz 5mm ¹H-¹³C ID, a Bruker Avance III 400 instrument with nanobay equipped with probe Broadband BBFO 5 mm direct, a Bruker Mercury Plus 400 NMR spectrometer equipped with a Bruker 400 BBO probe operating at 400 MHz. All deuterated

solvents contained typically 0.03% to 0.05% v/v tetramethylsilane, which was used as the reference signal (set at δ 0.00 for both ^1H and ^{13}C). In certain cases, ^1H Nuclear magnetic resonance (NMR) spectroscopy was carried out using a Bruker Advance 400 instrument operating at 400 MHz using the stated solvent at around room temperature unless otherwise stated. In all cases, NMR data were consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; br, broad.

[0242] Thin Layer Chromatography: Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel F254 (Merck) plates, R_f is the distance travelled by the compound divided by the distance travelled by the solvent on a TLC plate. Column chromatography was performed using an automatic flash chromatography system over silica gel cartridges or in the case of reverse phase chromatography over C18 cartridges. Alternatively, thin layer chromatography (TLC) was performed on Alugram® (Silica gel 60 F254) from Manchem-Nagel and UV was typically used to visualize the spots. Additional visualization methods were also employed in some cases. In these cases the TLC plate was developed with iodine (generated by adding approximately 1 g of I_2 to 10 g silica gel and thoroughly mixing), ninhydrin (available commercially from Aldrich), or Magic Stain (generated by thoroughly mixing 25 g $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$, 5 g $(\text{NH}_4)_2\text{Ce}(\text{IV})(\text{NO}_3)_6$ in 450 mL water and 50 mL concentrated H_2SO_4) to visualize the compound.

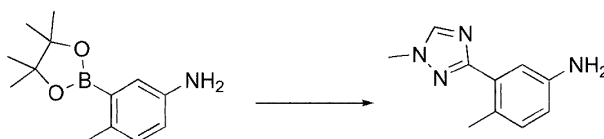
[0243] Liquid Chromatography-Mass Spectrometry and HPLC Analysis: HPLC analysis was performed on Shimadzu 20AB HPLC system with a photodiode array detector and Luna-C18(2) 2.0×50 mm, 5 μm column at a flow rate of 1.2 mL/min with a gradient solvent Mobile phase A (MPA, $\text{H}_2\text{O}+0.037\%$ (v/v) TFA): Mobile phase B (MPB, ACN+0.018% (v/v) TFA) (0.01 min, 10% MPB; 4 min, 80% MPB; 4.9 min, 80% MPB; 4.92 min, 10% MPB; 5.5 min, 10% MPB). LCMS was detected under 220 and 254 nm or used evaporative light scattering (ELSD) detection as well as positive electrospray ionization (MS). Semi-preparative HPLC was performed by either acidic or neutral conditions. Acidic: Luna C18 100 × 30 mm, 5 μm ; MPA: $\text{HCl}/\text{H}_2\text{O}=0.04\%$, or formic acid/ $\text{H}_2\text{O}=0.2\%$ (v/v); MPB: ACN. Neutral: Waters Xbridge 150 × 25, 5 μm ; MPA: 10 mM NH_4HCO_3 in H_2O ; MPB: ACN. Gradient for both conditions: 10% of MPB to 80% of MPB over 12 min at a flow rate of 20 mL/min, then 100% MPB over 2 min, 10% MPB over 2 min, UV detector. SFC analysis was performed on Thar analytical SFC system with a UV/Vis detector and series of chiral columns including AD, AS-H, OJ, OD, AY and IC, 4.6 × 100 mm, 3 μm column at a flow rate of 4 mL/min with a gradient solvent Mobile phase A (MPA, CO_2): Mobile phase B (MPB, $\text{MeOH}+0.05\%$ (v/v) IPA) (0.01 min, 10% MPB; 3 min, 40% MPB; 3.5 min, 40% MPB; 3.56-5 min, 10% MPB). SFC preparative was performed on Thar 80 preparative SFC system with a UV/Vis detector and series of chiral preparative columns including AD-H, AS-H, OJ-H, OD-H, AY-H and IC-H, 30×250 mm, 5 μm column at a flow rate of 65 mL/min with a gradient solvent Mobile phase A (MPA, CO_2): Mobile phase B (MPB, $\text{MeOH}+0.1\%$ (v/v) $\text{NH}_3\text{H}_2\text{O}$) (0.01 min, 10% MPB; 5 min, 40% MPB; 6 min, 40% MPB; 6.1-10 min, 10% MPB). LC-MS

data were also collected using an UPLC-MS Acquity™ system equipped with PDA detector and coupled to a Waters single quadrupole mass spectrometer operating in alternated positive and negative electrospray ionization mode. The column used was a Cortecs UPLC C18, 1.6 μ m, 2.1 $\times$ 50 mm. A linear gradient was applied, starting at 95% A (A: 0.1% formic acid in water) and ending at 95% B (B: 0.1% formic acid in MeCN) over 2.0 min with a total run time of 2.5 min. The column temperature was at 40 °C with the flow rate of 0.8 mL/min.

INTERMEDIATES

Intermediate 1

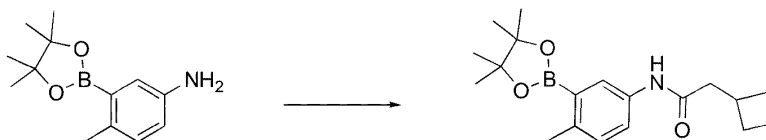
4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline



[0244] To a mixture of 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 g, 4.29 mmol) and 3-bromo-1-methyl-1,2,4-triazole (834 mg, 5.15 mmol) in 1,4-dioxane (10 mL) and H₂O (1 mL) was added Pd(dppf)Cl₂ (314 mg, 0.429 mmol) and K₂CO₃ (1.78 g, 12.87 mmol) at 25 °C under N₂. The mixture was heated to 100 °C and stirred for 16 h. Then the reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: m/z = 189.1 [M+H]⁺.

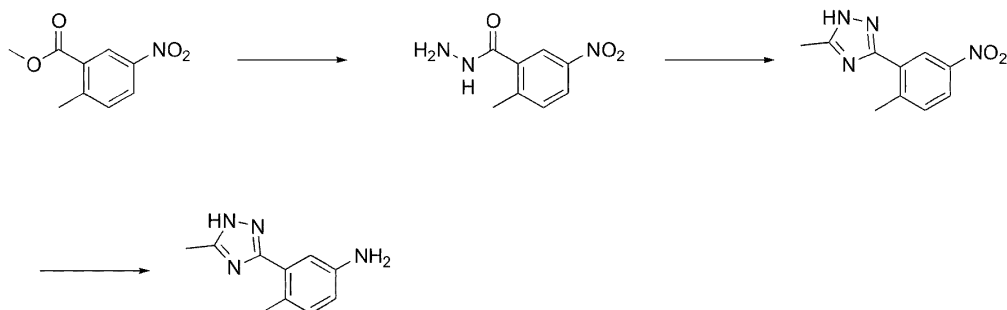
Intermediate 2

2-cyclobutyl-*N*-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide



[0245] To a mixture of 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2 g, 8.58 mmol) in DCM (20 mL) at 0 °C under N₂ was added TEA (1.74 g, 17.16 mmol) and 2-cyclobutylacetyl chloride (1.37 g, 10.30 mmol). The mixture was stirred at 0 °C for 1 h. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with DCM (3 $\times$ 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:0 to 5:1) to give the titled compound. LCMS: m/z = 330.3 [M+H]⁺.

Intermediate 3

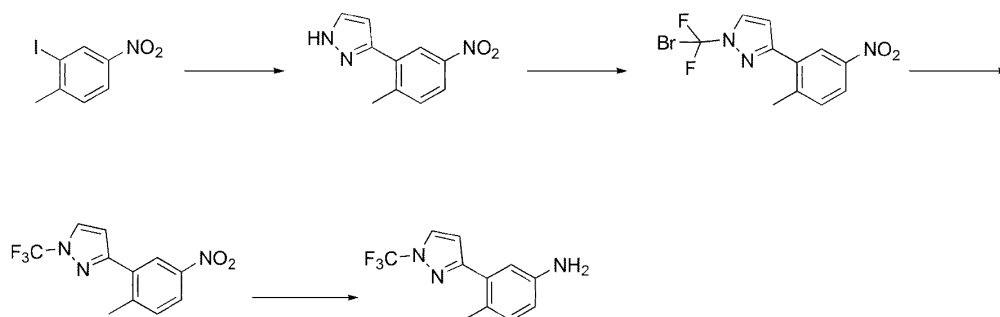
4-methyl-3-(5-methyl-1*H*-1,2,4-triazol-3-yl)aniline

[0246] 2-methyl-5-nitrobenzohydrazide: To a mixture of methyl 2-methyl-5-nitrobenzoate (2 g, 10.25 mmol) in EtOH (20 mL) at 25 °C under N₂ was added NH₂NH₂•H₂O (2.56 g, 51.24 mmol, 2.49 mL). The mixture was heated to 85 °C and stirred for 16 h. Then the mixture was concentrated under reduced pressure to give the titled compound.

[0247] 5-methyl-3-(2-methyl-5-nitrophenyl)-1*H*-1,2,4-triazole: To a mixture of 2-methyl-5-nitrobenzohydrazide (1.34 g, 6.87 mmol) and acetamidine hydrochloride (649 mg, 6.87 mmol) in H₂O (20 mL) at 25 °C under N₂ was added K₂CO₃ (1.90 g, 13.73 mmol). The mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was filtered and the solids were dried under reduced pressure to give the titled compound.

[0248] 4-methyl-3-(5-methyl-1*H*-1,2,4-triazol-3-yl)aniline: To a solution of 5-methyl-3-(2-methyl-5-nitrophenyl)-1*H*-1,2,4-triazole (200 mg, 0.92 mmol) in EtOAc (5 mL) at 25 °C was added 10% Pd/C (50 mg, 0.92 mmol). The suspension was degassed under vacuum and purged with H₂ several times. The reaction mixture was stirred under H₂ (15 psi) at 25 °C for 0.5 h. After stirring, the reaction mixture was filtered through a pad of Celite[®] and the filtrate was concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 189.0 [M+H]⁺.

Intermediate 4

4-methyl-3-(1-(trifluoromethyl)-1*H*-pyrazol-3-yl)aniline

[0249] 3-(2-methyl-5-nitrophenyl)-1*H*-pyrazole: A mixture of 2-iodo-1-methyl-4-nitrobenzene (5 g, 19.01 mmol), (1*H*-pyrazol-3-yl)boronic acid (4.25 g, 38.02 mmol), K₂CO₃ (5.25 g, 38.02 mmol) and

Pd(dppf)Cl₂ (1.39 g, 1.90 mmol) in 1,4-dioxane (100 mL) and H₂O (10 mL) was degassed and purged with N₂ three times. The mixture was heated to 90 °C and stirred for 16 h under N₂. The reaction mixture was filtered through a pad of Celite® and the filtrate concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 204.3 [M+H]⁺.

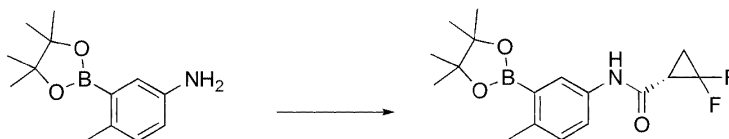
[0250] 1-(bromodifluoromethyl)-3-(2-methyl-5-nitrophenyl)-1H-pyrazole: To a mixture of 3-(2-methyl-5-nitrophenyl)-1H-pyrazole (580 mg, 2.85 mmol) in DMF (10 mL) at 0 °C under N₂ was added NaH (457 mg, 11.42 mmol, 60% in mineral oil). The mixture was stirred at 0 °C for 0.5 h, before adding dibromo(difluoro)methane (3.59 g, 17.13 mmol) at 0 °C and stirring for an additional 1 h. The reaction mixture was quenched by the addition of sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: m/z = 332.0, 334.0 [M+H]⁺.

[0251] 3-(2-methyl-5-nitrophenyl)-1-(trifluoromethyl)-1H-pyrazole: To a mixture of 1-(bromodifluoromethyl)-3-(2-methyl-5-nitrophenyl)-1H-pyrazole (1.5 g, 4.52 mmol) in DCM (20 mL) and MeCN (4 mL) at -78 °C under N₂ was added silver tetrafluoroborate (2.64 g, 13.55 mmol). The mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was adjusted to pH = 7-8 by the addition of sat. aq. NaHCO₃ and was then extracted with DCM (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound. LCMS: m/z = 272.1 [M+H]⁺.

[0252] 4-methyl-3-(1-(trifluoromethyl)-1H-pyrazol-3-yl)aniline: To a solution of 3-(2-methyl-5-nitrophenyl)-1-(trifluoromethyl)-1H-pyrazole (70 mg, 0.26 mmol) in EtOAc (2 mL) at 25 °C was added 10% Pd/C (30 mg, 0.13 mmol). The suspension was degassed under vacuum and purged with H₂ several times. Then the reaction mixture was stirred under H₂ (15 psi) at 25 °C for 1 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 242.2 [M+H]⁺.

Intermediate 5

(S)-2,2-difluoro-N-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxamide

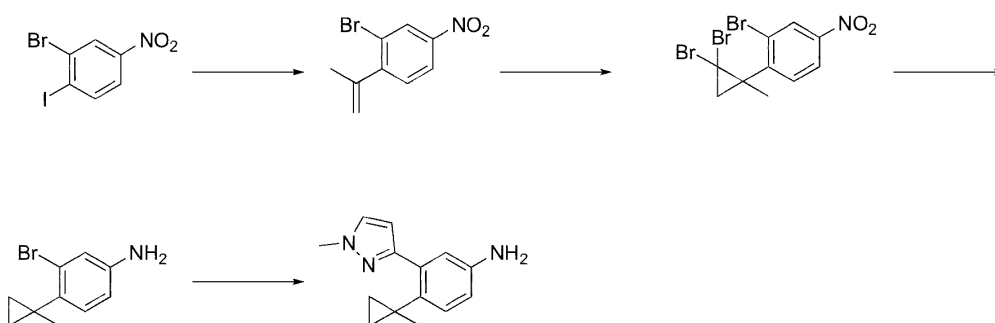


[0253] To a solution of 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 g, 4.29 mmol) in pyridine (10 mL) at 25 °C under N₂ was added (S)-2,2-difluorocyclopropanecarboxylic acid (628.42 mg, 5.15 mmol) and EDCI (1.64 g, 8.58 mmol). The mixture was stirred at 25 °C for 2 h. The

reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:0 to 9:1) to give the titled compound. LCMS: $m/z = 338.1$ $[M+H]^+$.

Intermediate 6

3-(1-methyl-1H-pyrazol-3-yl)-4-(1-methylcyclopropyl)aniline



[0254] 2-bromo-4-nitro-1-(prop-1-en-2-yl)benzene: To a mixture of 2-bromo-1-iodo-4-nitro-benzene (20 g, 60.99 mmol) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11.27 g, 67.09 mmol) in 1,4-dioxane (200 mL) and H₂O (20 mL) at 25 °C under N₂ was added K₂CO₃ (16.86 g, 121.99 mmol) and Pd(dppf)Cl₂•CH₂Cl₂ (4.98 g, 6.10 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The crude reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE) to give the titled compound.

[0255] 2-bromo-1-(2,2-dibromo-1-methylcyclopropyl)-4-nitrobenzene: To a mixture of 2-bromo-1-isopropenyl-4-nitro-benzene (5 g, 20.66 mmol) in bromoform (50 mL) at 25 °C under N₂ was added NaOH (33.05 g, 413 mmol, 25 mL, 50% purity in H₂O) and benzyltriethylammonium chloride (188 mg, 0.826 mmol). The reaction mixture was heated to 50 °C and stirred for 5 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was adjusted to pH = 7–8 by addition of HCl (2 M) and then extracted with MTBE (3 × 20 mL). The combined organic layers were washed with aq. sat. NaHCO₃, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:MTBE = 1:0 to 10:1) to give the titled compound.

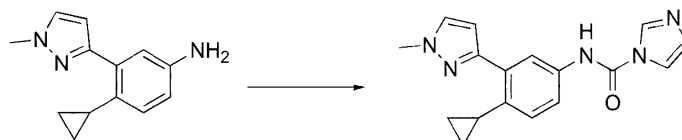
[0256] 3-bromo-4-(1-methylcyclopropyl)aniline: To a mixture of 2-bromo-1-(2,2-dibromo-1-methylcyclopropyl)-4-nitro-benzene (13 g, 31.41 mmol) in EtOH (100 mL) at 25 °C under N₂ was added Zn (30.81 g, 471 mmol) and NH₄Cl (33.60 g, 628 mmol). The mixture was heated to 90 °C and stirred for 5 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Welch Xtimate C18 250 ×

70 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 40%-70%, 10 min) to give the titled compound. LCMS: m/z = 226.1, 228.1 [M+H]⁺.

[0257] 3-(1-methyl-1*H*-pyrazol-3-yl)-4-(1-methylcyclopropyl)aniline: To a mixture of 3-bromo-4-(1-methylcyclopropyl)aniline (300 mg, 1.33 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (414 mg, 1.99 mmol) in 1,4-dioxane (5 mL) and H₂O (0.5 mL) at 25 °C under N₂ was added K₂CO₃ (367 mg, 2.65 mmol) and Pd(dppf)Cl₂ (97 mg, 0.133 mmol). The mixture was heated to 100 °C and stirred for 10 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 228.1 [M+H]⁺.

Intermediate 7

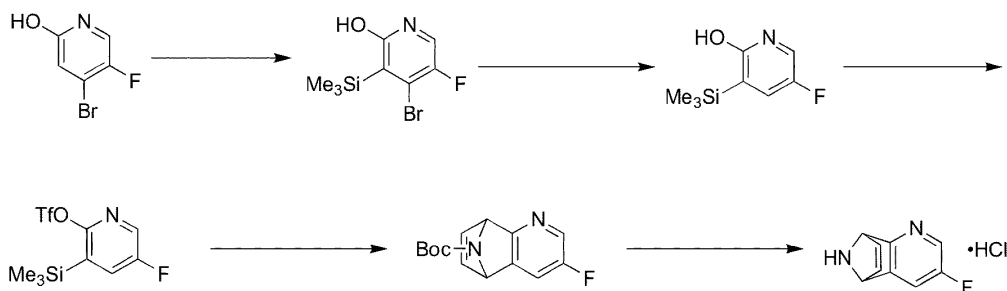
N-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-1*H*-imidazole-1-carboxamide



[0258] To a mixture of CDI (91 mg, 0.56 mmol) in DCM (3 mL) at -40 °C under N₂ was added 4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)aniline (100 mg, 0.469 mmol) in DCM (3 mL). The mixture was stirred at -40 °C for 1 h and the reaction mixture was used directly in the next step.

Intermediate 8

3-fluoro-5,8-dihydro-5,8-epiminoquinoline hydrochloride



[0259] 4-bromo-5-fluoro-3-(trimethylsilyl)pyridin-2-ol: To a mixture of 4-bromo-5-fluoropyridin-2-ol (2 g, 10.42 mmol) in THF (25 mL) at -78 °C under N₂ was added LDA (22.92 mmol, 2 M in THF, 11.46 mL). The mixture was stirred at -78 °C for 30 min, then the reaction mixture was warmed to 0 °C and TMSCl (2.26 g, 20.83 mmol) was added and stirred at 0 °C for 4 h. The reaction mixture was quenched by the addition of aq. sat. NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were combined, washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 264.0, 266.0 $[M+H]^+$.

[0260] 5-fluoro-3-(trimethylsilyl)pyridine-2-ol: To a mixture of 4-bromo-5-fluoro-3-(trimethylsilyl)pyridine-2-ol (847 mg, 3.21 mmol) in MeOH (10 mL) at 20 °C was added 10% Pd/C (100 mg, 3.21 mmol). The mixture was stirred at 20 °C under H_2 (15 psi) for 2 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 186.2 $[M+H]^+$.

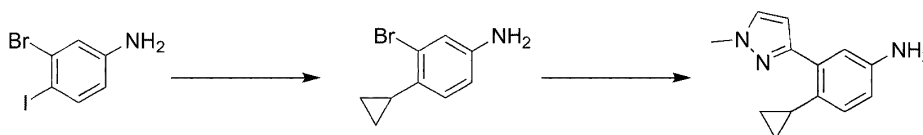
[0261] 5-fluoro-3-(trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate: To a mixture of 5-fluoro-3-(trimethylsilyl)pyridin-2-ol (450 mg, 2.43 mmol) in pyridine (5 mL) at 20 °C under N_2 was added Tf_2O (1.37 g, 4.86 mmol). The mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was adjusted to pH = 7–8 by addition of aq. sat. $NaHCO_3$ solution and then extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE) to give the titled compound. LCMS: m/z = 318.1 $[M+H]^+$.

[0262] *tert*-butyl 3-fluoro-5,8-dihydro-5,8-epiminoquinoline-9-carboxylate: To a mixture of 5-fluoro-3-(trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate (200 mg, 0.63 mmol) and *tert*-butyl 1*H*-pyrrole-1-carboxylate (527 mg, 3.15 mmol) in MeCN (5 mL) at 20 °C under N_2 was added CsF (191 mg, 1.26 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO_2 , PE:EtOAc = 3:1) to give the titled compound. LCMS: m/z = 263.2 $[M+H]^+$.

[0263] 3-fluoro-5,8-dihydro-5,8-epiminoquinoline hydrochloride: A mixture of *tert*-butyl 3-fluoro-5,8-dihydro-5,8-epiminoquinoline-9-carboxylate (50 mg, 0.19 mmol) in HCl/EtOAc (3 mL, 4 M) was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 163.0 $[M+H]^+$.

Intermediate 9

4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)aniline



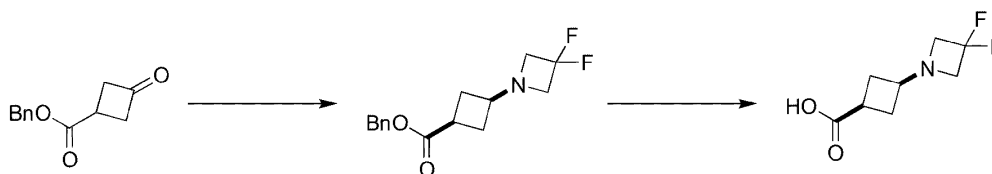
[0264] 3-bromo-4-cyclopropylaniline: To a solution of 3-bromo-4-iodo-aniline (10 g, 33.57 mmol) in toluene (160 mL) and H_2O (8 mL) at 20 °C under N_2 was added cyclopropylboronic acid (4.32 g, 50.35 mmol), K_3PO_4 (21.37 g, 100.70 mmol), tricyclohexylphosphine (1.88 g, 6.71 mmol, 2.18 mL)

and Pd(OAc)₂ (753 mg, 3.36 mmol). The mixture was heated to 120 °C and stirred for 12 h. The mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: m/z = 212.1, 214.1 [M+H]⁺.

[0265] 4-cyclopropyl-3-(1-methyl-1H-pyrazol-3-yl)aniline: To a solution of 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (13.49 g, 64.83 mmol) in 1,4-dioxane (30 mL) and H₂O (3 mL) at 25 °C under N₂ was added 3-bromo-4-cyclopropyl-aniline (5.5 g, 25.93 mmol), Pd(dppf)Cl₂ (1.90 g, 2.59 mmol) and K₂CO₃ (7.17 g, 51.87 mmol). The mixture was heated to 100 °C and stirred for 12 h. The mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: m/z = 214.2 [M+H]⁺.

Intermediate 10

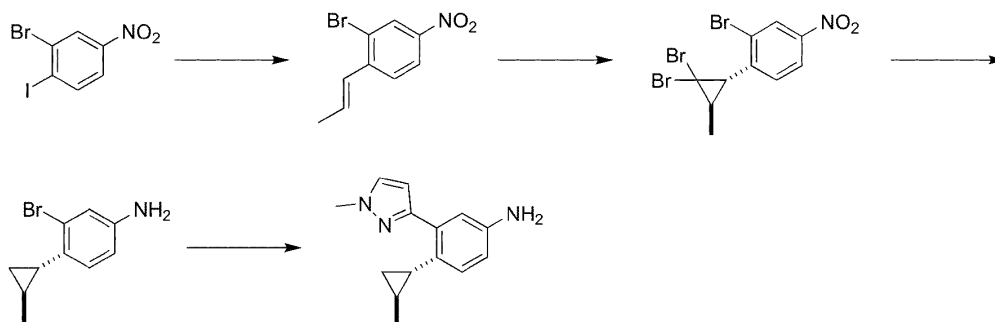
cis-3-(3,3-difluoroazetidin-1-yl)cyclobutane-1-carboxylic acid



[0266] benzyl *cis*-3-(3,3-difluoroazetidin-1-yl)cyclobutane-1-carboxylate: To a mixture of benzyl 3-oxocyclobutanecarboxylate (1 g, 4.90 mmol) and 3,3-difluoroazetidine (1.27 g, 9.79 mmol) in DCE (10 mL) at 25 °C under N₂ was added TEA (990 mg, 9.79 mmol) and HOAc (588 mg, 9.79 mmol). The mixture was warmed to 25 °C and stirred for 30 min, then the reaction was cooled to 0 °C and NaBH₃CN (923 mg, 14.69 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound.

[0267] *cis*-3-(3,3-difluoroazetidin-1-yl)cyclobutane-1-carboxylic acid: To a solution of benzyl *cis*-3-(3,3-difluoroazetidin-1-yl)cyclobutane-1-carboxylate (200 mg, 0.71 mmol) in THF (10 mL) at room temperature under N₂ was added 10% Pd/C (20 mg). The suspension was degassed under vacuum and purged with H₂ several times. The reaction mixture was then stirred under H₂ (15 psi) at 25 °C for 3 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 192.1 [M+H]⁺.

Intermediate 11

3-(1-methyl-1H-pyrazol-3-yl)-4-(*trans*-2-methylcyclopropyl)aniline

[0268] (*E*)-2-bromo-4-nitro-1-(prop-1-en-1-yl)benzene: To a mixture of 2-bromo-1-iodo-4-nitrobenzene (4 g, 12.20 mmol) and [(*E*)-prop-1-en-1-yl]boronic acid (1.05 g, 12.20 mmol) in 1,4-dioxane (60 mL) and H₂O (6 mL) at 25 °C under N₂ was added K₂CO₃ (5.06 g, 36.60 mmol) and Pd(dppf)Cl₂ (892 mg, 1.22 mmol). The reaction mixture was heated to 100 °C and stirred for 16 h. The reaction mixture was filtered through a Celite® pad and the filtrate was diluted with H₂O (40 mL) and extracted with MTBE (3 × 25 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE) to give the titled compound.

[0269] 2-bromo-1-((*trans*)-2,2-dibromo-3-methylcyclopropyl)-4-nitrobenzene: To a mixture of (*E*)-2-bromo-4-nitro-1-(prop-1-en-1-yl)benzene (3 g, 12.39 mmol) in bromoform (30 mL) at 25 °C under N₂ was added NaOH (15 g, 0.375 mol, 50% w/w, 15 mL H₂O) and benzyltriethylammonium chloride (112 mg, 0.49 mmol). The mixture was heated to 50 °C and stirred for 5 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was adjusted to pH = 7–8 with HCl (2 M) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with aq. sat. NaHCO₃ (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE) to give the titled compound.

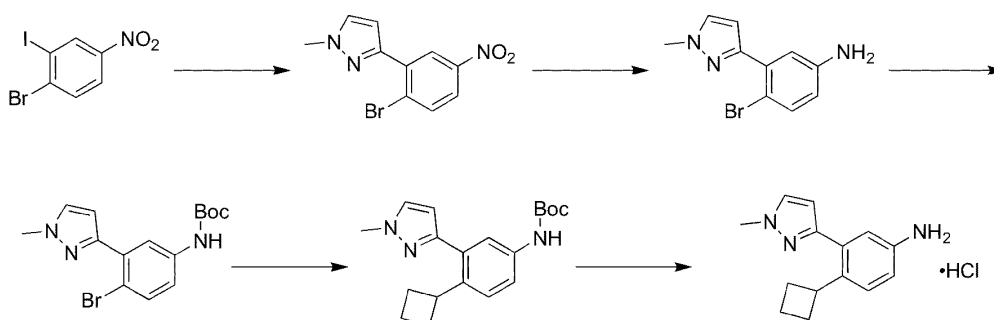
[0270] 2-bromo-1-((*trans*-2-methylcyclopropyl)-4-nitrobenzene: To a mixture of 2-bromo-1-[(*trans*)-2,2-dibromo-3-methyl-cyclopropyl]-4-nitro-benzene (3.3 g, 7.97 mmol) in EtOH (30 mL) at 25 °C under N₂ was added Zn (7.82 g, 119.60 mmol) and NH₄Cl (8.53 g, 159.46 mmol). The mixture was heated to 90 °C and stirred for 5 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: *m/z* = 226.1, 228.1 [M+H]⁺.

[0271] 3-(1-methyl-1H-pyrazol-3-yl)-4-(*trans*-2-methylcyclopropyl)aniline: To a mixture of 2-bromo-1-((*trans*-2-methylcyclopropyl)-4-nitrobenzene (410 mg, 1.81 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (565 mg, 2.72 mmol) in 1,4-dioxane (6 mL) and H₂O (0.6

mL) at 25 °C under N₂ was added K₂CO₃ (501 mg, 3.63 mmol) and Pd(dppf)Cl₂ (132 mg, 0.18 mmol). The mixture was heated to 100 °C and stirred for 16 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Waters Xbridge BEH C18 100 × 30 mm × 10 µm; mobile phase: A: NH₄HCO₃ in water, B: MeCN; B%: 25%-55%, 10 min) to give the titled compound. LCMS: m/z = 228.2 [M+H]⁺.

Intermediate 12

4-cyclobutyl-3-(1-methyl-1H-pyrazol-3-yl)aniline hydrochloride



[0272] 3-(2-bromo-5-nitrophenyl)-1-methyl-1H-pyrazole: To a mixture of 1-bromo-2-iodo-4-nitrobenzene (4 g, 12.20 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.8 g, 13.42 mmol) in 1,4-dioxane (70 mL) and H₂O (7 mL) at 20 °C under N₂ was added K₂CO₃ (5 g, 36.60 mmol) and Pd(dppf)Cl₂ (892 mg, 1.22 mmol). The mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound. LCMS: m/z = 282.2, 284.2 [M+H]⁺.

[0273] 4-bromo-3-(1-methyl-1H-pyrazol-3-yl)aniline: To a mixture of 3-(2-bromo-5-nitrophenyl)-1-methyl-1H-pyrazole (1.2 g, 4.25 mmol) in EtOH (10 mL) and H₂O (2 mL) at 20 °C was added Fe (950 mg, 17.02 mmol) and NH₄Cl (455 mg, 8.51 mmol). The mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 3:1 to 1:1) to give the titled compound. LCMS: m/z = 252.1, 254.1 [M+H]⁺.

[0274] tert-butyl (4-bromo-3-(1-methyl-1H-pyrazol-3-yl)phenyl)carbamate: To a mixture of 4-bromo-3-(1-methyl-1H-pyrazol-3-yl)aniline (700 mg, 2.78 mmol) in 1,4-dioxane (4 mL) and H₂O (6 mL) at 20 °C was added (Boc)₂O (908 mg, 4.16 mmol) and NaOH (5.55 mL, 2 M) and the mixture was stirred for 12 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column

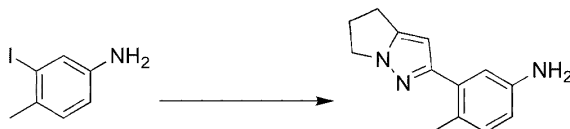
chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 352.1, 354.1 $[M+H]^+$.

[0275] *tert*-butyl (4-cyclobutyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)carbamate: To a solution of *tert*-butyl (4-bromo-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)carbamate (300 mg, 0.85 mmol) in DMA (1 mL) was added potassium cyclobutyltrifluoroborate (179 mg, 1.11 mmol), Na_2CO_3 (180 mg, 1.70 mmol), $NiCl_2 \cdot glyme$ (9 mg, 0.04 mmol), dtbbpy (11 mg, 0.04 mmol) and $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ (47 mg, 0.04 mmol). The reaction mixture was stirred at 25 °C for 16 h under two 34 W blue LEDs (vials approximately 6 cm away from the light source). The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (3×3 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 3:1 to 1:1) to give the titled compound. LCMS: m/z = 328.2 $[M+H]^+$.

[0276] 4-cyclobutyl-3-(1-methyl-1*H*-pyrazol-3-yl)aniline hydrochloride: A mixture of *tert*-butyl (4-cyclobutyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)carbamate (140 mg, 0.42 mmol) in HCl/EtOAc (5 mL, 4 M) was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 228.2 $[M+H]^+$.

Intermediate 13

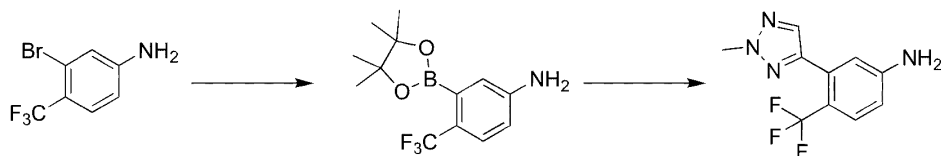
3-(5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-2-yl)-4-methylaniline



[0277] To a mixture of 3-iodo-4-methylaniline (352 mg, 1.51 mmol) and 2-(tributylstannyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (500 mg, 1.26 mmol) in DMF (8 mL) at 25 °C under N_2 was added bis(tri-*tert*-butylphosphine) (64 mg, 0.13 mmol). The reaction mixture was heated to 110 °C and stirred for 16 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 214.2 $[M+H]^+$.

Intermediate 14

3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-4-(trifluoromethyl)aniline



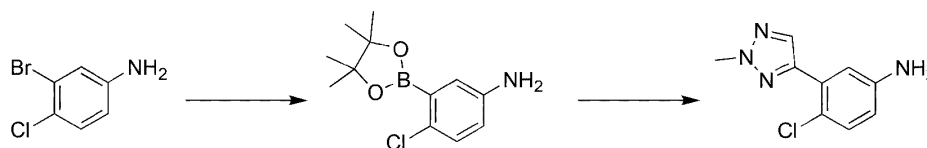
[0278] 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline: To a mixture of 3-bromo-4-(trifluoromethyl)aniline (5 g, 20.83 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-

dioxaborolane (7.93 g, 31.25 mmol) in DMSO (50 mL) at 25 °C under N₂ was added KOAc (5.11 g, 52.08 mmol) and Pd(dppf)Cl₂ (1.52 g, 2.08 mmol). The reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound. LCMS: m/z = 288.0 [M+H]⁺.

[0279] 3-(2-methyl-2H-1,2,3-triazol-4-yl)-4-(trifluoromethyl)aniline: To a mixture of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (1 g, 3.48 mmol) and 4-bromo-2-methyl-2H-1,2,3-triazole (846 mg, 5.22 mmol) in DMF (20 mL) and H₂O (2 mL) at 25 °C under N₂ was added K₂CO₃ (1.44 g, 10.45 mmol) and Pd(PPh₃)₄ (403 mg, 0.35 mmol). The reaction mixture was heated to 110 °C and stirred for 16 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: m/z = 243.2 [M+H]⁺.

Intermediate 15

4-chloro-3-(2-methyl-2H-1,2,3-triazol-4-yl)aniline



[0280] 4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: To a mixture of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8 g, 31.56 mmol) and 3-bromo-4-chloroaniline (4 g, 15.78 mmol) in DMF (80 mL) at 20 °C under N₂ was added KOAc (1.6 g, 15.78 mmol) and Pd(dppf)Cl₂ (577 mg, 0.78 mmol). The reaction mixture was heated to 95 °C and stirred for 2 h under N₂. The reaction mixture was diluted with H₂O (160 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: m/z = 254.1 [M+H]⁺.

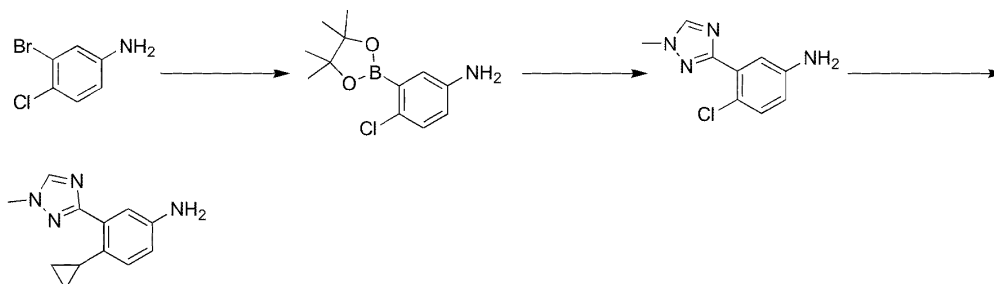
[0281] 4-chloro-3-(2-methyl-2H-1,2,3-triazol-4-yl)aniline: To a mixture of 4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 g, 3.94 mmol) and 4-bromo-2-methyl-2H-1,2,3-triazole (638 mg, 3.94 mmol) in DMF (10 mL) and H₂O (1 mL) at 20 °C under N₂ was added K₂CO₃ (1.64 g, 11.83 mmol) and Pd(PPh₃)₄ (455 mg, 0.39 mmol). The reaction mixture was heated to 100 °C and stirred for 12 h under N₂. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: m/z = 209.1 [M+H]⁺.

Intermediate 16

4-cyclopropyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)aniline

[0282] To a solution of 4-chloro-3-(2-methyltriazol-4-yl)aniline (300 mg, 1.44 mmol) in toluene (5 mL) and H₂O (0.5 mL) at 25 °C under N₂ was added cyclopropylboronic acid (247 mg, 2.88 mmol), K₃PO₄ (610 mg, 2.88 mmol), tris(cyclohexyl)phosphonium tetrafluoroborate (106 mg, 0.29 mmol) and Pd(OAc)₂ (32 mg, 0.14 mmol). The mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 1:1) to give the titled compound. LCMS *m/z* = 215.0 [M+H]⁺.

Intermediate 17

4-cyclopropyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline

[0283] 4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: To a solution of 3-bromo-4-chloro-aniline (5 g, 24.22 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (9.22 g, 36.33 mmol) in DMSO (50 mL) at 25 °C under N₂ was added KOAc (5.94 g, 60.54 mmol) and Pd(dppf)Cl₂ (1.77 g, 2.42 mmol). The reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was diluted with H₂O (150 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica column chromatography (PE:EtOAc = 10:1 to 5:1) to give the titled compound. LCMS: *m/z* = 254.1 [M+H]⁺.

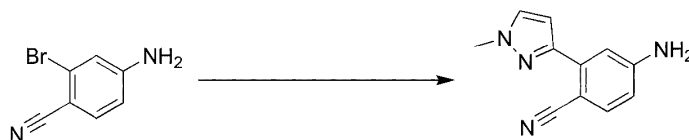
[0284] 4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline: To a solution of 4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 g, 3.94 mmol) and 3-bromo-1-methyl-1,2,4-triazole (639 mg, 3.94 mmol) in 1,4-dioxane (10 mL) and H₂O (1 mL) at room temperature under N₂ was added K₂CO₃ (1.64 g, 11.83 mmol) and Pd(dppf)Cl₂ (289 mg, 0.40 mmol). The reaction mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting

residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 209.1 $[M+H]^+$.

[0285] 4-cyclopropyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline: To a mixture of 4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (250 mg, 1.20 mmol) and potassium cyclopropyltrifluoroborate (531 mg, 3.59 mmol) in 1,4-dioxane (3 mL) under N_2 was added $Pd(OAc)_2$ (26 mg, 0.11 mmol), Cs_2CO_3 (1.17 g, 3.59 mmol) and bis(1-adamantyl)-butyl-phosphane (85 mg, 0.23 mmol). The reaction mixture was heated to 120 °C and stirred for 12 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 10:1) to give the titled compound. LCMS: m/z = 215.0 $[M+H]^+$.

Intermediate 18

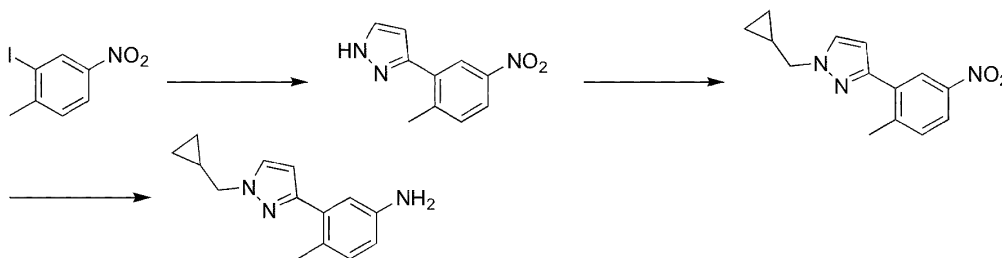
4-amino-2-(1-methyl-1*H*-pyrazol-3-yl)benzonitrile



[0286] To a solution of 4-amino-2-bromobenzonitrile (500 mg, 2.55 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (581 mg, 2.79 mmol) in 1,4-dioxane (12 mL) and H_2O (1.2 mL) at 20 °C under N_2 was added K_2CO_3 (877 mg, 6.34 mmol) and $Pd(dppf)Cl_2$ (186 mg, 0.25 mmol). The mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1 to 0:1) to give the titled compound.

Intermediate 19

3-(1-(cyclopropylmethyl)-1*H*-pyrazol-3-yl)-4-methylaniline



[0287] 3-(2-methyl-5-nitrophenyl)-1*H*-pyrazole: To a mixture of 2-iodo-1-methyl-4-nitro-benzene (9 g, 34.22 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (9.96 g, 51.32 mmol) in 1,4-dioxane (100 mL) and H_2O (10 mL) at 25 °C under N_2 was added K_2CO_3 (9.46 g, 68.43 mmol) and $Pd(dppf)Cl_2$ (2.50 g, 3.42 mmol). The mixture was heated to 100 °C and stirred for 16 h. The resulting residue was diluted with H_2O (100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic

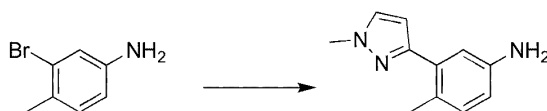
layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: m/z = 204.1 [M+H]⁺.

[0288] 1-(cyclopropylmethyl)-3-(2-methyl-5-nitrophenyl)-1H-pyrazole: To a mixture of 3-(2-methyl-5-nitrophenyl)-1H-pyrazole (1 g, 4.92 mmol) and bromomethylcyclopropane (797 mg, 5.91 mmol) in DMF (10 mL) at 20 °C under N₂ was added Cs₂CO₃ (4.01 g, 12.30 mmol) and KI (81 mg, 0.49 mmol). The mixture was heated to 50 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 1:1) to give the titled compound.

[0289] 3-(1-(cyclopropylmethyl)-1H-pyrazol-3-yl)-4-methylaniline: To a mixture of 1-(cyclopropylmethyl)-3-(2-methyl-5-nitrophenyl)-1H-pyrazole (600 mg, 2.33 mmol) in EtOH (6 mL) and H₂O (1.5 mL) at 20 °C under N₂ was added Fe (261 mg, 4.66 mmol) and NH₄Cl (499 mg, 9.33 mmol). The mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 0:1) to give the titled compound. LCMS: m/z = 228.2 [M+H]⁺.

Intermediate 20

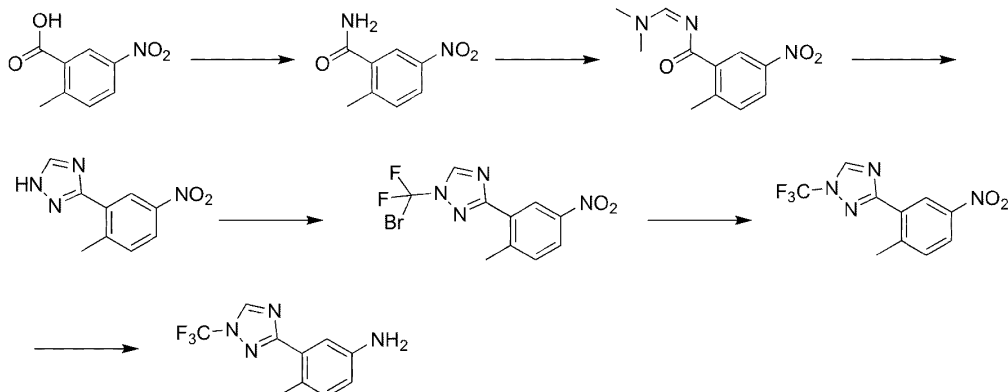
4-methyl-3-(1-methyl-1H-pyrazol-3-yl)aniline



[0290] To a solution of 3-bromo-4-methylaniline (2 g, 10.75 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.58 g, 12.90 mmol) in 1,4-dioxane (20 mL) and H₂O (2 mL) at 20 °C under N₂ was added K₂CO₃ (2.97 g, 21.50 mmol) and Pd(dppf)Cl₂ (786 mg, 1.07 mmol). The mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1 to 0:1) to give the titled compound. LCMS: m/z = 188.3 [M+H]⁺.

Intermediate 21

4-methyl-3-(1-(trifluoromethyl)-1H-1,2,4-triazol-3-yl)aniline



2-methyl-5-nitrobenzamide: To a mixture of 2-methyl-5-nitrobenzoic acid (15 g, 82.81 mmol) in SOCl_2 (100 mL) was added DMF (121 mg, 1.66 mmol) at 25 °C under N_2 . The mixture was heated to 70 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure. A mixture of the resulting residue (10 g, 50.10 mmol) in $\text{NH}_3 \cdot \text{H}_2\text{O}$ (100 mL) was stirred at 70 °C for 4 h. The reaction mixture was filtered and the filter cake was dried under reduced pressure to give the titled compound. LCMS: $m/z = 181.1$ $[\text{M}+\text{H}]^+$.

[0291] *N*-((dimethylamino)methylene)-2-methyl-5-nitrobenzamide: 2-methyl-5-nitrobenzamide (7.3 g, 40.52 mmol) was added to DMF·DMA (80 mL) at 25 °C under N_2 . The mixture was heated to 120 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: $m/z = 236.1$ $[\text{M}+\text{H}]^+$.

[0292] 3-(2-methyl-5-nitrophenyl)-1H-1,2,4-triazole: To a mixture of *N*-((dimethylamino)methylene)-2-methyl-5-nitrobenzamide (9.5 g, 40.38 mmol) in AcOH (100 mL) at 25 °C under N_2 was added $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (2.22 g, 44.42 mmol, 98% purity). The mixture was heated to 90 °C and stirred for 4 h. The reaction mixture was cooled to rt and H_2O (50 mL) was added. The solid was collected by filtration and dried under reduced pressure to give the titled compound. LCMS: $m/z = 205.1$ $[\text{M}+\text{H}]^+$.

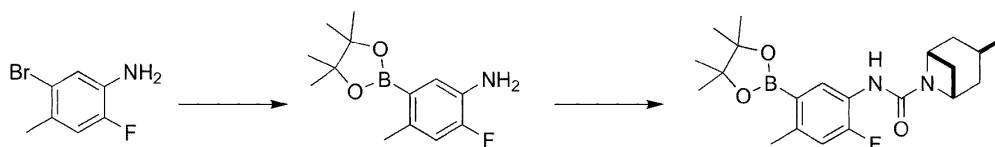
[0293] 1-(bromodifluoromethyl)-3-(2-methyl-5-nitrophenyl)-1H-1,2,4-triazole: To a mixture of 3-(2-methyl-5-nitrophenyl)-1H-1,2,4-triazole (3 g, 14.69 mmol) in DMF (30 mL) at 0 °C under N_2 was added NaH (1.18 g, 29.39 mmol, 60% in mineral oil) and the mixture was stirred at 0 °C for 30 min. Dibromo(difluoro)methane (9.25 g, 44.08 mmol) was added at 0 °C under N_2 and the mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was poured into aq. sat. NH_4Cl (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: $m/z = 333.1$, 335.1 $[\text{M}+\text{H}]^+$.

[0294] 3-(2-methyl-5-nitrophenyl)-1-(trifluoromethyl)-1H-1,2,4-triazole: To a mixture of 1-(bromodifluoromethyl)-3-(2-methyl-5-nitrophenyl)-1H-1,2,4-triazole (500 mg, 1.50 mmol) in DMSO (5 mL) at 25 °C under N₂ was added AgF (952.19 mg, 7.51 mmol). The mixture was heated to 140 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 3:1) to give the titled compound. LCMS: m/z = 273.1 [M+H]⁺.

[0295] 4-methyl-3-(1-(trifluoromethyl)-1H-1,2,4-triazol-3-yl)aniline: To a mixture of 3-(2-methyl-5-nitrophenyl)-1-(trifluoromethyl)-1H-1,2,4-triazole (100 mg, 367.40 μmol) in EtOH (2 mL) and H₂O (0.5 mL) at 25 °C under N₂ was added NH₄Cl (98 mg, 1.84 mmol) and Fe (103 mg, 1.84 mmol). The mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 243.0 [M+H]⁺.

Intermediate 22

***cis*-N-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide**



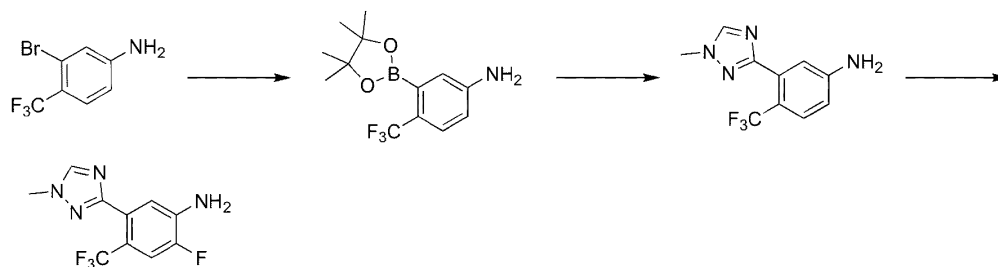
[0296] 2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline: To a mixture of 5-bromo-2-fluoro-4-methyl-aniline (10 g, 49.01 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (18.67 g, 73.52 mmol) in 1,4-dioxane (150 mL) and H₂O (15 mL) at 20 °C under N₂ was added KOAc (14.43 g, 147.03 mmol) and Pd(dppf)Cl₂ (3.59 g, 4.90 mmol). The mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (60 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound. LCMS: m/z = 252.3 [M+H]⁺.

[0297] *cis*-N-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a mixture of triphosgene (236 mg, 0.80 mmol) in THF (15 mL) at 0 °C under N₂ was added TEA (483 mg, 4.78 mmol) and 2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (400 mg, 1.59 mmol). The reaction mixture was warmed to 20 °C and *cis*-3-methyl-6-azabicyclo[3.1.1]heptane (300 mg, 2.70 mmol) and TEA (292 mg, 2.89 mmol) were added to the above mixture. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The

resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: $m/z = 389.2$ $[M+H]^+$.

Intermediate 23

2-fluoro-5-(1-methyl-1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline



[0298] 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline: To a solution of 3-bromo-4-(trifluoromethyl)aniline (3 g, 12.50 mmol) in DMSO (40 mL) at 25 °C under N_2 was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.76 g, 18.75 mmol), KOAc (3.07 g, 31.25 mmol) and Pd(dppf)Cl₂ (915 mg, 1.25 mmol). The mixture was heated to 80 °C and stirred for 12 h. The mixture was diluted with H₂O (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 100:1 to 10:1) to give the titled compound. LCMS: $m/z = 288.2$ $[M+H]^+$.

[0299] 3-(1-methyl-1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline: To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (1.35 g, 4.70 mmol) and 3-bromo-1-methyl-1H-1,2,4-triazole (914 mg, 5.64 mmol) in 1,4-dioxane (30 mL) and H₂O (3 mL) at 25 °C under N_2 was added K₂CO₃ (1.95 g, 14.11 mmol) and Pd(dppf)Cl₂ (344 mg, 0.47 mmol). The mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:0 to 0:1) to give the titled compound. LCMS: $m/z = 243.2$ $[M+H]^+$.

[0300] 2-fluoro-5-(1-methyl-1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline: To a solution of 3-(1-methyl-1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline (340 mg, 1.40 mmol) in MeCN (5 mL) at 25 °C under N_2 was added SelectfluorTM (597 mg, 1.68 mmol). The mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 4:1 to 1:1) to give the titled compound. LCMS: $m/z = 261.1$ $[M+H]^+$.

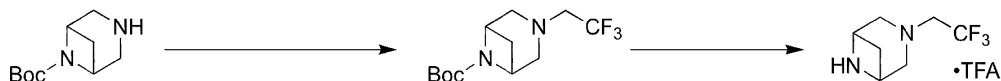
Intermediate 24

3-(1-methyl-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)aniline

[0301] To a solution of 3-bromo-4-(trifluoromethyl)aniline (2 g, 8.33 mmol) in 1,4-dioxane (50 mL) and H₂O (5 mL) at 25 °C under N₂ was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.73 g, 8.33 mmol), K₂CO₃ (2.30 g, 16.67 mmol) and Pd(dppf)Cl₂ (610 mg, 0.83 mmol). The reaction mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 100:1 to 1:1) to give the titled compound. LCMS: $m/z = 242.2$ [M+H]⁺.

Intermediate 25

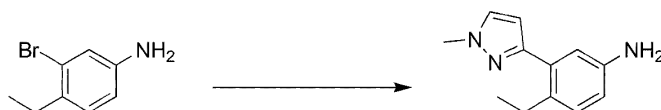
3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptane trifluoroacetate



[0302] *tert*-butyl 3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate: To a mixture of *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (1 g, 5.04 mmol) in THF (20 mL) at 0 °C under N₂ was added DIEA (1.96 g, 15.13 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.40 g, 6.05 mmol). The mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:MTBE = 5:1 to 1:1) to give the titled compound. LCMS: $m/z = 281.2$ [M+H]⁺.

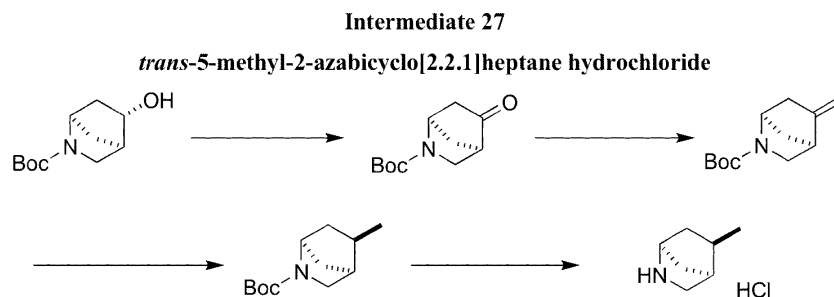
[0303] 3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.1.1]heptane trifluoroacetate: To a solution of 3-bromo-4-(trifluoromethyl)aniline (1.2 g, 4.28 mmol) in DCM (15 mL) at 25 °C under N₂ was added TFA (5 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give the titled compound.

Intermediate 26

4-ethyl-3-(1-methyl-1*H*-pyrazol-3-yl)aniline

[0304] To a solution of 3-bromo-4-ethyl-aniline (200 mg, 1.00 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (312 mg, 1.50 mmol) in 1,4-dioxane (5 mL) and H₂O (0.5 mL) at 20 °C under N₂ was added K₂CO₃ (276 mg, 2.00 mmol) and Pd(dppf)Cl₂ (73 mg, 0.10 mmol).

The reaction mixture was heated to 100 °C and stirred for 16 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 202.1 $[M+H]^+$.



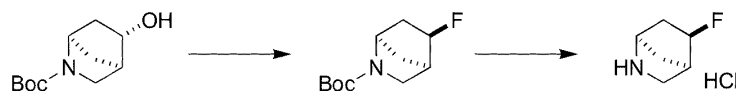
[0305] *tert*-butyl-5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate: To a solution of *tert*-butyl (*cis*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.00 g, 4.69 mmol) in DCM (15 mL) at 0 °C under N₂ was added DMP (5.97 g, 14.07 mmol). The mixture was warmed to 20 °C and stirred for 16 h. The reaction mixture was quenched by addition of aq. sat. Na₂S₂O₃ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 3:1) to give the titled compound.

[0306] *tert*-butyl-5-methylene-2-azabicyclo[2.2.1]heptane-2-carboxylate: To a solution of *tert*-butyl-5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (500 mg, 2.37 mmol) in THF (16 mL) at 0 °C under N₂ was added Tebbe reagent (0.5 M, 9.47 mL). The mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was adjusted to pH = 7 by the addition of aq. sat. NaHCO₃ and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 3:1) to give the titled compound.

[0307] *tert*-butyl (*trans*)-5-methyl-2-azabicyclo[2.2.1]heptane-2-carboxylate: To a solution of *tert*-butyl-5-methylene-2-azabicyclo[2.2.1]heptane-2-carboxylate (540 mg, 2.58 mmol) in MeOH (5 mL) at 25 °C under N₂ was added 10% Pd/C (250 mg). The suspension was degassed under vacuum and purged with H₂ three times. The reaction mixture was stirred at 25 °C for 1 h under H₂ (15 psi). The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give the titled compound.

[0308] *trans*-5-methyl-2-azabicyclo[2.2.1]heptane hydrochloride: A solution of *tert*-butyl (*trans*)-5-methyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (350 mg, 1.66 mmol) in HCl/EtOAc (10 mL, 4 M) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 112.2 $[M+H]^+$.

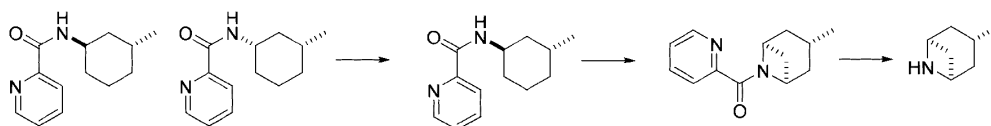
Intermediate 28

trans-5-fluoro-2-azabicyclo[2.2.1]heptane hydrochloride

[0309] ***tert*-butyl (*trans*)-5-fluoro-2-azabicyclo[2.2.1]heptane-2-carboxylate:** To a mixture of *tert*-butyl (*cis*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.8 g, 3.75 mmol) in DCM (10 mL) at 0 °C under N₂ was added DAST (1.21 g, 7.50 mmol). The mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was poured into aq. sat. NaHCO₃ (20 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1) to give the titled compound.

[0310] ***trans*-5-fluoro-2-azabicyclo[2.2.1]heptane hydrochloride:** A solution of *tert*-butyl (*trans*)-5-fluoro-2-azabicyclo[2.2.1]heptane-2-carboxylate (90 mg, 0.418 mmol) in HCl/EtOAc (2 mL, 4 M) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the titled compound.

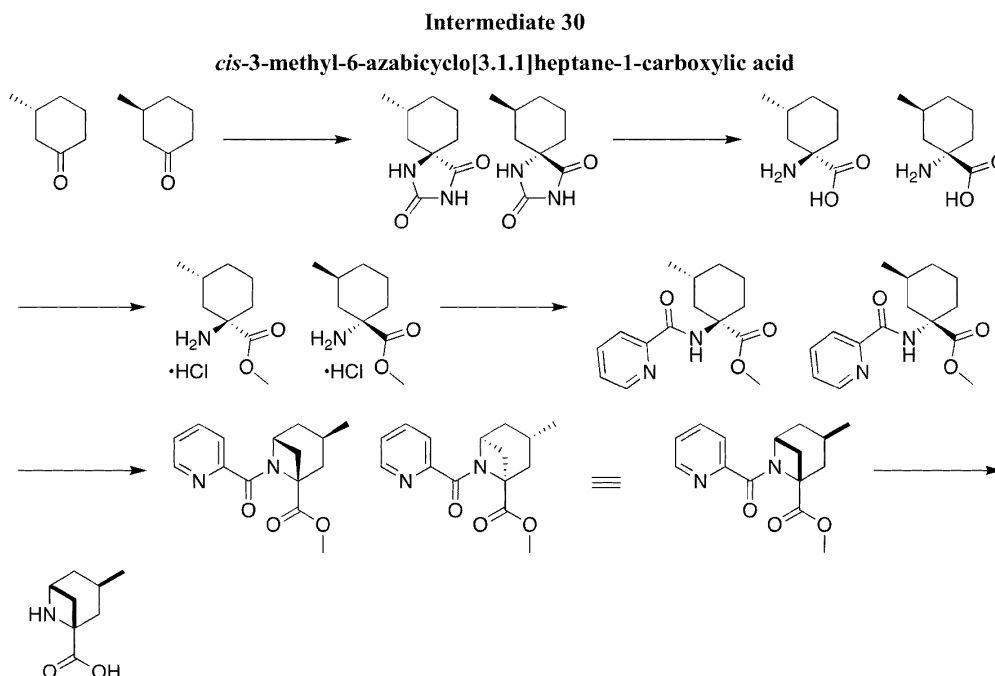
Intermediate 29

cis-3-Methyl-6-azabicyclo[3.1.1]heptane

[0311] ***N*-(*trans*-3-methylcyclohexyl)picolinamide:** A mixture of *N*-(*trans*-3-methylcyclohexyl)picolinamide and *N*-(*cis*-3-methylcyclohexyl)picolinamide was purified by prep-HPLC (Phenomenex Luna C18 250 × 100 mm × 15 μm; mobile phase: A: 10 mM TFA in water, B: MeCN; B in A: 40%-70%, over 20 min) to provide the separated *cis* and *trans* isomers as the first and second eluting peaks respectively. The second eluting peak was concentrated under reduced pressure, adjusted to pH = 7-8 with aq. sat. NaHCO₃ solution and extracted with DCM (3 × 300 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 219.2 [M+H]⁺.

[0312] **(*cis*-3-Methyl-6-azabicyclo[3.1.1]heptan-6-yl)(pyridin-2-yl)methanone** To a mixture of *N*-(*trans*-3-methylcyclohexyl)picolinamide (6 g, 27.49 mmol) in 1,1,2,2-tetrachloroethane (200 mL) at 25 °C under N₂ was added AgOAc (13.76 g, 82.46 mmol), benzoquinone (1.49 g, 13.74 mmol), Na₃PO₄ (13.52 g, 82.46 mmol), 1,2,3,4,5-pentafluoro-6-iodo-benzene (80.80 g, 274.86 mmol) and Pd(OAc)₂ (1.23 g, 5.50 mmol). The mixture was heated to 145 °C and stirred for 12 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: *m/z* = 217.0 [M+H]⁺.

[0313] ***cis*-3-Methyl-6-azabicyclo[3.1.1]heptane:** To a mixture of (*cis*-3-methyl-6-azabicyclo[3.1.1]heptan-6-yl)(pyridin-2-yl)methanone (2.4 g, 11.1 mmol) in EtOH (30 mL) at 25 °C under N₂ was added NaOH (4.44 g, 111 mmol). The mixture was heated to 90 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure (water pump, below 35 °C) to give a crude mixture. The mixture was stirred in DCM (20 mL) and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure (water pump, below 35 °C). The work-up procedure was repeated 2–3 times or until the concentrated residue contained no solids to give the titled compound as the free base. The free base was converted to the TFA salt by the addition of TFA and stirring for 0.5 h at 20 °C before concentrating under reduced pressure. Alternatively, a mixture of the free base in MTBE at –20 °C treated with 4M HCl/MTBE (1.2 equiv) and stirred for 10 minutes gave the HCl salt. LCMS: *m/z* = 112.2 [M+H]⁺.



[0314] **(5*R*,7*R*)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione and (5*S*,7*S*)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione:** To a mixture of (*R*)-3-methylcyclohexan-1-one and (*S*)-3-methylcyclohexan-1-one (50 g, 445.76 mmol, 54.59 mL) in EtOH (250 mL) and H₂O (250 mL) at 20 °C under N₂ was added (NH₄)₂CO₃ (128.49 g, 1.34 mol) and KCN (43.54 g, 669 mmol). The mixture was heated to 65 °C and stirred for 3 h. The reaction mixture was filtered, and the filter cake was washed with H₂O and dried under reduced pressure. The crude product was triturated with EtOH at 20 °C for 30 min, filtered, and the solid was dried under reduced pressure to give the titled compounds. LCMS: *m/z* = 183.2 [M+H]⁺.

[0315] (1*R*,3*R*)-1-amino-3-methylcyclohexane-1-carboxylic acid and (1*S*,3*S*)-1-amino-3-methylcyclohexane-1-carboxylic acid: To a solution of (5*R*,7*R*)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione and (5*S*,7*S*)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (78.5 g, 430.80 mmol) in H₂O (1000 mL) at 25 °C was added Ba(OH)₂ (738 g, 4.31 mol). The mixture was heated to 140 °C and stirred for 12 h in a 5 L autoclave. The reaction mixture was cooled to 0 °C and the pH was adjusted to pH = 3 with 3 M H₂SO₄. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give the titled compounds. LCMS: *m/z* = 158.2 [M+H]⁺.

[0316] methyl (1*R*,3*R*)-1-amino-3-methylcyclohexane-1-carboxylate hydrochloride and methyl (1*S*,3*S*)-1-amino-3-methylcyclohexane-1-carboxylate hydrochloride: To a mixture of (1*R*,3*R*)-1-amino-3-methylcyclohexane-1-carboxylic acid and (1*S*,3*S*)-1-amino-3-methylcyclohexane-1-carboxylic acid (60 g, 382 mmol) in MeOH (600 mL) at 0 °C under N₂ was added SOCl₂ (227 g, 1.91 mol, 138.43 mL). The mixture was heated to 75 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled compounds. LCMS: *m/z* = 172.2 [M+H]⁺.

[0317] methyl (1*R*,3*R*)-3-methyl-1-(picolinamido)cyclohexane-1-carboxylate and methyl (1*S*,3*S*)-3-methyl-1-(picolinamido)cyclohexane-1-carboxylate: To a solution of methyl (1*R*,3*R*)-1-amino-3-methylcyclohexane-1-carboxylate hydrochloride and methyl (1*S*,3*S*)-1-amino-3-methylcyclohexane-1-carboxylate hydrochloride (24 g, 140 mmol) and picolinic acid (25.88 g, 210 mmol) in DCM (300 mL) at 0 °C under N₂ was added DIEA (54.34 g, 420 mmol, 73.24 mL), DMAP (1.71 g, 14 mmol) and EDCI (40.30 g, 210 mmol). The mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was diluted with H₂O (200 mL) and extracted with DCM (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compounds. LCMS: *m/z* = 277.2 [M+H]⁺.

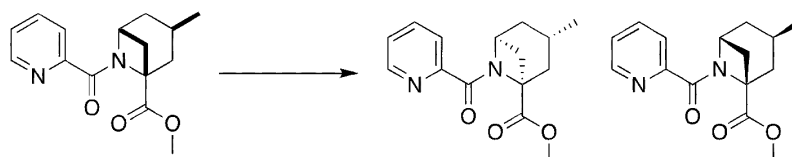
[0318] methyl (1*R*,3*R*) 2-(3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptan-1-yl)-2-oxoacetate and methyl (1*S*,3*S*) 2-(3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptan-1-yl)-2-oxoacetate: To a solution of methyl (1*R*,3*R*)-3-methyl-1-(picolinamido)cyclohexane-1-carboxylate and methyl (1*S*,3*S*)-3-methyl-1-(picolinamido)cyclohexane-1-carboxylate (19 g, 68.76 mmol) in 1,1,2,2-tetrachloroethane (900 mL) at 25 °C under N₂ was added Na₃PO₄ (33.82 g, 206 mmol, 33.82 mL), 1,2,3,4,5-pentafluoro-6-iodo-benzene (202.12 g, 688 mmol), AgOAc (34.43 g, 206 mmol, 10.56 mL), benzoquinone (3.72 g, 34 mmol, 7.74 mL) and Pd(OAc)₂ (3.09 g, 13.75 mmol). The mixture was heated to 145 °C and stirred for 16 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compounds. LCMS: *m/z* = 275.2 [M+H]⁺.

[0319] *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a solution of methyl *cis*-2-(3-methyl-6-(pyridine-2-carbonyl)-6-azabicyclo[3.1.1]heptane-1-carboxylate (10 g, 36.45 mmol) in EtOH at 25 °C under N₂ (150 mL) was added NaOH (14.58 g, 364.55 mmol). The mixture was heated to 90 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure and the resulting

residue was diluted with H₂O (100 mL) and cooled to 0 °C before the solution was acidified to pH = 4 with conc. HCl. The solution was lyophilized to give the titled compound. LCMS: m/z = 156.1 [M+H]⁺.

Intermediate 31 and 32

Methyl-(1*R*,3*S*,5*S*)-3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptane-1-carboxylate and methyl (1*S*,3*R*,5*R*)-3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptane-1-carboxylate

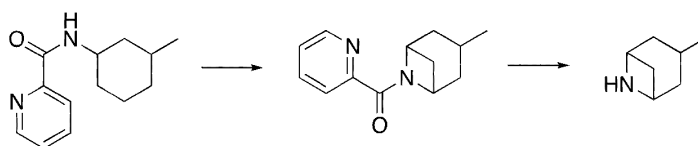


[0320] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK 250 mm × 50 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in *i*-PrOH MeOH; B% in A: 20%-20%, 3 min; Flow rate: 200 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 100 bar) to give methyl *cis*-3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptane-1-carboxylate (peak 1 in SFC)

Intermediate 31. LCMS: m/z = 275.2 [M+H]⁺ and methyl *cis*-3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptane-1-carboxylate (peak 2 in SFC) **Intermediate 32.** LCMS: m/z = 275.2 [M+H]⁺.

Intermediate 33

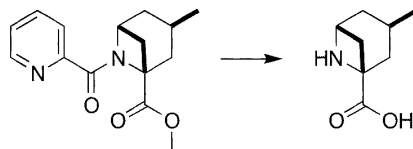
Methyl-6-azabicyclo[3.1.1]heptane



[0321] **Methyl-6-azabicyclo[3.1.1]heptan-6-yl(pyridin-2-yl)methanone:** To a mixture of *N*-(3-methylcyclohexyl)picolinamide (20 g, 91.62 mmol) in 1,1,2,2-tetrachloroethane (300 mL) was added AgOAc (45.88 g, 274.86 mmol), benzoquinone (4.95 g, 45.81 mmol), Na₃PO₄ (45 g, 274.86 mmol), 1,2,3,4,5-pentafluoro-6-iodo-benzene (269 g, 916.20 mmol) and Pd(OAc)₂ (2.06 g, 9.16 mmol) at 25 °C under N₂. The mixture was stirred at 145 °C for 12 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 217.10 [M+H]⁺.

[0322] **3-Methyl-6-azabicyclo[3.1.1]heptane:** To a mixture of (3-methyl-6-azabicyclo[3.1.1]heptan-6-yl)(pyridin-2-yl)methanone (2.7 g, 12.48 mmol) in EtOH (50 mL) was added NaOH (4.99 g, 124.84 mmol) at 25 °C under N₂. The mixture was stirred at 90 °C for 4 h. The reaction mixture was concentrated under reduced pressure (water pump, below 35 °C) to give a mixture containing the product, NaOH and the sodium salt of the acid. The mixture was stirred in DCM (20 mL) and filtered through a Celite® pad. The filtrate was concentrated under reduced pressure (water pump, below 35 °C). The work-up procedure was repeated 2–3 times or until the concentrated residue contained no solids to give the titled compound as a 10:1 mixture of *cis* and *trans* isomers. LCMS: m/z = 112.2 [M+H]⁺.

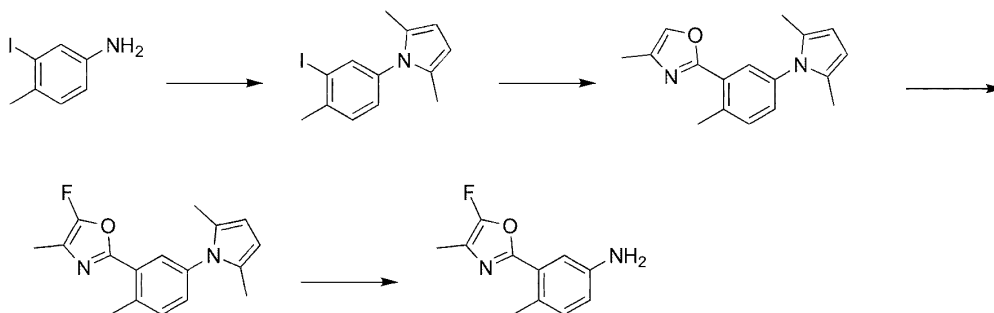
Intermediate 34

cis-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid

[0323] To a solution of methyl *cis*-3-methyl-6-picolinoyl-6-azabicyclo[3.1.1]heptane-1-carboxylate (Intermediate 31) (3 g, 11 mmol) in EtOH (30 mL) was added NaOH (4.37 g, 109 mmol) at 25 °C under N₂. The reaction mixture was heated to 90 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure, adjusted to pH = 5 with 12 M HCl at 0 °C and lyophilized to give the titled compound. LCMS: *m/z* = 156.1 [M+H]⁺.

Intermediate 35

3-(5-fluoro-4-methyloxazol-2-yl)-4-methylaniline



[0324] **1-(3-iodo-4-methylphenyl)-2,5-dimethyl-1*H*-pyrrole:** To a mixture of 3-iodo-4-methylaniline (5 g, 21.45 mmol) in toluene (50 mL) at 25 °C under N₂ was added *p*-TsOH (37 mg, 0.21 mmol) and hexane-2,5-dione (2.94 g, 25.75 mmol). The reaction mixture was heated to 110 °C and stirred for 1 h. The mixture was adjusted to pH = 7–8 by addition of aq. sat. NaHCO₃ (60 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 5:1) to give the titled compound. LCMS: *m/z* = 312.0 [M+H]⁺.

[0325] **2-(5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-methylphenyl)-4-methyloxazole:** To a mixture of 4-methyloxazole (334 mg, 4.02 mmol) in THF (3 mL) at –78 °C under N₂ was added *n*-BuLi (4.02 mmol, 1.61 mL, 2.5 M in hexane). The mixture was stirred at –78 °C for 10 min then ZnCl₂ (9.34 mmol, 4.82 mL, 2 M in THF) was added and stirred for an additional 15 min. The reaction mixture was warmed to 20 °C and added to a solution of 1-(3-iodo-4-methylphenyl)-2,5-dimethyl-1*H*-pyrrole (500 mg, 1.61 mmol) and Pd(PPh₃)₂Cl₂ (113 mg, 0.16 mmol) in THF (5 mL) at 20 °C under N₂. The combined reaction mixture was heated at 60 °C and stirred for 20 min under microwave irradiation. The reaction mixture was quenched by addition of aq. sat. NH₄Cl (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The

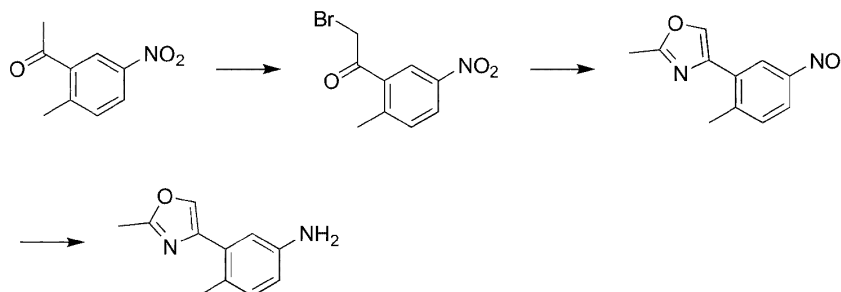
resulting residue was purified by silica gel column chromatography (PE:EtOAc = 15:1 to 5:1) to give the titled compound. LCMS: $m/z = 267.1$ $[M+H]^+$.

[0326] 2-(5-(2,5-dimethyl-1H-pyrrol-1-yl)-2-methylphenyl)-5-fluoro-4-methyloxazole: To a solution of 2-(5-(2,5-dimethyl-1H-pyrrol-1-yl)-2-methylphenyl)-4-methyloxazole (750 mg, 2.82 mmol) in THF (14 mL) at -78°C under N_2 was added $n\text{-BuLi}$ (3.38 mmol, 1.35 mL, 2.5 M in hexane). The mixture was stirred at -78°C for 45 min and then a solution of NFSI (1.07 g, 3.38 mmol) in THF (1 mL) was added and stirred for 1 h. The reaction mixture was quenched by addition of aq. sat. NH_4Cl (20 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 5:1) to give the titled compound. LCMS: $m/z = 285.1$ $[M+H]^+$.

[0327] 3-(5-fluoro-4-methyloxazol-2-yl)-4-methylaniline: To a mixture of 2-(5-(2,5-dimethyl-1H-pyrrol-1-yl)-2-methylphenyl)-5-fluoro-4-methyloxazole (140 mg, 0.5 mmol) in EtOH (1.5 mL) and H_2O (0.5 mL) at 25°C under N_2 was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (411 mg, 5.91 mmol) and TEA (299 mg, 2.95 mmol). The mixture was heated to 90°C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the crude material was diluted with H_2O (5 mL) and extracted with EtOAc (3×3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO_2 , PE:EtOAc = 2:1) to give the titled compound. LCMS: $m/z = 207.1$ $[M+H]^+$.

Intermediate 36

4-methyl-3-(2-methyloxazol-4-yl)aniline



[0328] 2-bromo-1-(2-methyl-5-nitrophenyl)ethan-1-one: To a mixture of 1-(2-methyl-5-nitrophenyl)ethan-1-one (500 mg, 2.79 mmol) in AcOH (5 mL) at 0°C under N_2 was added Br_2 (446 mg, 2.79 mmol). The reaction mixture was warmed to 25°C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the crude material was diluted with H_2O (15 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the titled compound.

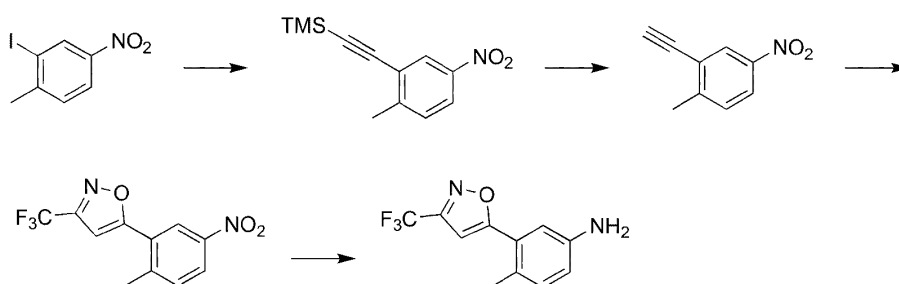
[0329] 2-methyl-4-(2-methyl-5-nitrophenyl)oxazole: To a mixture of 2-bromo-1-(2-methyl-5-nitrophenyl)ethan-1-one (500 mg, 1.94 mmol) in NMP (10 mL) at 25°C was added acetamide (286 mg, 4.84 mmol). The mixture was heated to 100°C and stirred for 12 h. The reaction mixture was diluted

with H₂O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound.

[0330] 4-methyl-3-(2-methyloxazol-4-yl)aniline: To a solution of 2-methyl-4-(2-methyl-5-nitro-phenyl)oxazole (240 mg, 1.10 mmol) in MeOH (2 mL) under Ar₂ was added 10% Pd/C (50 mg). The suspension was degassed under vacuum and purged with H₂ several times. The reaction mixture was stirred at 25 °C for 0.5 h under H₂ (15 psi), filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 189.0 [M+H]⁺.

Intermediate 37

4-methyl-3-[3-(trifluoromethyl)isoxazol-5-yl]aniline



[0331] trimethyl-[2-(2-methyl-5-nitro-phenyl)ethynyl]silane: To a solution of 2-iodo-1-methyl-4-nitro-benzene (5 g, 19.01 mmol) and ethynyl(trimethyl)silane (4.67 g, 47.52 mmol) in THF (50 mL) at 20 °C under N₂ was added TEA (5.77 g, 57.03 mmol), CuI (181 mg, 0.95 mmol) and Pd(PPh₃)₂Cl₂ (667 mg, 0.95 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was diluted with H₂O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (PE:EtOAc = 1:0 to 5:1) to give the titled compound.

[0332] 2-ethynyl-1-methyl-4-nitro-benzene: To a solution of trimethyl-[2-(2-methyl-5-nitro-phenyl)ethynyl]silane (3.7 g, 15.86 mmol) in MeOH (50 mL) at 20 °C under N₂ was added K₂CO₃ (4.38 g, 31.71 mmol). The mixture was stirred at 20 °C for 10 min. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with H₂O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE:EtOAc = 30:1 to 10:1) to give the titled compound.

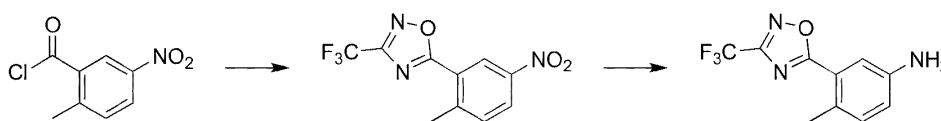
[0333] 5-(2-methyl-5-nitro-phenyl)-3-(trifluoromethyl)-1,2,4-oxadiazole: A mixture of 2-ethynyl-1-methyl-4-nitro-benzene (500 mg, 3.10 mmol), 2,2,2-trifluoroethanamine (922 mg, 9.31 mmol), *tert*-butyl nitrite (960 mg, 9.31 mmol), CuI (59 mg, 0.31 mmol), AcOH (75 mg, 1.24 mmol) and ZnBr₂ (1.40 g, 6.21 mmol) in CHCl₃ (10 mL) was stirred at 20 °C under N₂ for 16 h. The mixture was concentrated

under reduced pressure and the resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 10:1) to give the titled compound.

[0334] 4-methyl-3-[3-(trifluoromethyl)isoxazol-5-yl]aniline: To a solution of 5-(2-methyl-5-nitro-phenyl)-3-(trifluoromethyl)isoxazole (200 mg, 0.735 mmol) in EtOAc (5 mL) under Ar₂ was added 10% Pd/C (100 mg). The atmosphere was replaced and degassed with H₂ and the reaction mixture was stirred at 20 °C for 3 h under H₂ (15 psi). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 3:1) to give the titled compound. LCMS: m/z = 243.0 [M+H]⁺.

Intermediate 38

4-methyl-3-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]aniline

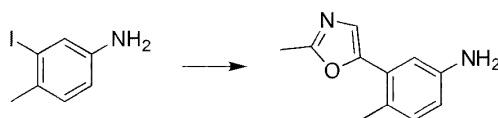


[0335] 5-(2-methyl-5-nitro-phenyl)-3-(trifluoromethyl)-1,2,4-oxadiazole: To a solution of 2-methyl-5-nitro-benzoyl chloride (130 mg, 0.651 mmol) and 2,2,2-trifluoro-*N*-hydroxy-acetamidine (83 mg, 0.651 mmol) in THF (2 mL) at 0 °C was added DIEA (337 mg, 2.61 mmol). The reaction mixture was warmed to 20 °C and stirred for 16 h and then heated to 70 °C and stirred for 4 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: m/z = 274.1 [M+H]⁺.

[0336] 4-methyl-3-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]aniline: To a mixture of 5-(2-methyl-5-nitro-phenyl)-3-(trifluoromethyl)-1,2,4-oxadiazole (100 mg, 0.366 mmol) in EtOH (2 mL) at 25 °C under N₂ was added SnCl₂ (278 mg, 1.46 mmol). The mixture was stirred at 80 °C for 6 h. The mixture was cooled to 20 °C and poured into 5% aq. NaOH (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: m/z = 244.1 [M+H]⁺.

Intermediate 39

4-methyl-3-(2-methyloxazol-5-yl)aniline

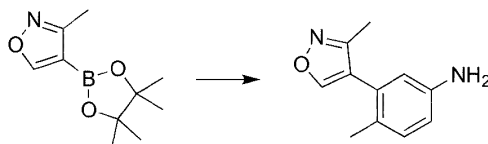


[0337] To a solution of 3-iodo-4-methyl-aniline (1.05 g, 4.51 mmol) in DMF (20 mL) was added 2-methyloxazole (562 mg, 6.76 mmol), KOAc (884 mg, 9.01 mmol) and Pd(PPh₃)₄ (521 mg, 0.45 mmol) at 20 °C under N₂. The reaction mixture was heated to 110 °C and stirred for 12 h. The mixture was filtered through a pad of Celite® and the filtrate was diluted with H₂O (40 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄,

filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: $m/z = 189.2$ $[M+H]^+$.

Intermediate 40

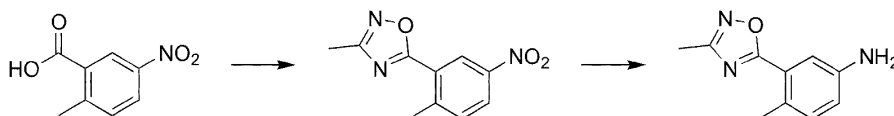
4-methyl-3-(3-methylisoxazol-4-yl)aniline



[0338] To a mixture of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (130 mg, 0.622 mmol) and 3-iodo-4-methylaniline (145 mg, 0.622 mmol) in 1,4-dioxane (7 mL) and H₂O (0.7 mL) at 25 °C under N₂ was added K₂CO₃ (172 mg, 1.24 mmol) and Pd(dppf)Cl₂ (46 mg, 0.062 mmol). The reaction mixture was heated to 100 °C and stirred for 6 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: $m/z = 189.2$ $[M+H]^+$.

Intermediate 41

4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)aniline

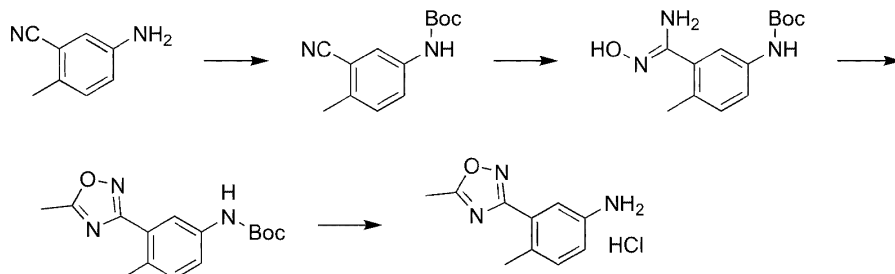


[0339] 3-methyl-5-(2-methyl-5-nitrophenyl)-1,2,4-oxadiazole: To a solution of 2-methyl-5-nitrobenzoic acid (1 g, 5.52 mmol) in DMF (15 mL) at 25 °C under N₂ was added CDI (985 mg, 6.07 mmol). The reaction mixture was stirred at 25 °C for 12 h. Then *N*-hydroxyacetimidamide (410 mg, 5.54 mmol) was added to the above mixture and the reaction mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (45 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 2:1) to give the titled compound. LCMS: $m/z = 220.1$ $[M+H]^+$.

[0340] 4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)aniline: To a solution of 3-methyl-5-(2-methyl-5-nitrophenyl)-1,2,4-oxadiazole (690 mg, 3.15 mmol) in EtOH (20 mL) at 25 °C under N₂ was added SnCl₂ (2.39 g, 12.59 mmol). The reaction mixture was heated to 90 °C and stirred for 6 h. The reaction mixture was adjusted to pH = 7–8 with aq. sat. NaHCO₃, then filtered through a pad of Celite®. The filtrate was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 2:1) to give the titled compound. LCMS: $m/z = 190.2$ $[M+H]^+$.

Intermediate 42

4-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)aniline hydrochloride



[0341] *tert*-butyl (3-cyano-4-methylphenyl)carbamate: To a solution of 5-amino-2-methylbenzonitrile (2 g, 15.13 mmol) in THF (25 mL) at 25 °C under N₂ was added (Boc)₂O (3.30 g, 15.13 mmol) and TEA (1.53 g, 15.13 mmol). The reaction mixture was heated to 50 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: *m/z* = 233.2 [M+H]⁺.

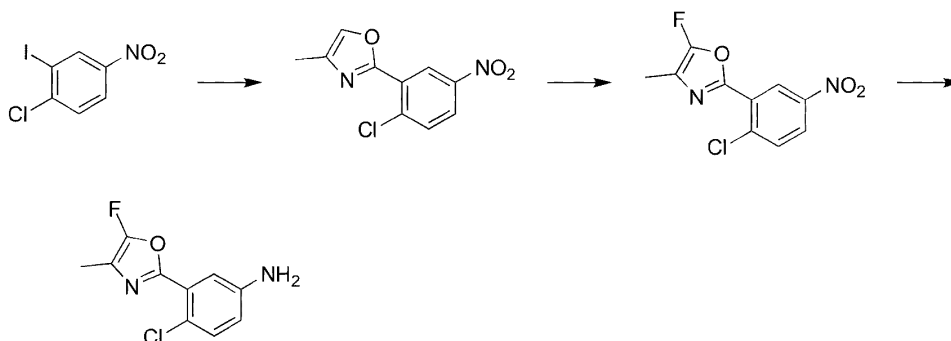
[0342] *tert*-butyl (3-(*N'*-hydroxycarbamimidoyl)-4-methylphenyl)carbamate: To a solution of *tert*-butyl (3-cyano-4-methylphenyl)carbamate (500 mg, 2.15 mmol) in EtOH (10 mL) at 25 °C under N₂ was added hydroxylamine (284 mg, 4.31 mmol). The reaction mixture was heated to 90 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 266.2 [M+H]⁺.

[0343] *tert*-butyl (4-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamate: To a solution of *tert*-butyl (3-(*N'*-hydroxycarbamimidoyl)-4-methylphenyl)carbamate (100 mg, 0.38 mmol) in DCM (2 mL) at 0 °C under N₂ was added pyridine (36 mg, 0.45 mmol) and acetyl chloride (35 mg, 0.45 mmol). The reaction mixture was warmed to 25 °C, stirred for 12 h, and then concentrated under reduced pressure. To the resulting residue was added DMF (2 mL), followed by TEA (66 mg, 0.65 mmol) at 25 °C under N₂. The reaction mixture was heated to 110 °C and stirred for 5 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 1:1) to give the titled compound. LCMS: *m/z* = 234.2 [M-*t*Bu+H]⁺.

[0344] 4-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)aniline: A solution of *tert*-butyl (4-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamate (110 mg, 0.38 mmol) in HCl/EtOAc (10 mL, 4 M) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 190.2 [M+H]⁺.

Intermediate 43

4-chloro-3-(5-fluoro-4-methyloxazol-2-yl)aniline

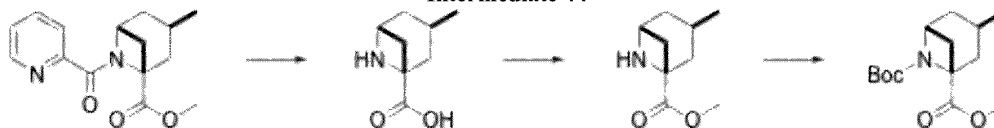


[0345] 2-(2-chloro-5-nitrophenyl)-4-methyloxazole: To a solution of 1-chloro-2-iodo-4-nitro-benzene (2 g, 7.06 mmol) in 1,4-dioxane (30 mL) at 25 °C under N₂ was added tricyclohexylphosphonium tetrafluoroborate (779 mg, 2.12 mmol), 4-methyloxazole (1.17 g, 14.11 mmol), DBU (2.15 g, 14.11 mmol), CuI (403 mg, 2.12 mmol) and Pd(OAc)₂ (316 mg, 1.41 mmol). The reaction mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound. LCMS: m/z = 239.0 [M+H]⁺.

[0346] 2-(2-chloro-5-nitrophenyl)-5-fluoro-4-methyloxazole: To a solution of LDA (3.14 mmol, 1.57 mL, 2 M in THF) in THF (10 mL) at -78 °C under N₂ was added 2-(2-chloro-5-nitro-phenyl)-4-methyloxazole (500 mg, 2.10 mmol) and the reaction mixture was stirred at -78 °C for 0.5 h. NFSI (1.32 g, 4.19 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was poured into aq. sat. NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound. LCMS: m/z = 257.1 [M+H]⁺.

[0347] 4-chloro-3-(5-fluoro-4-methyloxazol-2-yl)aniline: To a solution of 2-(2-chloro-5-nitro-phenyl)-5-fluoro-4-methyl-oxazole (50 mg, 0.19 mmol) in EtOH (5 mL) and H₂O (1 mL) was added Fe (21 mg, 0.38 mmol) and NH₄Cl (52 mg, 0.97 mmol). The reaction mixture was heated to 70 °C and stirred for 2 h, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: m/z = 227.1 [M+H]⁺.

Intermediate 44



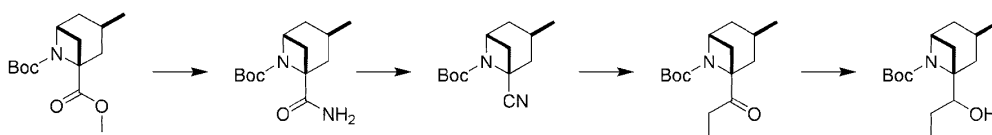
[0348] *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a solution of *cis*-methyl 3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylate (Intermediate 31) (10 g, 36.45 mmol) in EtOH (150 mL) at 25 °C under N₂ was added NaOH (14.58 g, 364.55 mmol). The reaction mixture was heated to 90 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with H₂O (100 mL) and the solution was adjusted to pH = 4 with conc. HCl at 0 °C. The solution was lyophilized to give the titled compound. LCMS: *m/z* = 156.1 [M+H]⁺.

[0349] *cis*-methyl 3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylate methyl hydrochloride: To a solution of *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (25 g crude, 35.44 mmol, 22% purity) in MeOH (300 mL) at 0 °C under N₂ was added dropwise SOCl₂ (8.4 g, 70.88 mmol). The mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled product. LCMS: *m/z* = 170.2 [M+H]⁺.

[0350] *cis*-6-*tert*-butyl 1-methyl 3-methyl-6-azabicyclo[3.1.1]heptane-1,6-dicarboxylate: To a solution of *cis*-methyl 3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylate methyl hydrochloride (26 g crude, 35.34 mmol, 23% purity) in DCM (300 mL) and MeOH (30 mL) at 0 °C under N₂ was added Boc₂O (15.43 g, 70.68 mmol), TEA (7.15 g, 70.68 mmol) and DMAP (431 mg, 3.53 mmol). The mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 5:1) to give the titled compound. LCMS: *m/z* = 270.2 [M+H]⁺.

Intermediates 45 and 46

cis-tert-butyl 1-(1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate



[0351] *cis-tert*-butyl 1-carbamoyl-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate: A mixture of *cis*-6-*tert*-butyl 1-methyl 3-methyl-6-azabicyclo[3.1.1]heptane-1,6-dicarboxylate Intermediate 44 (2 g, 7.43 mmol) in NH₃•H₂O (50 mL) was stirred at 20 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 199.2 [M-*t*Bu+H]⁺.

[0352] *cis-tert*-butyl 1-cyano-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate: To a solution of *cis-tert*-butyl 1-carbamoyl-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate (1.68 g, 6.61 mmol) in THF (50 mL) at 25 °C under N₂ was added Burgess reagent (4.72 g, 19.82 mmol). The reaction mixture was heated to 65 °C and stirred for 3 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with MTBE (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over

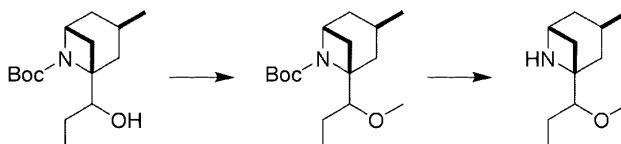
anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 5:1) to give the titled compound.

[0353] *cis-tert-butyl 3-methyl-1-propionyl-6-azabicyclo[3.1.1]heptane-6-carboxylate*: To a solution of *cis-tert-butyl 1-cyano-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (900 mg, 3.81 mmol) in THF (20 mL) at 0 °C under N₂ was added dropwise EtMgBr (3.17 mL, 9.52 mmol, 3M in THF). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with aq. sat. NH₄Cl (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound.

[0354] *cis-tert-butyl 1-((S)-1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* and *cis-tert-butyl 1-((R)-1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate*: To a solution of *cis-tert-butyl 3-methyl-1-propionyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (600 mg, 2.24 mmol) in MeOH (10 mL) was added NaBH₄ (102 mg, 2.69 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give *cis-tert-butyl 1-((S)-1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (Intermediate 45) as the first eluting isomer and *cis-tert-butyl 1-((R)-1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (Intermediate 46) as the second eluting isomer.

Intermediate 47

cis-1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane



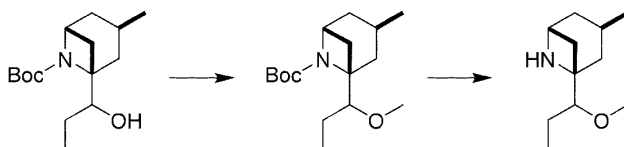
[0355] *cis-tert-butyl 1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate*: To a solution of *cis-tert-butyl 1-(1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (Intermediate 45) (100 mg, 0.37 mmol) in DMF (3 mL) at 0 °C was added NaH (45 mg, 1.11 mmol, 60% w/w). The reaction solution was stirred at 0 °C for 0.5 h, MeI (211 mg, 1.48 mmol) was added and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with aq. sat. NH₄Cl (6 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 5:1) to give the titled compound.

[0356] *cis-1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane*: To a solution of *cis-tert-butyl 1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (50 mg, 0.18 mmol) in DCM (2 mL) at 0 °C was added 2,6-dimethylpyridine (142 mg, 1.32 mmol) and TMSOTf (118 mg, 0.53 mmol) in

DCM (0.5 mL). The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled compound.

Intermediate 48

cis-1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane

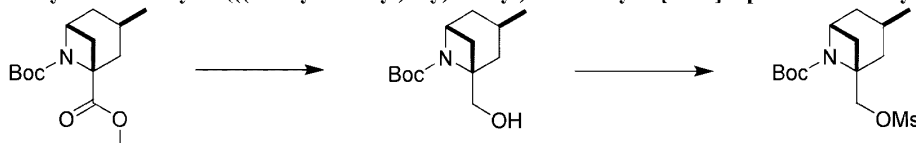


[0357] *cis*-*tert*-butyl 1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate: To a solution of *cis*-*tert*-butyl 1-(1-hydroxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate (Intermediate 46) (100 mg, 0.37 mmol) in DMF (2 mL) at 0 °C was added NaH (45 mg, 1.11 mmol, 60% w/w). The reaction mixture was stirred for 0.5 h, MeI (211 mg, 1.48 mmol) was added and the reaction mixture was stirred for 2 h. The reaction mixture was poured into aq. sat. NH₄Cl (6 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 5:1) to give the titled compound. LCMS: *m/z* = 228.2 [M-*t*Bu+H]⁺.

[0358] *cis*-1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane: To a solution of *cis*-*tert*-butyl 1-(1-methoxypropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate (50 mg, 0.18 mmol) in DCM (2 mL) at 0 °C was added 2,6-dimethylpyridine (142 mg, 1.32 mmol) and TMSOTf (118 mg, 0.53 mmol). The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled compound.

Intermediate 49

tert-butyl *cis*-3-methyl-1-(((methylsulfonyl)oxy)methyl)-6-azabicyclo[3.1.1]heptane-6-carboxylate



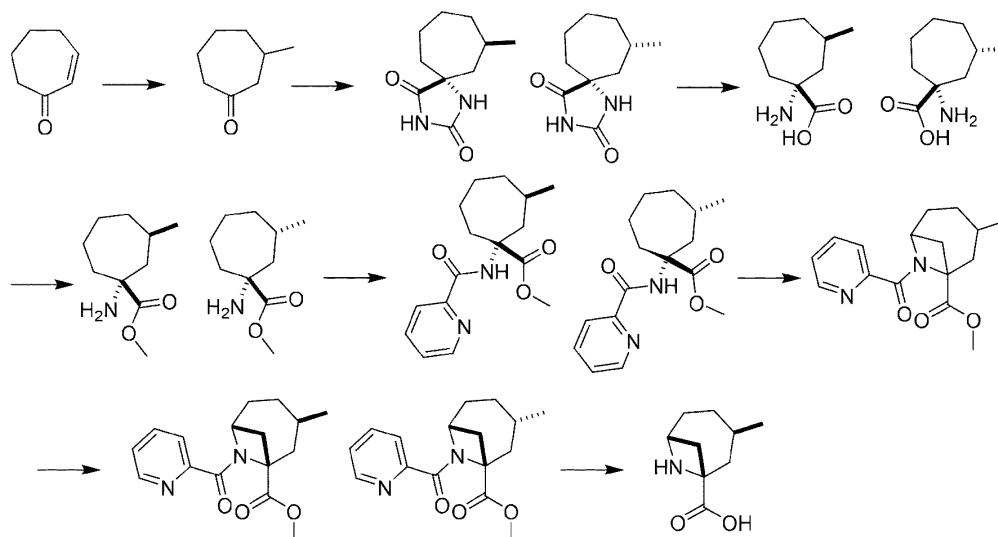
[0359] *tert*-butyl *cis*-1-(hydroxymethyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate: To a mixture of 6-(*tert*-butyl) 1-methyl *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1,6-dicarboxylate (Intermediate 44) (2.5 g, 9.28 mmol) in MeOH (50 mL) at 0 °C under N₂ was added NaBH₄ (2.11 g, 55.69 mmol) and CaCl₂ (4.12 g, 37.13 mmol). The reaction mixture was heated to 50 °C and stirred for 2 h. The reaction mixture was diluted with aq. sat. NH₄Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 186.2 [M-*t*-Bu+H]⁺.

[0360] *tert*-butyl *cis*-3-methyl-1-(((methylsulfonyl)oxy)methyl)-6-azabicyclo[3.1.1]heptane-6-carboxylate: To a mixture of *tert*-butyl *cis*-1-(hydroxymethyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate (500 mg, 2.07 mmol) and TEA (419.31 mg, 4.14 mmol) in DCM (10 mL) at 0 °C was added MsCl (356 mg, 3.11 mmol) and DMAP (25 mg, 0.21 mmol). The mixture was warmed to 20 °C and

stirred for 2 h. The reaction mixture was diluted with aq. sat. NH_4Cl (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound.

Intermediate 50

cis-3-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid



[0361] 3-methylcycloheptanone: Solution 1: {cyclohept-2-enone (70 g, 635.48 mmol) }, {CuBr (9.12 g, 63.55 mmol) } in {THF (2100 mL) }; Solution 2: {AlMe₃ (2 M, 413.06 mL) }; Solution 1 was added by Pump 1 {S1,P1,53.744 mL/min} to flow reactor 1 {FLR1, PFA, CSTRs, 80 mL,40 °C, FLR1, PFA, CSTRs, 80 mL, 40 °C }. Solution 2 was added by Pump 2 {S2, P2, 10.256 mL/min} to flow reactor 1 {FLR1, PFA, CSTRs, 80 mL, 40 °C, FLR1, PFA, CSTRs, 80 mL, 40 °C }. Pump 1 and Pump 2 were started at the same time. The residence time of flow reactor 1 was {FLR1, 2.5 min}. The mixture was collected in a bottle containing 3 L ice water and the reaction mixture was extracted with EtOAc (3×1 L). The combined organic layers were washed with brine (1 L), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 10:1) to give the titled compound.

[0362] *cis*-7-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione and *trans*-7-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione: To a solution of 3-methylcycloheptanone (32 g, 253.57 mmol) in EtOH (240 mL) and H₂O (240 mL) at 25 °C under N₂ was added (NH₄)₂CO₃ (73.09 g, 760.72 mmol) and TMSCN (37.73 g, 380.36 mmol). The reaction mixture was heated to 65 °C and stirred for 4 h. The reaction mixture was diluted with H₂O (800 mL) and a precipitate was formed. The precipitate was filtered and the filter cake was washed with H₂O 3 times and dried under vacuum to give the titled compounds. LCMS: $m/z = 197.2$ [M+H]⁺.

[0363] *cis*-1-amino-3-methylcycloheptanecarboxylic acid and *trans*-1-amino-3-

methylcycloheptanecarboxylic acid: To a solution of *cis*-7-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione and *trans*-7-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione (42 g, 214 mmol) in H₂O (1 L) at 25 °C was added Ba(OH)₂·10H₂O (675 g, 2.14 mol). The reaction mixture was heated to 140 °C and stirred for 12 h. The reaction mixture was adjusted to pH = 3 with H₂SO₄ (6 M), filtered, and the filtrate was concentrated under reduced pressure to give the titled compounds. LCMS: m/z = 172.2 [M+H]⁺.

[0364] *cis*-methyl 1-amino-3-methylcycloheptanecarboxylate and *trans*-methyl 1-amino-3-

methylcycloheptanecarboxylate: To a solution of *cis*-1-amino-3-methylcycloheptanecarboxylic acid and *trans*-1-amino-3-methylcycloheptanecarboxylic acid (79 g, 230.68 mmol) in MeOH (600 mL) at 0 °C was added SOCl₂ (137.22 g, 1.15 mol). The reaction mixture was heated to 75 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled compounds. LCMS: m/z = 186.2 [M+H]⁺.

[0365] *cis*-methyl 3-methyl-1-(picolinamido)cycloheptanecarboxylate and *trans*-methyl 3-methyl-1-(picolinamido)cycloheptanecarboxylate:

To a solution of *cis*-methyl 1-amino-3-methylcycloheptanecarboxylate and *trans*-methyl 1-amino-3-methylcycloheptanecarboxylate (79 g, 234.53 mmol) in DCM (700 mL) at 25 °C was added picolinic acid (37.53 g, 304.89 mmol) and DIEA (151.56 g, 1.17 mol). The reaction mixture was cooled to 0 °C and T4P (253.48 g, 351.80 mmol, 50% purity in EtOAc) was added dropwise to the reaction mixture. The reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (1 L) and extracted with DCM (3 × 300 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 3:1 to 1:1) to give the titled compounds. LCMS: m/z = 291.2 [M+H]⁺.

[0366] *cis*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate and *trans*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate:

To a solution of *cis*-methyl 3-methyl-1-(picolinamido)cycloheptanecarboxylate and *trans*-methyl 3-methyl-1-(picolinamido)cycloheptanecarboxylate (22 g, 75.77 mmol) in 1,1,2,2-tetrachloroethane (700 mL) at 25 °C under N₂ was added Na₃PO₄ (37.26 g, 227.31 mmol), AgOAc (37.94 g, 227.31 mmol), BQ (4.10 g, 37.88 mmol), 1,2,3,4,5-pentafluoro-6-iodo-benzene (222.73 g, 757.69 mmol) and Pd(OAc)₂ (3.40 g, 15.15 mmol). The reaction mixture was heated to 145 °C and stirred for 12 h. The reaction mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: m/z = 289.1 [M+H]⁺.

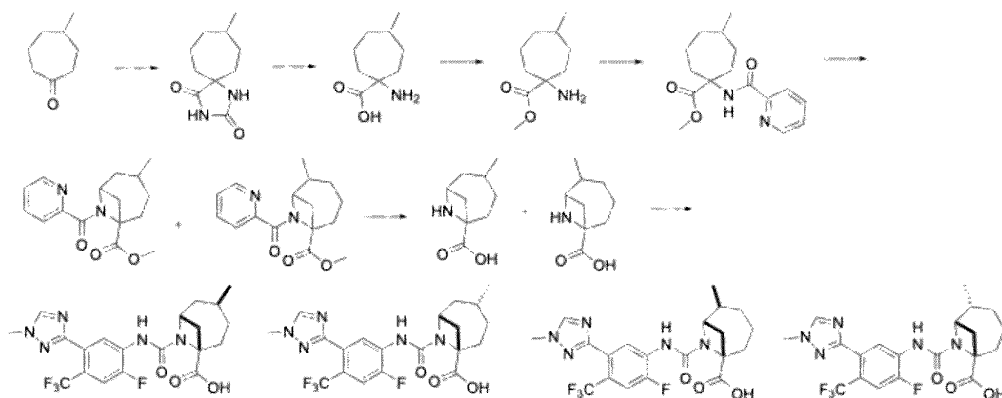
[0367] *cis*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate and *trans*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate:

The mixture of *cis*- and *trans*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate (26 g, 90.17 mmol) was purified by prep-HPLC (column: Xselect CSH C18 100 × 30 mm × 5 µm; mobile phase: A: 0.1% TFA in water, B: MeCN; B% in A: 40% over 8 min). The eluent of the two peaks were adjusted to pH = 7 with aq. sat. Na₂CO₃ and

extracted with EtOAc (3×500 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give *cis*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate (Peak 1 in HPLC) and *trans*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate (Peak 2 in HPLC).

[0368] *cis*-3-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid: To a solution of *cis*-methyl 3-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate (7.8 g, 27.05 mmol) in EtOH (150 mL) at 20°C was added NaOH (32.46 g, 811 mmol). The reaction mixture was heated to 130°C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure, the resulting residue was adjusted to pH = 2 by the addition of conc. HCl, then the reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: $m/z = 170.1$ $[\text{M}+\text{H}]^+$.

Intermediates 51 and 52



[0369] *cis*-8-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione and *trans*-8-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione: To a solution of 4-methylcycloheptanone (13 g, 103.01 mmol) in EtOH (130 mL) and H_2O (130 mL) was added TMSCN (15.33 g, 154.52 mmol) and $(\text{NH}_4)_2\text{CO}_3$ (29.69 g, 309.04 mmol) at 20°C . The mixture was stirred at 60°C for 3 h. The reaction mixture was diluted with H_2O (200 mL), the precipitate was collected by filtration, washed with H_2O and dried under reduced pressure to give the titled compounds. LCMS: $m/z = 197.2$ $[\text{M}+\text{H}]^+$.

[0370] *cis*-1-amino-4-methylcycloheptanecarboxylic acid and *trans*-1-amino-4-methylcycloheptanecarboxylic acid: To a mixture of *cis*-8-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione and *trans*-8-methyl-1,3-diazaspiro[4.6]undecane-2,4-dione (12 g, 61.15 mmol) in H_2O (400 mL) was added $\text{Ba}(\text{OH})_2$ (193 g, 611.48 mmol) at 25°C . The reaction mixture was stirred at 140°C for 12 h. The reaction mixture was adjusted to pH = 4 with 6 M H_2SO_4 at 0°C and filtered. The filtrate was concentrated under reduced pressure to give the titled compounds.

[0371] *cis*-methyl 1-amino-4-methylcycloheptanecarboxylate and *trans*-methyl 1-amino-4-methylcycloheptanecarboxylate: To a solution of *cis*-1-amino-4-methylcycloheptanecarboxylic acid and *trans*-1-amino-4-methylcycloheptanecarboxylic acid (20 g, 60.73 mmol) in MeOH (160 mL) was added dropwise SOCl_2 (36.13 g, 303.67 mmol) at 0°C under N_2 . The mixture was stirred at 75°C for 12

h. The reaction mixture was concentrated under reduced pressure to give the titled compounds. LCMS: $m/z = 186.2 [M+H]^+$.

[0372] *cis*-methyl 4-methyl-1-(picolinamido)cycloheptanecarboxylate and *trans*-methyl 4-methyl-1-(picolinamido)cycloheptanecarboxylate: To a solution of picolinic acid (18.69 g, 151.81 mmol), *cis*-methyl 1-amino-4-methylcycloheptanecarboxylate and *trans*-methyl 1-amino-4-methylcycloheptanecarboxylate (11.25 g, 60.72 mmol) in DCM (300 mL) was added dropwise DIEA (47.09 g, 364.35 mmol) and T4P (87.51 g, 121.45 mmol, 50% purity in EtOAc) at 0 °C under N₂. The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H₂O (300 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 3:1) to give the titled compounds. LCMS: $m/z = 291.2 [M+H]^+$.

[0373] *cis*-methyl 4-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate, *trans*-methyl 4-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate, *cis*-methyl 5-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate, and *trans*-methyl 5-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate: To a solution of *cis*-methyl 4-methyl-1-(picolinamido)cycloheptanecarboxylate and *trans*-methyl 4-methyl-1-(picolinamido)cycloheptanecarboxylate (2 g, 6.89 mmol) in 1,1,2,2-tetrachloroethane (60 mL) was added BQ (372 mg, 3.44 mmol), Na₃PO₄ (3.39 g, 20.66 mmol), AgOAc (3.45 g, 20.66 mmol), 1,2,3,4,5-pentafluoro-6-iodo-benzene (20.25 g, 68.88 mmol) and Pd(OAc)₂ (309 mg, 1.38 mmol) at 20 °C under N₂. The reaction solution was stirred at 140 °C for 12 h. The reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 4:1 to 3:1) to give the four titled compounds as a mixture. LCMS: $m/z = 289.1 [M+H]^+$.

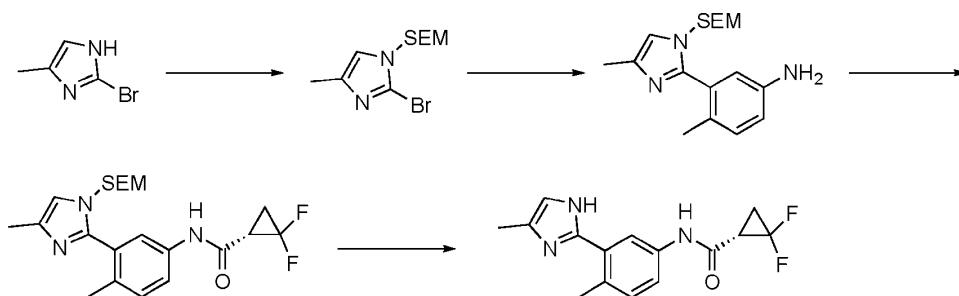
[0374] *cis*-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, *trans*-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, *cis*-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, and *trans*-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid: To a solution of *cis*-methyl 4-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate, *trans*-methyl 4-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate, *cis*-methyl 5-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate, and *trans*-methyl 5-methyl-7-picolinoyl-7-azabicyclo[4.1.1]octane-1-carboxylate (1.30 g, 4.51 mmol) in EtOH (20 mL) was added NaOH (1.80 g, 45.09 mmol) at 20 °C. The mixture was stirred at 110 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with H₂O (10 mL) and adjusted to pH = 4 with HCl (8 M) at 0 °C, then lyophilized to give the four titled compounds as a mixture. LCMS: $m/z = 170.2 [M+H]^+$.

[0375] *cis*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, *trans*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid,

and *cis*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, and *trans*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid: To a solution of triphosgene (205 mg, 0.69 mmol) in THF (10 mL) was added dropwise a solution of TEA (467 mg, 4.61 mmol) and 2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline (400 mg, 1.54 mmol) in THF (10 mL) at 0 °C under N₂. The mixture was stirred at 0 °C for 1 h. A mixture of *cis*-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, *trans*-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, *cis*-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, and *trans*-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid (2.53 g crude, 15% purity) and TEA (467 mg, 4.61 mmol) were added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 1 h, diluted with H₂O (0.5 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Welch Xtimate C18 250 × 70 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water; B: MeCN; B% in A: 10%-40%, over 17 min) to give a mixture of *cis*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, *trans*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-4-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid, and *cis*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid (peak 1 in HPLC), LCMS: *m/z* = 456.2 [M+H]⁺ (Intermediate 51) and *trans*-7-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-5-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid (peak 2 in HPLC), LCMS: *m/z* = 456.2 [M+H]⁺ (Intermediate 52).

Example A-1

(*S*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyl-1*H*-imidazol-2-yl)phenyl)cyclopropane-1-carboxamide



[0376] **2-bromo-4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole:** To a mixture of 2-bromo-4-methyl-1*H*-imidazole (1 g, 6.21 mmol) in THF (15 mL) at 0 °C under N₂ was added NaH (298.11 mg, 7.45 mmol, 60% in mineral oil). The mixture was stirred at 0 °C for 15 min, then SEMCl (1.24 g, 7.45 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, diluted with aq. sat. NH₄Cl (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The

resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:0 to 3:1) to give the titled compound. LCMS: m/z = 291.1, 293.1 $[M+H]^+$.

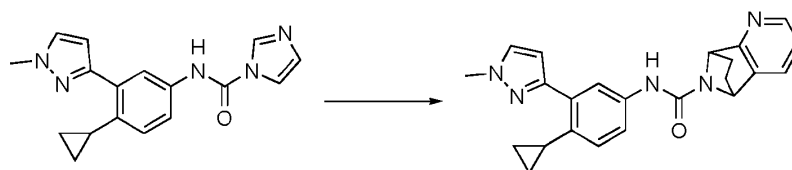
[0377] 4-methyl-3-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)aniline: To a mixture of 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (100 mg, 0.429 mmol) and 2-[(2-bromo-4-methylimidazol-1-yl)methoxy]ethyltrimethylsilane (187 mg, 0.64 mmol) in 1,4-dioxane (5 mL) and H₂O (0.5 mL) at 25 °C under N₂ was added K₂CO₃ (178 mg, 1.29 mmol) and Pd(PPh₃)₄ (50 mg, 0.043 mmol). The reaction mixture was heated to 100 °C and stirred for 12 h. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 3 : 1 to 1:1) to give the titled compound.

[0378] (S)-2,2-difluoro-N-(4-methyl-3-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)phenyl)cyclopropane-1-carboxamide: To a mixture of 4-methyl-3-[4-methyl-1-(2-trimethylsilylethoxymethyl)imidazole-2-yl]aniline (200 mg, 0.63 mmol) and (S)-2,2-difluorocyclopropanecarboxylic acid (92 mg, 0.756 mmol) in pyridine (2 mL) at 0 °C under N₂ was added EDCI (181 mg, 0.945 mmol). The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:0 to 1:1) to give the titled compound.

[0379] (S)-2,2-difluoro-N-(4-methyl-3-(4-methyl-1H-imidazol-2-yl)phenyl)cyclopropane-1-carboxamide: To a mixture of (S)-2,2-difluoro-N-[4-methyl-3-[4-methyl-1-(2-trimethylsilylethoxymethyl)imidazole-2-yl]phenyl]cyclopropanecarboxamide (180 mg, 0.427 mmol) in DCM (1.5 mL) at 25 °C under N₂ was added TFA (770 mg, 6.75 mmol). The reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 10%-40%, 8 min) to give the titled compound. LCMS: m/z = 292.2 $[M+H]^+$.

Example A-2

N-(4-cyclopropyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-5,6,7,8-tetrahydro-5,8-epiminoquinoline-9-carboxamide

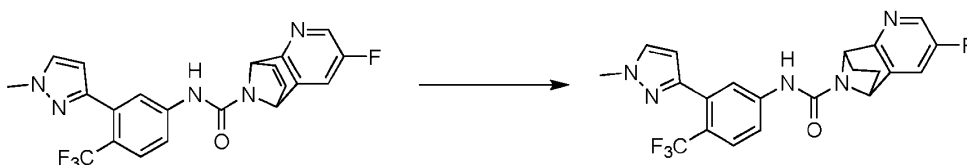


[0380] To a mixture of 3,11-diazatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene hydrochloride (30 mg, 0.162 mmol) and N-(4-cyclopropyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-1H-imidazole-1-carboxamide (50 mg, 0.163 mmol) in DCM (3 mL) at 25 °C under N₂ was added TEA (50 mg, 0.49 mmol). The mixture was heated to 50 °C and stirred for 30 min. The reaction mixture was concentrated under reduced

pressure and the resulting residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 30%-55%, 10 min) to give the titled compound. LCMS: m/z = 386.0 [M+H]⁺.

Example A-3

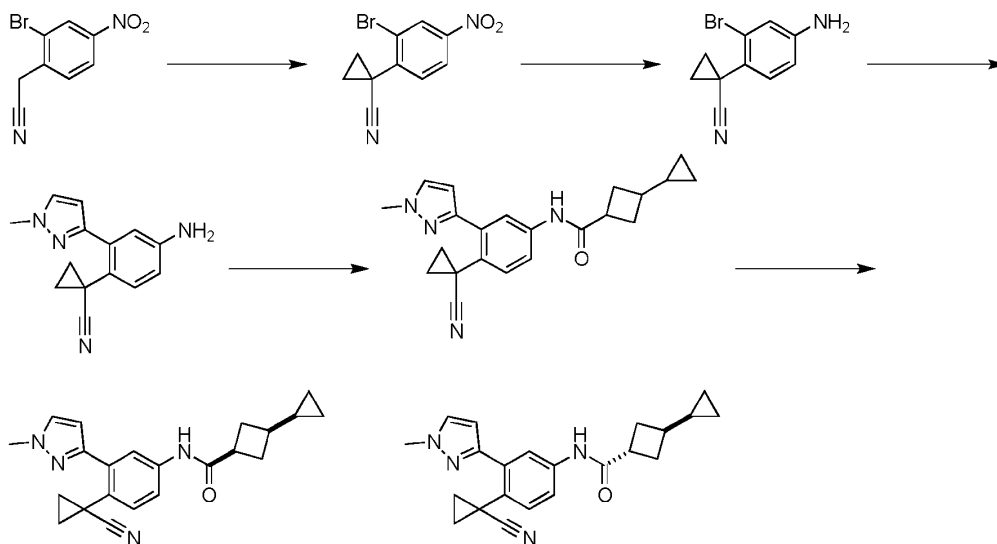
3-fluoro-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-5,8-epiminoquinoline-9-carboxamide



[0381] To a solution of 3-fluoro-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-5,8-dihydro-5,8-epiminoquinoline-9-carboxamide (5 mg, 0.12 mmol) in EtOAc (2 mL) under N₂ was added 10% Pd/C (0.5 mg). The suspension was degassed under vacuum and purged with H₂ several times. The reaction mixture was stirred under H₂ (15 psi) at 20 °C for 5 min before the reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure to give the titled compound. LCMS: m/z = 432.2 [M+H]⁺.

Examples A-4 and A-5

cis-*N*-(4-(1-cyanocyclopropyl)-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide and *trans*-*N*-(4-(1-cyanocyclopropyl)-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide



[0382] **1-(2-bromo-4-nitrophenyl)cyclopropane-1-carbonitrile:** To a mixture of 2-(2-bromo-4-nitrophenyl)acetonitrile (1.5 g, 6.25 mmol) in toluene (30 mL) and H₂O (3 mL) at 25 °C under N₂ was added KOH (3.49 g, 62.50 mmol), tetrabutylammonium bromide (403 mg, 1.25 mmol) and 1,2-

dibromoethane (2.34 g, 12.45 mmol). The mixture was heated to 75 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:MTBE = 5:1 to 1:1) to give the titled compound.

[0383] 1-(4-amino-2-bromophenyl)cyclopropane-1-carbonitrile: To a mixture of 1-(2-bromo-4-nitrophenyl)cyclopropane-1-carbonitrile (240 mg, 0.90 mmol) in EtOH (5 mL) and H₂O (1 mL) at 25 °C under N₂ was added NH₄Cl (240 mg, 4.49 mmol) and Fe (251 mg, 4.49 mmol). The mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure to provide the titled compound. LCMS: m/z = 237.1, 239.1 [M+H]⁺.

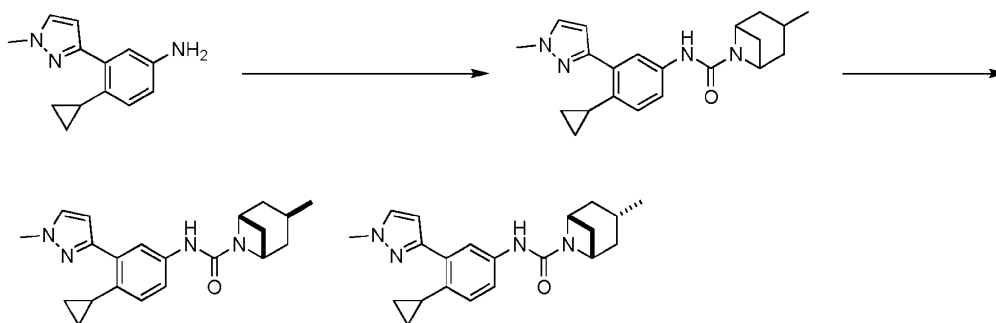
[0384] 1-(4-amino-2-(1-methyl-1H-pyrazol-3-yl)phenyl)cyclopropane-1-carbonitrile: To a mixture of 1-(4-amino-2-bromophenyl)cyclopropane-1-carbonitrile (200 mg, 0.84 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (263 mg, 1.26 mmol) in 1,4-dioxane (3 mL) and H₂O (0.3 mL) at 25 °C under N₂ was added K₂CO₃ (350 mg, 2.54 mmol) and Pd(dppf)Cl₂ (62 mg, 0.08 mmol). The reaction mixture was heated to 110 °C and stirred for 4 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 1:1) to give the titled compound. LCMS: m/z = 239.0 [M+H]⁺.

[0385] N-(4-(1-cyanocyclopropyl)-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide: To a mixture of 1-(4-amino-2-(1-methyl-1H-pyrazol-3-yl)phenyl)cyclopropane-1-carbonitrile (100 mg, 0.42 mmol) in pyridine (3 mL) at 0 °C under N₂ was added 3-cyclopropylcyclobutane-1-carboxylic acid (71 mg, 0.50 mmol) and EDCI (161 mg, 0.84 mmol). The mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 30%-60%, over 8 min) to give the titled compound. LCMS: m/z = 361.1 [M+H]⁺.

[0386] *cis*-N-(4-(1-cyanocyclopropyl)-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide (A-4) and *trans*-N-(4-(1-cyanocyclopropyl)-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide (A-5): The mixture was separated by SFC (Instrument: Waters SFC 80Q preparative SFC; Column: ChiralPak IH, 250 mm × 30 mm × 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in IPA; B% in A: 40%-40%, 4 min; Flow rate: 50 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 100 bar) to give *cis*-N-(4-(1-cyanocyclopropyl)-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide (peak 1 in SFC) Example A-4. LCMS: m/z = 361.2 [M+H]⁺ and *trans*-N-(4-(1-cyanocyclopropyl)-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-3-cyclopropylcyclobutane-1-carboxamide (peak 2 in SFC) Example A-5. LCMS: m/z = 361.2 [M+H]⁺.

Examples A-6 and A-7

cis-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide and *trans*-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide

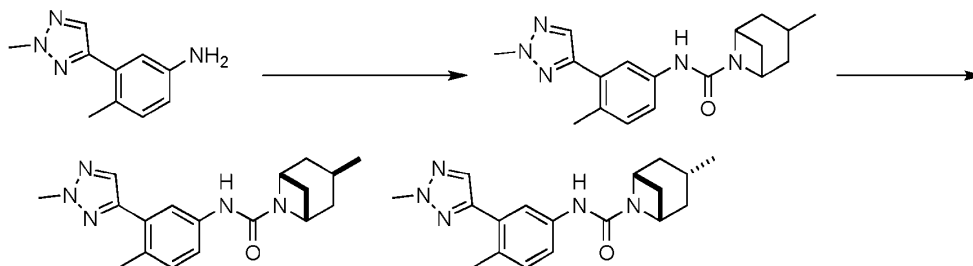


[0387] *N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a mixture of CDI (182 mg, 1.13 mmol) in DCM (3 mL) at -40°C under N_2 was added 4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)aniline (200 mg, 937.8 mL) in DCM (3 mL). The mixture was warmed to 25°C and stirred for 2 h. 3-Methyl-6-azabicyclo[3.1.1]heptane (109 mg, 1.95 mmol) in DCM (3 mL) and TEA (198 mg, 1.95 mmol) were added and the reaction mixture was stirred at 25°C for 12 h. The reaction mixture was diluted with H_2O (2 mL) and extracted with DCM (3×1 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex C18 75×30 mm $\times$ 3 μm ; mobile phase: A: 10 mM NH_4HCO_3 in water, B: MeCN; B in A: 25%-55%, 8 min) to give the titled compound. LCMS: $m/z = 351.0$ $[\text{M}+\text{H}]^+$.

[0388] *cis*-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-6) and *trans*-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-7): The mixture was separated by SFC separation (Column: REGIS(s.s) WHELK-O1, 250 mm $\times$ 30 mm $\times$ 10 μm ; Mobile phase: A: CO_2 , B: 0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ in EtOH; B% in A: 35%-35%, Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35°C ; System back pressure: 120 bar) to give *cis*-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-6. LCMS: $m/z = 351.2$ $[\text{M}+\text{H}]^+$ and *trans*-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-7. LCMS: $m/z = 351.2$ $[\text{M}+\text{H}]^+$.

Examples A-8 and A-9

cis-3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and *trans*-3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide

**[0389] 3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-**

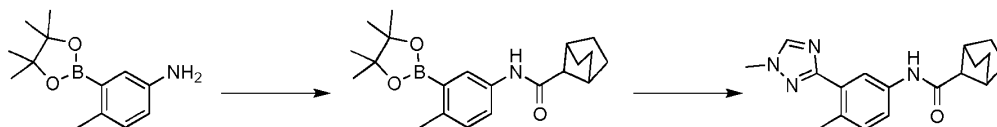
azabicyclo[3.1.1]heptane-6-carboxamide: To a mixture of CDI (103 mg, 0.64 mmol) in DCM (3 mL) at -40°C under N_2 was added 4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)aniline (100 mg, 0.53 mmol) and the mixture was stirred at -40°C for 1 h. The reaction mixture was warmed to 25°C under N_2 and 3-methyl-6-azabicyclo[3.1.1]heptane (95 mg, 0.85 mmol) (*cis*:*trans*~2:1) and TEA (129 mg, 1.28 mmol) in DCM (2 mL) were added and the mixture was stirred for 16 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO_2 , PE:EtOAc = 1:2) to give the titled compound. LCMS: $m/z = 326.0$ $[\text{M}+\text{H}]^+$.

[0390] *cis*-3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-

azabicyclo[3.1.1]heptane-6-carboxamide (A-8) and *trans*-3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-9): The mixture of diastereomers was separated by SFC (REGIS(s,s) WHELK-O1 (250 mm $\times$ 30 mm, 10 μm ; Mobile phase: A: CO_2 , B: 0.1% $\text{NH}_3\text{H}_2\text{O}$ in MeOH; B% in A: 30%-30%, 13 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35°C ; System back pressure: 120 bar)) to give *cis*-3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-8. LCMS: $m/z = 326.2$ $[\text{M}+\text{H}]^+$ and *trans*-3-methyl-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-9. LCMS: $m/z = 326.2$ $[\text{M}+\text{H}]^+$.

Example A-10

N-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)bicyclo[2.2.1]heptane-7-carboxamide

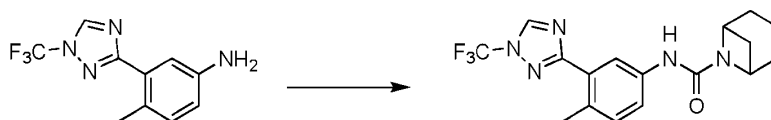


[0391] *N*-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)bicyclo[2.2.1]heptane-7-carboxamide: To a solution of 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (200 mg, 0.86 mmol) in pyridine (6 mL) at 0 °C under N₂ was added bicyclo[2.2.1]heptane-7-carboxylic acid (100 mg, 0.71 mmol) and EDCI (274 mg, 1.43 mmol). The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1 to 0:1) to give the titled compound. LCMS: *m/z* = 356.3 [M+H]⁺.

[0392] *N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)bicyclo[2.2.1]heptane-7-carboxamide (A-10): To a solution of *N*-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)bicyclo[2.2.1]heptane-7-carboxamide (50 mg, 0.14 mmol) in 1,4-dioxane (3 mL) and H₂O (0.3 mL) at 20 °C under N₂ was added 3-bromo-1-methyl-1*H*-1,2,4-triazole (27 mg, 0.17 mmol), K₂CO₃ (58 mg, 0.42 mmol) and Pd(dppf)Cl₂. The reaction mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (2 × 3 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B in A: 35%-60% B, 8 min) to give the titled compound. LCMS: *m/z* = 311.2 [M+H]⁺.

Example A-11

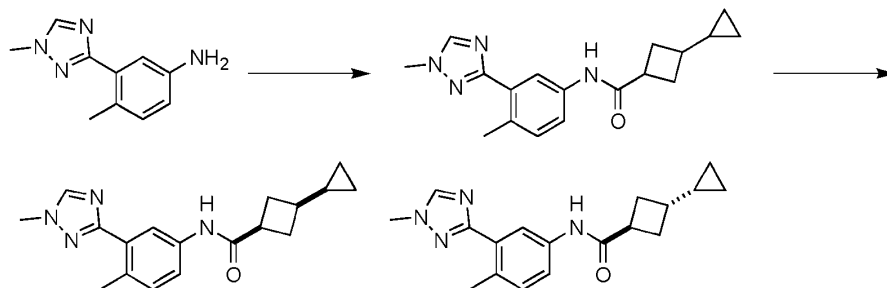
***N*-(4-methyl-3-(1-(trifluoromethyl)-1*H*-1,2,4-triazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide**



[0393] To a mixture of CDI (28 mg, 0.17 mmol) in DMF (3 mL) at -40 °C under N₂ was added a mixture of 4-methyl-3-(1-(trifluoromethyl)-1*H*-1,2,4-triazol-3-yl)aniline (50 mg, 0.5 mmol) in DMF (3 mL). The mixture was warmed to 25 °C and stirred for 1 h. Then 6-azabicyclo[3.1.1]heptane (20 mg, 0.2 mmol) in DMF (2 mL) and TEA (11 mg, 0.1 mmol) was added to the reaction mixture and the mixture was stirred for 1 h. The reaction mixture was diluted with H₂O (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 20%-50%, 8 min) to give the titled compound. LCMS: *m/z* = 366.2 [M+H]⁺.

Examples A-12 and A-13

cis-3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide and *trans*-3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide



[0394] 3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide: To a solution of 4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (56 mg, 0.29 mmol) in pyridine (2 mL) at 0 °C under N₂ was added 3-cyclopropylcyclobutane-1-carboxylic acid (50 mg, 0.36 mmol) and EDCI (114 mg, 0.59 mmol). The mixture was warmed to 20 °C and stirred for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B in A: 30%-60% B, 8 min) to give the titled compound. LCMS: *m/z* = 311.2 [M+H]⁺.

[0395] *cis*-3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide (A-12) and *trans*-3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide (A-13): The mixture of diastereomers was separated by SFC (DAICEL CHIRALPAK IC, 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 37%-37%, 19 min; Flow rate: 70 g/min; Wavelength: 220 & 254 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis*-3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide (peak 1 in SFC) Example A-12. LCMS: *m/z* = 311.2 [M+H]⁺ and *trans*-3-cyclopropyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)cyclobutane-1-carboxamide (peak 2 in SFC) Example A-13. LCMS: *m/z* = 311.2 [M+H]⁺.

Example A-14

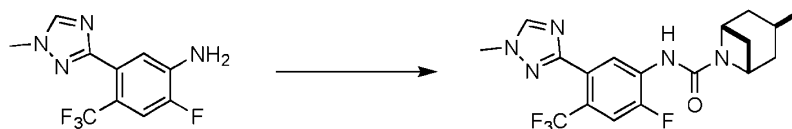
cis-*N*-(2-fluoro-4-methyl-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0396] To a mixture of *cis*-*N*-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (30 mg, 0.08 mmol) and 3-bromo-1-methyl-1*H*-1,2,4-triazole (15 mg, 0.093 mmol) in 1,4-dioxane (2 mL) and H₂O (0.2 mL) at 20 °C under N₂ was added K₂CO₃ (32 mg, 0.23 mmol) and Pd(dppf)Cl₂ (6 mg, 0.008 mmol). The reaction mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: A: NH₄HCO₃ in water, B: MeCN; B%: 20%-50%, 8 min) to give the titled compound. LCMS: *m/z* = 344.2 [M+H]⁺.

Example A-15

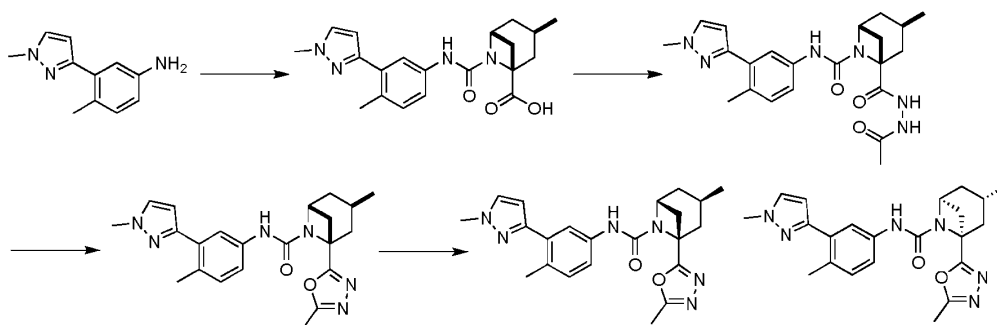
cis-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0397] To a mixture of triphosgene (29 mg, 0.10 mmol) in THF (1 mL) at 0 °C under N₂ was added TEA (58 mg, 0.58 mmol) and 2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline (50 mg, 0.19 mmol) in THF (1 mL) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was warmed to 25 °C, then *cis*-3-methyl-6-azabicyclo[3.1.1]heptane trifluoroacetate (79 mg, 0.35 mmol) was added and the mixture was stirred for 12 h. The reaction mixture was diluted with H₂O (1 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 150 × 40 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B in A: 25%-55% over 8 min) to give the titled compound. LCMS: *m/z* = 398.1 [M+H]⁺.

Examples A-16 and A-17

(1*S*,3*R*,5*R*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0398] *cis*-3-methyl-6-((4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a solution of triphosgene (317 mg, 1.07 mmol) in THF (8 mL) at 0 °C under N₂ was added a solution of TEA (865 mg, 8.55 mmol, 1.19 mL) and 4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)aniline (400 mg, 2.14 mmol) in THF (8 mL) and the mixture was stirred at 0 °C for 1 h. Then the reaction mixture was warmed to 25 °C and *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (2.62 g, 3.20 mmol, 23% purity) and TEA (432 mg, 4.27 mmol) was added then stirred for an additional 2 h. The reaction mixture was quenched by the addition of H₂O (3 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Welch Xtimate C18 250 × 70 mm × 10 μm; mobile phase: A: 0.1% NH₃H₂O, B: EtOH; B% in A: 5%-35%, 20 min) to give the titled compound. LCMS: *m/z* = 369.2 [M+H]⁺.

[0399] *cis*-1-(2-acetylhydrazine-1-carbonyl)-3-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-3-methyl-6-((4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (200 mg, 0.54 mmol) and acetylhydrazine (45 mg, 0.61 mmol) in DMF (5 mL) at 25 °C under N₂ was added HATU (258 mg, 0.68 mmol) and DIEA (211 mg, 1.63 mmol). Then the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc) to give the titled compound. LCMS: *m/z* = 425.2 [M+H]⁺.

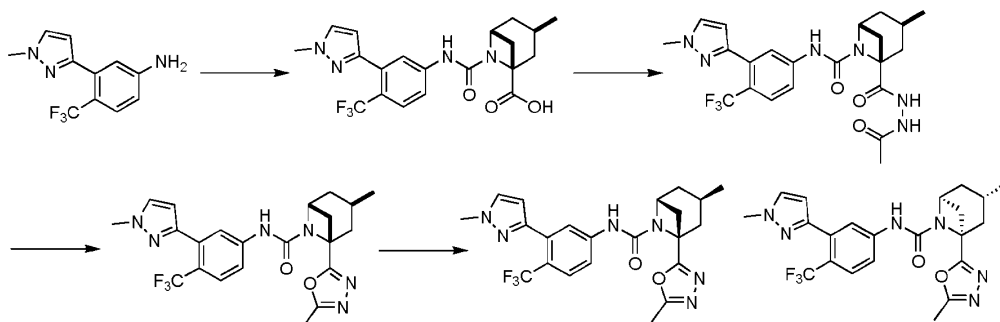
[0400] *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-1-(2-acetylhydrazine-1-carbonyl)-3-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (200 mg, 0.47 mmol) in MeCN (10 mL) at 25 °C under N₂ was added *p*-TsCl (135 mg, 0.71 mmol) and Cs₂CO₃ (614 mg, 1.88 mmol). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, DCM: MeOH = 10:1) to give the titled compound. LCMS: *m/z* = 407.2 [M+H]⁺.

[0401] (1*S*,3*R*,5*R*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK IG (250 mm × 30 mm × 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 42%-42%, 13 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-16. LCMS: *m/z* = 407.2 [M+H]⁺ and *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-

methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-17. LCMS: $m/z = 407.2$ $[M+H]^+$

Examples A-18 and A-19

(1*S*,3*R*,5*R*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0402] *cis*-3-methyl-6-((3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a mixture of triphosgene (307 mg, 1.04 mmol) in THF (15 mL) at 0 °C under N₂ was added TEA (629 mg, 6.22 mmol) and 3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)aniline (500 mg, 2.07 mmol) in THF (15 mL) dropwise. The reaction mixture was warmed to 20 °C and stirred for 1 h. Then to the mixture was added 3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (2.90 g, 3.74 mmol, 23% purity) and stirred for 1 h. The reaction mixture was diluted with H₂O (5 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Phenomenex luna C18 250 × 70 mm × 10 μm; mobile phase: A: NH₄HCO₃ in water, B: MeCN; B% in A: 10%-40%, 20 min) to give the titled compound. LCMS: $m/z = 423.2$ $[M+H]^+$.

[0403] *cis*-1-(2-acetylhydrazine-1-carbonyl)-3-methyl-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-3-methyl-6-((3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (360 mg, 0.85 mmol) in DMF (10 mL) at 0 °C under N₂ was added acetylhydrazine (94 mg, 1.28 mmol), DIEA (220 mg, 1.70 mmol) and HATU (648 mg, 1.70 mmol). The reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with DCM:MeOH (v:v = 10:1) = (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, DCM:MeOH = 10:1) to give the titled compound. LCMS: $m/z = 479.2$ $[M+H]^+$.

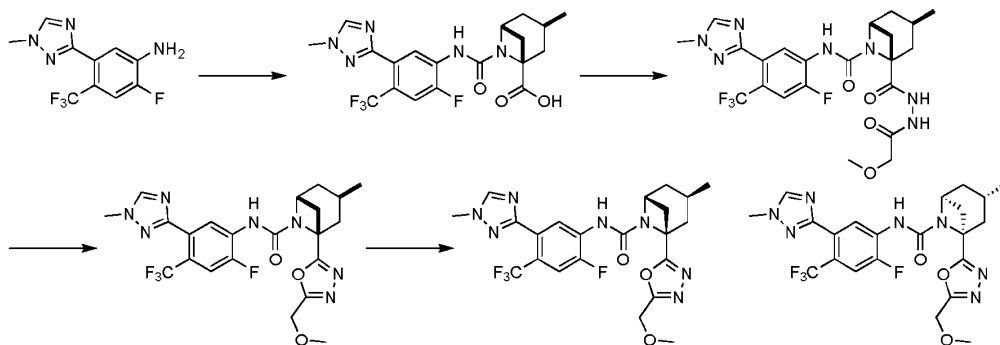
[0404] *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-1-(2-acetylhydrazine-1-carbonyl)-3-methyl-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-

azabicyclo[3.1.1]heptane-6-carboxamide (150 mg, 0.31 mmol) in MeCN (5 mL) at 25 °C under N₂ was added *p*-TsCl (89 mg, 0.47 mmol) and Cs₂CO₃ (408 mg, 1.25 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, DCM:MeOH = 10:1) to give the titled compound. LCMS: *m/z* = 461.2 [M+H]⁺.

[0405] (1*S*,3*R*,5*R*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: The mixture of enantiomers was separated by SFC (ChiralPak IH 250 mm × 30 mm × 10 μm; mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B % in A: 20%-20%, 14 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-18. LCMS: *m/z* = 461.1 [M+H]⁺ and *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-19. LCMS: *m/z* = 461.1 [M+H]⁺.

Examples A-20 and A-21

(1*S*,3*R*,5*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0406] *cis*-6-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a mixture of triphosgene (257 mg, 0.86 mmol) in THF (15 mL) at 0 °C under N₂ was added 2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)aniline (450 mg, 1.73 mmol) and TEA (525 mg, 5.19 mmol) in THF (15 mL) dropwise. The mixture was warmed to 20 °C and stirred for 1 h. Then the reaction was cooled to 0 °C and *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (1.34 g, 2.08 mmol, 23% purity) in THF (15 mL)

and TEA (525 mg, 5.19 mmol) were added. The mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was quenched by the addition of H₂O (2 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Phenomenex C18 80 × 40 mm × 3 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B in A: 10%-40% B, 8 min) to give the titled compound. LCMS: m/z = 442.1 [M+H]⁺.

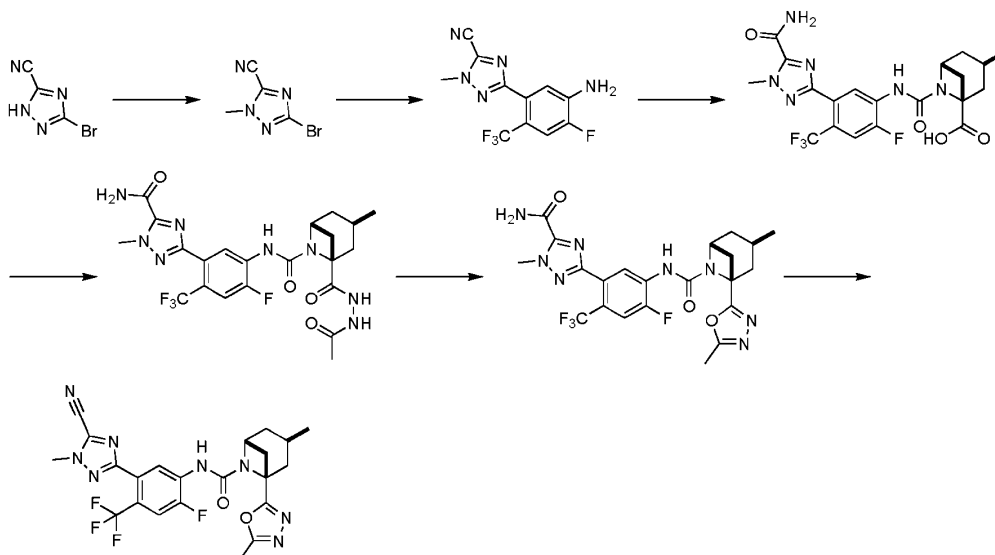
[0407] *cis-N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(2-(2-methoxyacetyl)hydrazine-1-carbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-6-((2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (250 mg, 0.57 mmol) in DMF (5 mL) at 25 °C under N₂ was added 2-methoxyacetohydrazide (88 mg, 0.85 mmol), DIEA (220 mg, 1.70 mmol) and HATU (431 mg, 1.13 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: m/z = 528.1 [M+H]⁺.

[0408] *cis-N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a mixture of *cis-N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(2-(2-methoxyacetyl)hydrazine-1-carbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (150 mg, 0.28 mmol) in MeCN (5 mL) at 20 °C under N₂ was added Cs₂CO₃ (371 mg, 1.14 mmol) and *p*-TsCl (81 mg, 0.43 mmol). The reaction mixture was stirred at 20 °C for 2 h, diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: m/z = 510.1 [M+H]⁺.

[0409] (1*S*,3*R*,5*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK IG, 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 50%-50%, 15 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis-N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) (Example A-20). LCMS: m/z = 510.1 [M+H]⁺ and *cis-N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) (Example A-21). LCMS: m/z = 510.1 [M+H]⁺.

Example A-22

cis-N-(5-(5-cyano-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0410] 3-bromo-1-methyl-1*H*-1,2,4-triazole-5-carbonitrile: To a mixture of 3-bromo-1*H*-1,2,4-triazole-5-carbonitrile (500 mg, 2.89 mmol) in DMF (5 mL) at 25 °C was added K₂CO₃ (599 mg, 4.34 mmol) and MeI (615 mg, 4.34 mmol) and the mixture was stirred for 12 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 3:1 to 1:1) to give the titled compound. LCMS: *m/z* = 187.0, 189.0 [M+H]⁺.

[0411] 3-(5-amino-4-fluoro-2-(trifluoromethyl)phenyl)-1-methyl-1*H*-1,2,4-triazole-5-carbonitrile: To a mixture of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (1.17 g, 3.85 mmol) and 3-bromo-1*H*-1,2,4-triazole-5-carbonitrile (600 mg, 3.21 mmol) in 1,4-dioxane (8 mL) and H₂O (2 mL) at 25 °C under N₂ was added K₂CO₃ (887 mg, 6.42 mmol) and Pd(dppf)Cl₂ (235 mg, 0.32 mmol). The reaction mixture was heated to 100 °C and stirred for 4 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1 to 0:1) to give the titled compound. LCMS: *m/z* = 286.1 [M+H]⁺.

[0412] *cis*-6-((5-(5-carbamoyl-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a mixture of triphosgene (88 mg, 0.3 mol) in THF (5 mL) at 0 °C under N₂ was added 3-(5-amino-4-fluoro-2-(trifluoromethyl)phenyl)-1-methyl-1*H*-1,2,4-triazole-5-carbonitrile (170 mg, 0.6 mmol) and TEA (181

mg, 1.79 mmol) dropwise. The mixture was warmed to 25 °C and stirred for 1 h. Then *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (Intermediate 34) (450 mg, 0.71 mmol, 24% purity) and TEA (301 mg, 2.97 mmol) were added to the mixture and stirred for 2 h. The reaction mixture was diluted with H₂O (5 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Phenomenex C18 80 × 40 mm × 3 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 10%-40%, 8 min) to give the titled compound. LCMS: *m/z* = 485.1 [M+H]⁺.

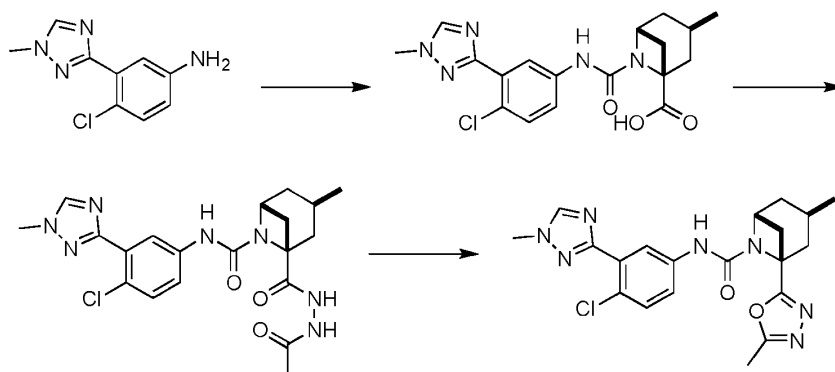
[0413] *cis*-1-(2-acetylhydrazine-1-carbonyl)-*N*-(5-(5-carbamoyl-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-6-((5-(5-carbamoyl-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (70 mg, 0.13 mmol) and acetylhydrazine (19 mg, 0.26 mmol) in DMF (2 mL) at 25 °C was added DIEA (67 mg, 0.51 mmol) and HATU (73 mg, 0.19 mmol) and the mixture was stirred for 1 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 541.1 [M+H]⁺.

[0414] *cis*-*N*-(5-(5-carbamoyl-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-1-(2-acetylhydrazine-1-carbonyl)-*N*-(5-(5-carbamoyl-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (70 mg, 0.13 mmol) in MeCN (4 mL) at 25 °C was added Cs₂CO₃ (169 mg, 0.52 mmol) and *p*-TsCl (37 mg, 0.19 mmol) and the mixture was stirred for 1 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 523.1 [M+H]⁺.

[0415] *cis*-*N*-(5-(5-cyano-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-*N*-(5-(5-carbamoyl-1-methyl-1*H*-1,2,4-triazol-3-yl)-2-fluoro-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (80 mg, 0.15 mmol) in 1,4-dioxane (1 mL) at 0 °C under N₂ was added pyridine (61 mg, 0.77 mmol) and TFAA (64 mg, 0.31 mmol). The reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 30%-60%, over 8 min) to give the titled compound. LCMS: *m/z* = 505.2 [M+H]⁺.

Example A-23

cis-N-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0416] *cis*-6-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a solution of bis(trichloromethyl) carbonate (142 mg, 0.48 mmol) in THF (6 mL) at 0 °C under N₂ was added 4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (200 mg, 0.96 mmol) and TEA (291 mg, 2.88 mmol) in THF (6 mL). The reaction mixture was warmed to 25 °C and stirred for 1 h. Then *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (Intermediate 34) (606 mg, 0.94 mmol, 24% purity) and TEA (259 mg, 2.56 mmol) were added and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of H₂O (2 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Phenomenex luna C18 250 × 70 mm × 15 μm; mobile phase: A: 0.2 % FA in water, B: MeCN; B% in A: 20%-50%, 20 min) to give the titled compound. LCMS: *m/z* = 390.1 [M+H]⁺.

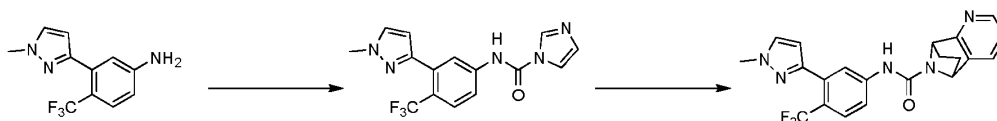
[0417] *cis*-1-(2-acetylhydrazine-1-carbonyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-6-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (195 mg, 0.5 mmol) in DMF (2 mL) at 20 °C under N₂ was added acetylhydrazine (56 mg, 0.75 mmol), DIEA (129 mg, 1 mmol) and HATU (380 mg, 1 mmol). The reaction mixture was stirred for 2 h. The mixture was diluted with H₂O (10 mL) and extracted with DCM:MeOH (v:v = 10:1) (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 446.1 [M+H]⁺.

[0418] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-23): To a solution of *cis*-1-(2-acetylhydrazine-1-carbonyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (450 mg, 1.01 mmol, crude) in MeCN (8 mL) at 20 °C was added *p*-TsCl (289 mg, 1.51 mmol) and Cs₂CO₃ (1.32 g, 4.04 mmol). The reaction mixture was stirred for 2 h, diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers

were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Waters Xbridge Prep OBD C18 $150 \times 40 \text{ mm} \times 10 \mu\text{m}$; mobile phase: A: 10 mM NH_4HCO_3 in water, B: MeCN; B% in A: 30%-45%, 8 min) and further purified by prep-TLC (SiO_2 , EtOAc) to give the titled compound. LCMS: $m/z = 428.1$ $[\text{M}+\text{H}]^+$.

Example A-24

N-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-5,8-epiminoquinoline-9-carboxamide



[0419] *N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-1*H*-imidazole-1-carboxamide:

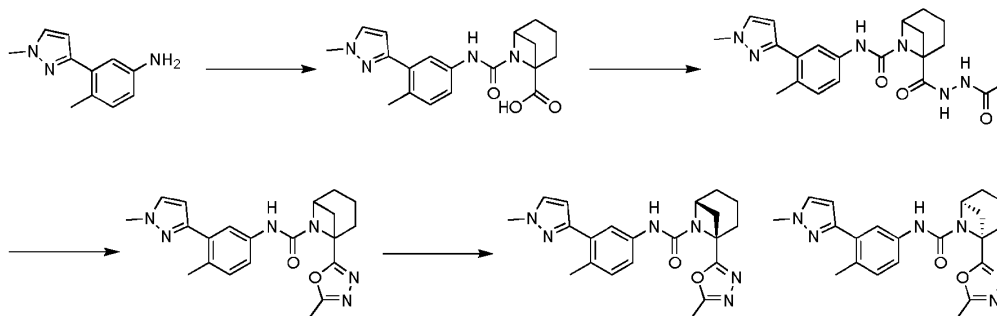
To a solution of CDI (40 mg, 0.25 mmol) in DCM (2 mL) at 0 °C under N_2 was added a mixture of 3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)aniline (50 mg, 0.21 mmol) in DCM (2 mL) dropwise. The mixture was warmed to 30 °C and stirred for 24 h before using the solution directly in the next step.

[0420] *N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-5,8-epiminoquinoline-9-carboxamide:

To a solution of *N*-(3-(1-methyl-1*H*-pyrazol-3-yl)-4-(trifluoromethyl)phenyl)-1*H*-imidazole-1-carboxamide (69 mg, 0.21 mmol) in DCM (2 mL) at 20 °C under N_2 was added 5,6,7,8-tetrahydro-5,8-epiminoquinoline hydrochloride (41 mg, 0.23 mmol) and TEA (63 mg, 0.62 mmol). The reaction mixture was heated to 50 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (Phenomenex C18 $80 \times 40 \text{ mm} \times 3 \mu\text{m}$; mobile phase: A: 10 mM NH_4HCO_3 in water, B: MeCN; B% in A: 20%-50% 8 min) to give the titled compound. LCMS: $m/z = 414.2$ $[\text{M}+\text{H}]^+$.

Examples A-25 and A-26

(1*S*,5*R*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,5*S*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0421] 6-((4-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid:

To a solution of CDI (1.04 g, 6.41 mmol) in DCM (15 mL) -20 °C under N_2 was added

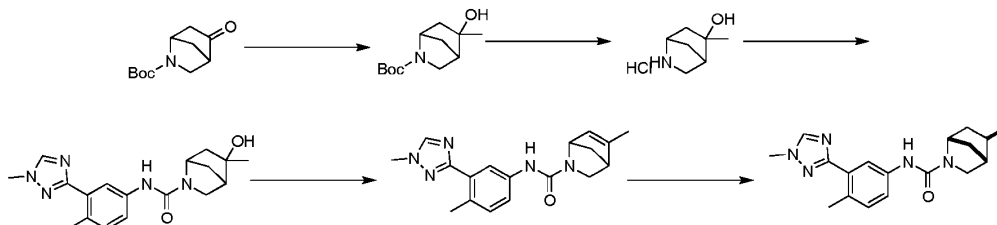
a mixture of 4-methyl-3-(1-methyl-1H-pyrazol-3-yl)aniline (1.00 g, 5.34 mmol) in DCM dropwise. The reaction mixture was warmed to 25 °C and stirred for 3 h. Then 6-azabicyclo[3.1.1]heptane-1-carboxylic acid (4.51 g, 6.41 mmol, 20% purity) was added to above mixture and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with H₂O (2 mL) then concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Welch Xtimate C18 250 × 70 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water; B: MeCN; B% in A: 0%-30%, over 20 min) to provide the titled compound. LCMS: m/z = 355.3 [M+H]⁺.

[0422] 1-(2-acetylhydrazine-1-carbonyl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of 6-((4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (400 mg, 1.13 mmol) in DMF (8 mL) at 0 °C under N₂ was added acetylhydrazine (125 mg, 1.69 mmol), DIEA (292 mg, 2.26 mmol) and HATU (858 mg, 2.26 mmol). The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EE (EtOAc:EtOH = 3:1) = 1:1 to 1:2) to give the titled compound. LCMS: m/z = 411.3 [M+H]⁺.

[0423] 1-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of 1-(2-acetylhydrazine-1-carbonyl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (250 mg, 0.61 mmol) in MeCN (12 mL) at 25 °C under N₂ was added Cs₂CO₃ (794 mg, 2.44 mmol) and *p*-TsCl (174 mg, 0.91 mmol) and the reaction mixture was stirred for 2 h. The mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 1:2) to give the titled compound. LCMS: m/z = 393.2 [M+H]⁺.

[0424] (1*S*,5*R*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,5*S*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: The mixture of enantiomers was separated by SFC (DAICEL CHIRALCEL IG (250 mm × 30 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 50%-50%, 14 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give 1-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-25. LCMS: m/z = 393.2 [M+H]⁺ and 1-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-26. LCMS: m/z = 393.2 [M+H]⁺

Example A-27

***cis*-5-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide**

[0425] *tert*-butyl 5-hydroxy-5-methyl-2-azabicyclo[2.2.1]heptane-2-carboxylate: To a solution of *tert*-butyl 5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (2.5 g, 11.83 mmol) in THF (25 mL) at 0 °C under N₂ was added MeMgBr (3 M in Et₂O, 6 mL) and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of aq. sat. NH₄Cl (25 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound.

[0426] 5-methyl-2-azabicyclo[2.2.1]heptan-5-ol hydrochloride: To a solution of *tert*-butyl 5-hydroxy-5-methyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (500 mg, 2.20 mmol) in EtOAc (5 mL) at 20 °C was added HCl/EtOAc (4 M, 20 mL) and the mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 128.2 [M+H]⁺.

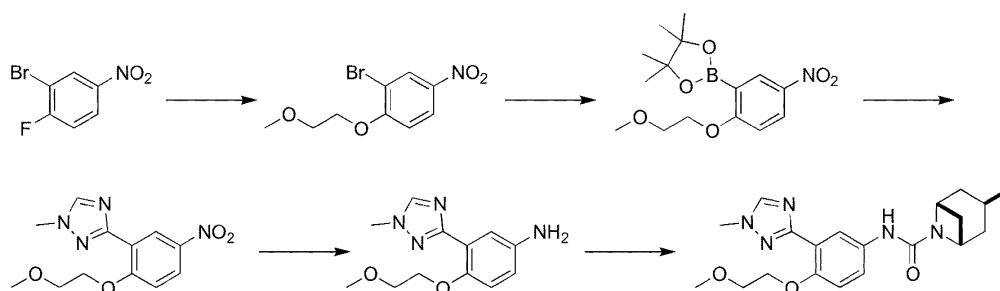
[0427] 5-hydroxy-5-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide: To a mixture of triphosgene (551 mg, 1.86 mmol) in THF (5 mL) at 0 °C under N₂ was added a mixture of TEA (1.13 g, 11.16 mmol) and 4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (700 mg, 3.72 mmol) in THF (10 mL). The reaction mixture was stirred at 0 °C for 1 h. Then a solution of TEA (1.13 g, 11.16 mmol) and 5-methyl-2-azabicyclo[2.2.1]heptan-5-ol hydrochloride (609 mg, 3.72 mmol) in THF (10 mL) was added at 0 °C. The resulting mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM:*i*-PrOH (v:v = 3:1) (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 342.2 [M+H]⁺.

[0428] 5-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxamide: To a solution of 5-hydroxy-5-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide (600 mg, 1.76 mmol) in DCM (10 mL) at 0 °C under N₂ was added SOCl₂ (418 mg, 3.51 mmol) and TEA (88.17 mg, 8.79 mmol). The reaction mixture was warmed to 20 °C and stirred for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (MeOH:EtOAc = 0:1 to 10:1) to give the titled compound. LCMS: *m/z* = 324.2 [M+H]⁺.

[0429] *cis*-5-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide (A-27): To a mixture of 5-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-2-azabicyclo[2.2.1]hept-5-ene-2-carboxamide (150 mg, 0.46 mmol) in EtOH (15 mL) under N₂ was added 10% Pd/C (150 mg, 0.06 mmol). The suspension was degassed under vacuum and purged with H₂ several times. The reaction mixture was stirred at 20 °C for 16 h under H₂ (15 psi), filtered through a Celite® pad, the filtrate was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 20%-50% B, 8.0 min) and further purified by prep-TLC (SiO₂, PE:(EtOAc:EtOH = 3:1) = 1:1) to give the titled compound as a mixture of enantiomers. LCMS: *m/z* = 326.2 [M+H]⁺.

Example A-28

cis-*N*-(4-(2-methoxyethoxy)-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0430] 2-bromo-1-(2-methoxyethoxy)-4-nitrobenzene: To a solution of 2-methoxyethan-1-ol (1.7 g, 22.73 mmol) in DMF (40 mL) at 0 °C under N₂ was added NaH (909 mg, 22.73 mmol, 60% in mineral oil) and the mixture was stirred at 0 °C for 30 min. 2-Bromo-1-fluoro-4-nitrobenzene (5 g, 22.73 mmol) was added to the reaction mixture at 0 °C, the mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was quenched by the addition of aq. sat. NH₄Cl (100 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1) to give the titled compound.

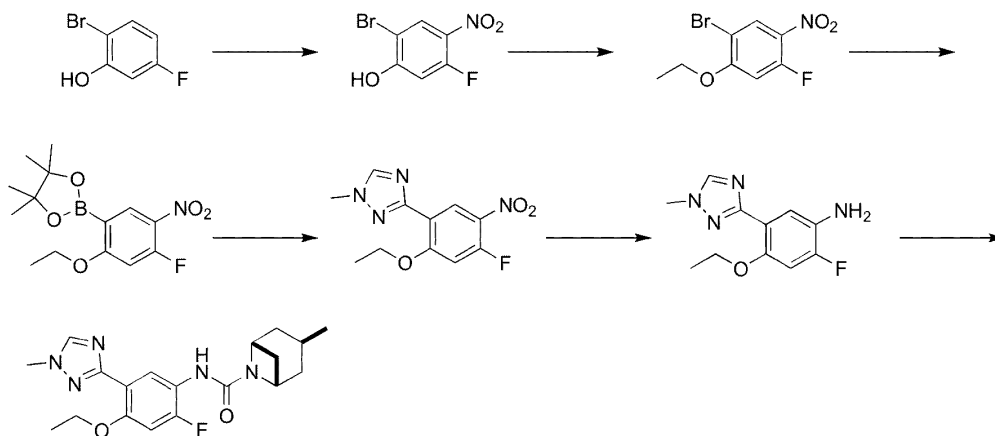
[0431] 2-(2-(2-methoxyethoxy)-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a solution of 2-bromo-1-(2-methoxyethoxy)-4-nitrobenzene (2 g, 7.24 mmol) in 1,4-dioxane (25 mL) at 20 °C under N₂ was added 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.60 g, 18.11 mmol), KOAc (2.13 g, 21.73 mmol) and Pd(dppf)Cl₂ (530 mg, 0.72 mmol). The reaction mixture was heated to 90 °C and stirred for 6 h, filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1) and slurried with PE to give the titled compound.

[0432] 3-(2-(2-methoxyethoxy)-5-nitrophenyl)-1-methyl-1*H*-1,2,4-triazole: To a solution of 2-(2-(2-methoxyethoxy)-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 1.55 mmol) in 1,4-dioxane (8 mL) and H₂O (1 mL) at 20 °C under N₂ was added 3-bromo-1-methyl-1*H*-1,2,4-triazole (376 mg, 2.32 mmol), Xphos (148 mg, 0.31 mmol), K₃PO₄ (821 mg, 3.87 mmol) and cataCXium A Pd G3 (113 mg, 0.15 mmol). The reaction mixture was heated to 90 °C and stirred for 12 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc) to give the titled compound. LCMS: $m/z = 279.2$ [M+H]⁺.

[0433] 4-(2-methoxyethoxy)-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline: To a solution of 3-(2-(2-methoxyethoxy)-5-nitrophenyl)-1-methyl-1*H*-1,2,4-triazole (150 mg, 0.54 mmol) in EtOH (4 mL) and H₂O (1 mL) was added Fe (151 mg, 2.70 mmol) and NH₄Cl (144 mg, 2.70 mmol) at 20 °C under N₂. The mixture was stirred at 70 °C for 2 h. The reaction mixture was filtered through a Celite[®] pad and the filtrate was concentrated under reduced pressure. The crude product was triturated in DCM:MeOH (V:V = 10:1) (10 mL) to give the titled compound. LCMS: $m/z = 249.2$ [M+H]⁺.

[0434] *cis*-*N*-(4-(2-methoxyethoxy)-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-28): To a mixture of triphosgene (36 mg, 0.12 mmol) in THF (2 mL) at 0 °C under N₂ was added a mixture of TEA (73.36 mg, 72 mmol) and 4-(2-methoxyethoxy)-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (60 mg, 0.24 mmol) in THF (2 mL). The reaction mixture was stirred at 0 °C for 1 h. Then a solution of TEA (73.36 mg, 0.72 mmol) and *cis*-3-methyl-6-azabicyclo[3.1.1]heptane (54 mg, 0.48 mmol) in THF (2 mL) was added at 0 °C and the reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 20%-50% B, 8.0 min) to give the titled compound. LCMS: $m/z = 386.2$ [M+H]⁺.

Example A-29

***cis*-N-(4-ethoxy-2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide**

[0435] 2-bromo-5-fluoro-4-nitrophenol: To a mixture of 2-bromo-5-fluorophenol (5 g, 26.18 mmol) in DCM (30 mL) at 0 °C under N₂ was added H₂SO₄ (15 mL) and fuming HNO₃ (1.73 g, 27.49 mmol). The reaction mixture was stirred at 0 °C for 2 h, diluted with H₂O (20 mL) and extracted with MTBE (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 5:1) to give the titled compound.

[0436] 1-bromo-2-ethoxy-4-fluoro-5-nitrobenzene: To a mixture of 2-bromo-5-fluoro-4-nitrophenol (1.4 g, 5.93 mmol) in MeCN (15 mL) at 25 °C under N₂ was added K₂CO₃ (2.05 g, 14.83 mmol) and EtI (2.78 g, 17.80 mmol). The reaction mixture was heated to 60 °C and stirred for 12 h, diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound.

[0437] 2-(2-ethoxy-4-fluoro-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a mixture of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.83 g, 7.20 mmol) and 1-bromo-2-ethoxy-4-fluoro-5-nitrobenzene (760 mg, 2.88 mmol) in 1,4-dioxane (15 mL) at 25 °C under N₂ was added Pd(dppf)Cl₂ (211 mg, 0.3 mmol) and KOAc (847 mg, 8.63 mmol). The reaction mixture was heated to 100 °C and stirred for 6 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 to 1:1) to give the titled compound.

[0438] 3-(2-ethoxy-4-fluoro-5-nitrophenyl)-1-methyl-1*H*-1,2,4-triazole: To a mixture of 2-(2-ethoxy-4-fluoro-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (440 mg, 1.41 mmol) and 3-bromo-1-

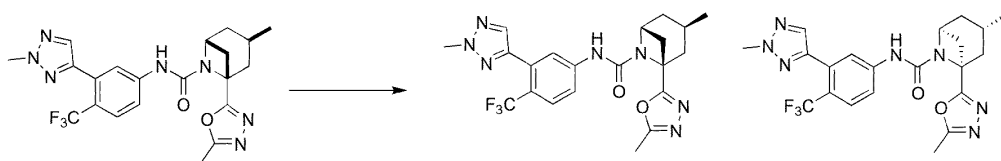
methyl-1*H*-1,2,4-triazole (344 mg, 2.12 mmol) in 1,4-dioxane (5 mL) and H₂O (0.5 mL) at 25 °C under N₂ was added XPhos (135 mg, 0.3 mmol), K₃PO₄ (751 mg, 3.54 mmol) and cataCXium A Pd G3 (103 mg, 0.1 mmol). The reaction mixture was heated to 90 °C and stirred for 12 h, diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 1:1) to give the titled compound. LCMS: *m/z* = 267.1 [M+H]⁺.

[0439] 4-ethoxy-2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline: To a mixture of 3-(2-ethoxy-4-fluoro-5-nitrophenyl)-1-methyl-1*H*-1,2,4-triazole (190 mg, 0.7 mmol) in EtOH (4 mL) and H₂O (1 mL) at 25 °C under N₂ was added Fe (199 mg, 3.57 mmol) and NH₄Cl (191 mg, 3.57 mmol). The mixture was heated to 80 °C and stirred for 2 h, filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound.

[0440] *cis*-*N*-(4-ethoxy-2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a mixture of triphosgene (31.40 mg, 0.106 mmol) in THF (1 mL) at 0 °C under N₂ was added 4-ethoxy-2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (50 mg, 0.215 mmol) and TEA (42.83 mg, 0.423 mmol) and the reaction mixture was stirred at 0 °C for 1 h. *cis*-3-Methyl-6-azabicyclo[3.1.1]heptane (38.59 mg, 0.38 mmol) was added to the reaction mixture at 0 °C. Subsequently, the reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30mm × 3 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 20%-50% 8.0 min) to give the titled compound. LCMS: *m/z* = 374.2 [M+H]⁺.

Examples A-30 and A-31

(1*S*,3*R*,5*R*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide

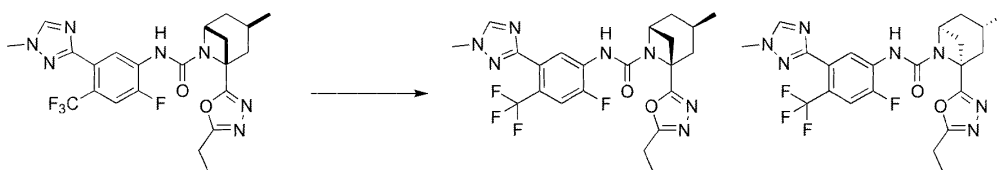


[0441] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK IC (250 mm × 50 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃·H₂O in IPA; B% in A: 40%-45%, 8 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-30.

LCMS: $m/z = 462.2$ $[M+H]^+$ and *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(2-methyl-2*H*-1,2,3-triazol-4-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC)
Example A-31. LCMS: $m/z = 462.2$ $[M+H]^+$.

Examples A-32 and A-33

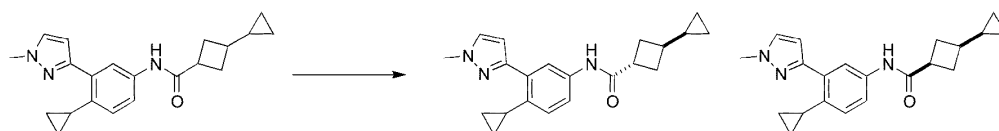
(1*S*,3*R*,5*R*)-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0442] The mixture of enantiomers was separated by SFC (column: DAICEL CHIRALPAK IG (250 mm $\times$ 30 mm $\times$ 10 μ m; Mobile phase: A: CO₂, B: 0.1% NH₃.H₂O in IPA; B% in A: 50%, 8 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis*-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-32. LCMS: $m/z = 494.2$ $[M+H]^+$ and *cis*-1-(5-ethyl-1,3,4-oxadiazol-2-yl)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-33. LCMS: $m/z = 494.2$ $[M+H]^+$

Examples A-34 and A-35

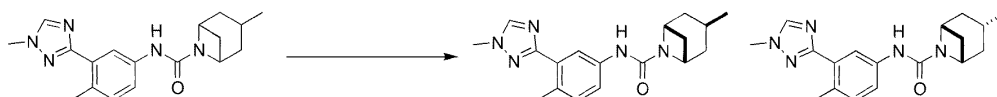
***trans*-3-cyclopropyl-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)cyclobutane-1-carboxamide and *cis*-3-cyclopropyl-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)cyclobutane-1-carboxamide**



[0443] The mixture of diastereomers was separated by SFC (DAICEL CHIRALPAK AD (250 mm $\times$ 30 mm $\times$ 10 μ m); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 33%-33%, 7 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *trans*-3-cyclopropyl-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)cyclobutane-1-carboxamide (peak 1 in SFC) Example A-34, LCMS: $m/z = 336.2$ $[M+H]^+$ and *cis*-3-cyclopropyl-*N*-(4-cyclopropyl-3-(1-methyl-1*H*-pyrazol-3-yl)phenyl)cyclobutane-1-carboxamide (peak 2 in SFC) Example A-35, LCMS: $m/z = 336.2$ $[M+H]^+$.

Examples A-36 and A-37

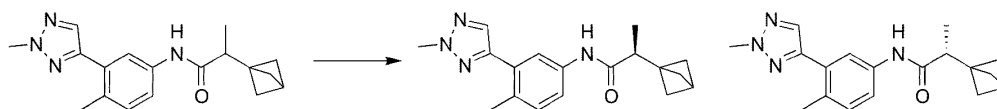
cis-3-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and *trans*-3-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0444] The mixture of diastereomers was separated by SFC (REGIS (s,s) WHELK-O1 250 mm × 30 mm, 10 μm; mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 45%-45%, 12 min, Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis*-3-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) Example A-36. LCMS: *m/z* = 326.2 [M+H]⁺ and *trans*-3-methyl-*N*-(4-methyl-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) Example A-37. LCMS: *m/z* = 326.2 [M+H]⁺.

Examples A-38 and A-39

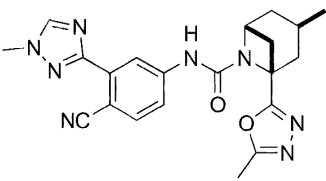
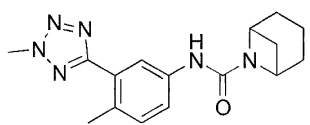
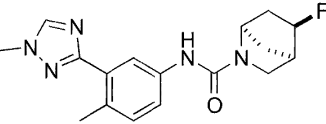
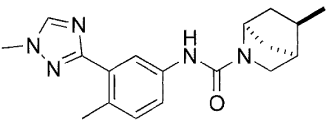
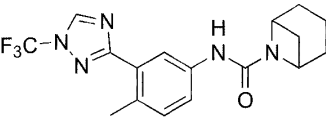
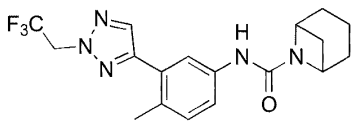
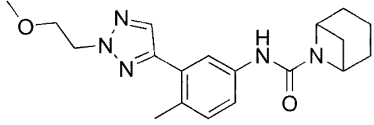
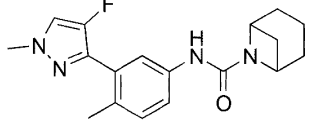
(*S*)-2-(bicyclo[1.1.1]pentan-1-yl)-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)propanamide and (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)propanamide

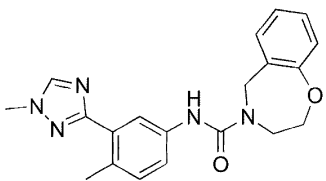
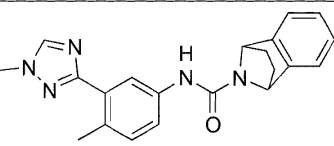
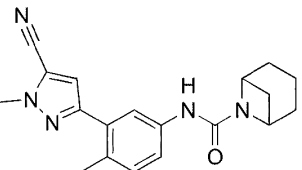
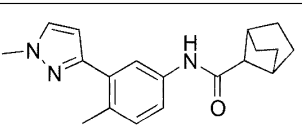
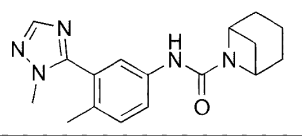
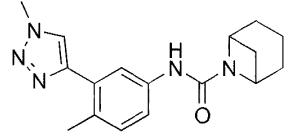
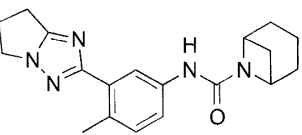
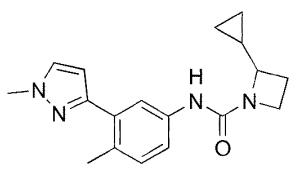


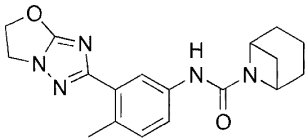
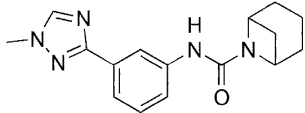
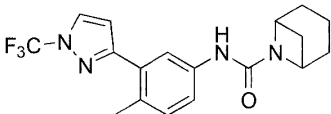
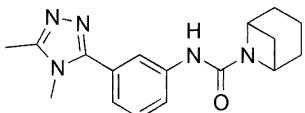
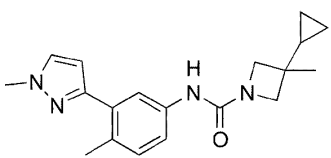
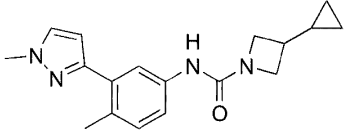
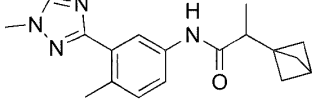
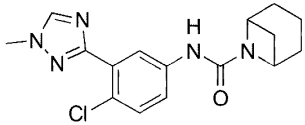
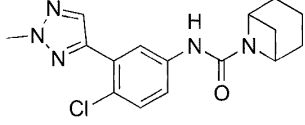
[0445] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK AD, 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in IPA; B% in A: 25%-25%, 9 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give 2-(bicyclo[1.1.1]pentan-1-yl)-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)propanamide (peak 1 in SFC) Example A-38, LCMS: *m/z* = 311.2 [M+H]⁺ and 2-(bicyclo[1.1.1]pentan-1-yl)-*N*-(4-methyl-3-(2-methyl-2*H*-1,2,3-triazol-4-yl)phenyl)propanamide (peak 2 in SFC) Example A-39, LCMS: *m/z* = 311.2 [M+H]⁺.

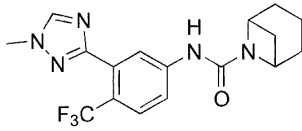
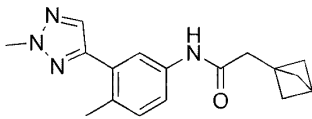
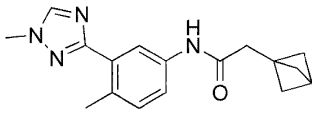
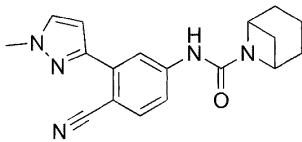
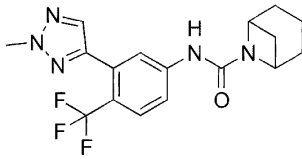
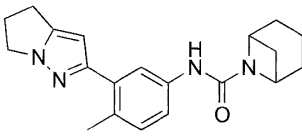
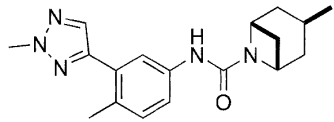
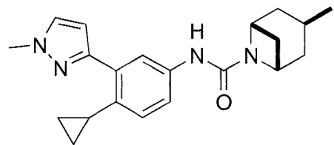
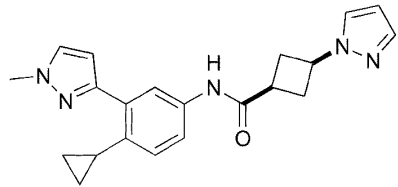
[0446] The following compounds were, or can be, made via similar procedures as those described herein.

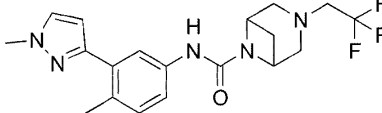
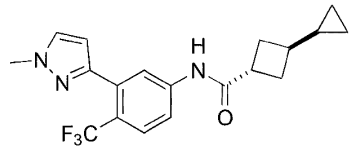
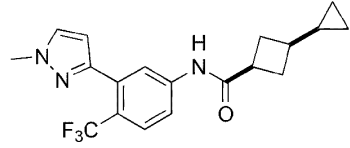
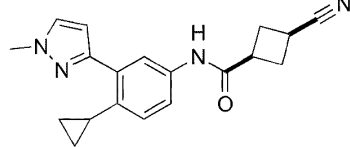
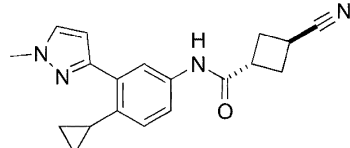
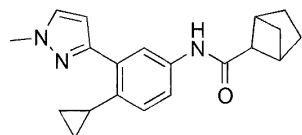
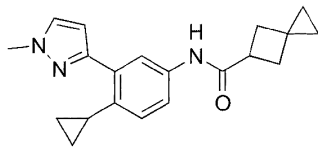
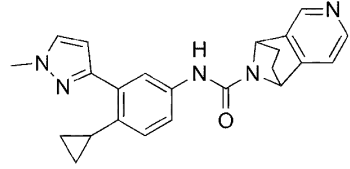
Ex.	Structure	LCMS
A-40	Single unknown enantiomer prepared from Intermediate 34	<i>m/z</i> = 427.0 [M+H] ⁺

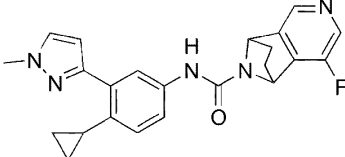
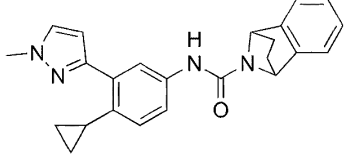
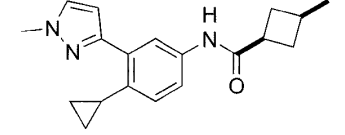
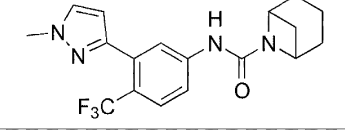
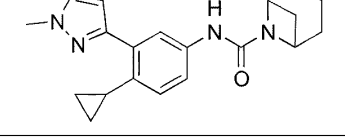
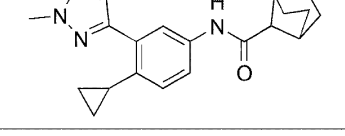
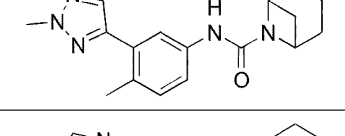
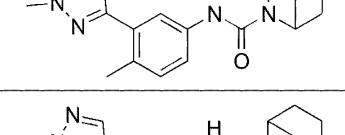
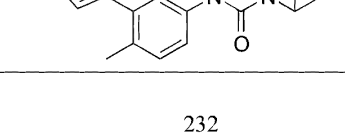
Ex.	Structure	LCMS
A-41	 Single unknown enantiomer prepared from Intermediate 34	m/z = 419.1 [M+H] ⁺
A-42		m/z = 313.2 [M+H] ⁺
A-43	 Mixture of enantiomers	m/z = 330.2 [M+H] ⁺
A-44	 Mixture of enantiomers	m/z = 326.2 [M+H] ⁺
A-45		m/z = 366.2 [M+H] ⁺
A-46		m/z = 380.1 [M+H] ⁺
A-47		m/z = 356.2 [M+H] ⁺
A-48		m/z = 329.1 [M+H] ⁺

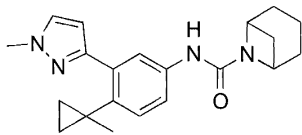
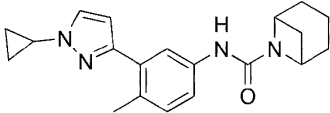
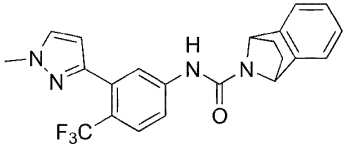
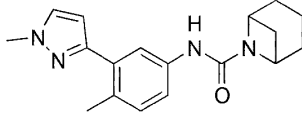
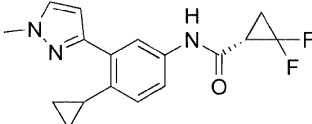
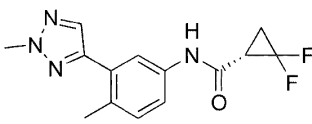
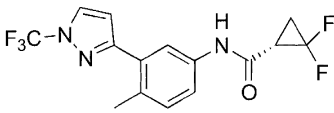
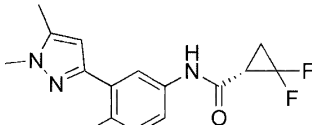
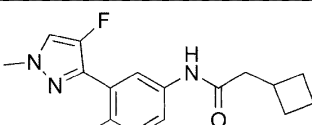
Ex.	Structure	LCMS
A-49		m/z = 364.2 [M+H] ⁺
A-50		m/z = 360.2 [M+H] ⁺
A-51		m/z = 336.2 [M+H] ⁺
A-52		m/z = 310.2 [M+H] ⁺
A-53		m/z = 312.2 [M+H] ⁺
A-54		m/z = 312.2 [M+H] ⁺
A-55		m/z = 338.2 [M+H] ⁺
A-56	 Mixture of enantiomers	m/z = 311.2 [M+H] ⁺

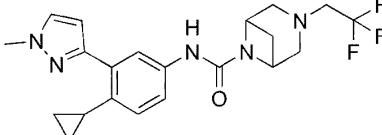
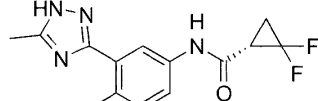
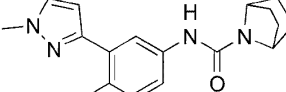
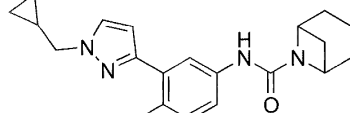
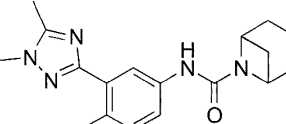
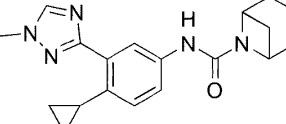
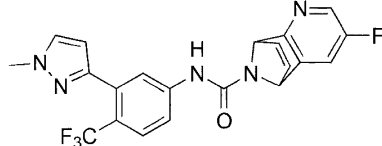
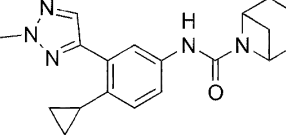
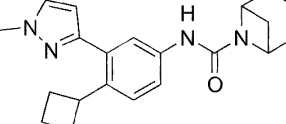
Ex.	Structure	LCMS
A-57		m/z = 340.2 [M+H] ⁺
A-58		m/z = 298.2 [M+H] ⁺
A-59		m/z = 365.1 [M+H] ⁺
A-60		m/z = 312.2 [M+H] ⁺
A-61		m/z = 325.2 [M+H] ⁺
A-62		m/z = 311.2 [M+H] ⁺
A-63	 Mixture of enantiomers	m/z = 311.2 [M+H] ⁺
A-64		m/z = 332.1 [M+H] ⁺
A-65		m/z = 332.1 [M+H] ⁺

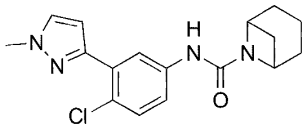
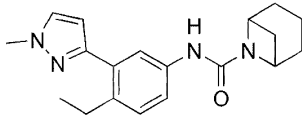
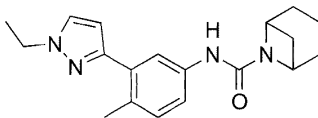
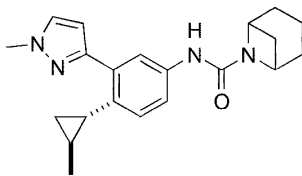
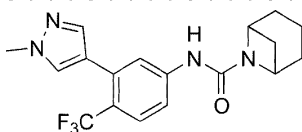
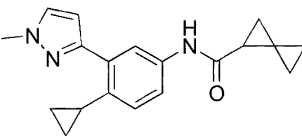
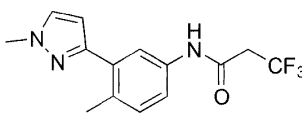
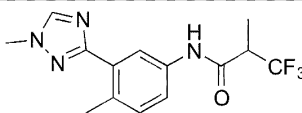
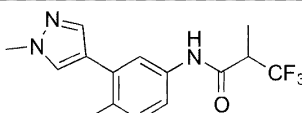
Ex.	Structure	LCMS
A-66		m/z = 366.2 [M+H] ⁺
A-67		m/z = 297.2 [M+H] ⁺
A-68		m/z = 297.2 [M+H] ⁺
A-69		m/z = 322.2 [M+H] ⁺
A-70		m/z = 366.2 [M+H] ⁺
A-71		m/z = 337.2 [M+H] ⁺
A-72		m/z = 326.2 [M+H] ⁺
A-73		m/z = 351.3 [M+H] ⁺
A-74		m/z = 362.2 [M+H] ⁺

Ex.	Structure	LCMS
A-75		m/z = 394.2 [M+H] ⁺
A-76		m/z = 364.2 [M+H] ⁺
A-77		m/z = 364.2 [M+H] ⁺
A-78		m/z = 321.2 [M+H] ⁺
A-79		m/z = 321.2 [M+H] ⁺
A-80		m/z = 322.2 [M+H] ⁺
A-81		m/z = 322.2 [M+H] ⁺
A-82	 Mixture of enantiomers	m/z = 386.0 [M+H] ⁺

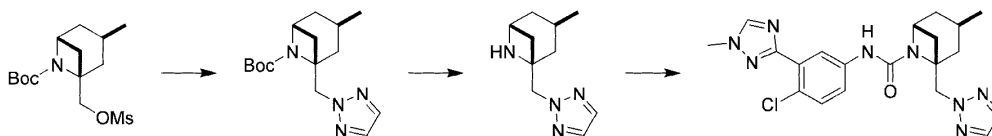
Ex.	Structure	LCMS
A-83	 Mixture of enantiomers	$m/z = 404.2$ [M+H] ⁺
A-84		$m/z = 385.3$ [M+H] ⁺
A-85		$m/z = 310.2$ [M+H] ⁺
A-86		$m/z = 365.2$ [M+H] ⁺
A-87		$m/z = 337.2$ [M+H] ⁺
A-88		$m/z = 336.2$ [M+H] ⁺
A-89		$m/z = 312.2$ [M+H] ⁺
A-90		$m/z = 312.2$ [M+H] ⁺
A-91		$m/z = 311.2$ [M+H] ⁺

Ex.	Structure	LCMS
A-92		m/z = 351.2 [M+H] ⁺
A-93		m/z = 337.2 [M+H] ⁺
A-94		m/z = 413.2 [M+H] ⁺
A-95		m/z = 311.2 [M+H] ⁺
A-96		m/z = 318.2 [M+H] ⁺
A-97		m/z = 293.1 [M+H] ⁺
A-98		m/z = 346.1 [M+H] ⁺
A-99		m/z = 306.2 [M+H] ⁺
A-100		m/z = 302.2 [M+H] ⁺

Ex.	Structure	LCMS
A-101		m/z = 420.2 [M+H] ⁺
A-102		m/z = 293.1 [M+H] ⁺
A-103		m/z = 311.2 [M+H] ⁺
A-104		m/z = 351.2 [M+H] ⁺
A-105		m/z = 326.2 [M+H] ⁺
A-106		m/z = 338.2 [M+H] ⁺
A-107	 Mixture of enantiomers	m/z = 430.2 [M+H] ⁺
A-108		m/z = 338.2 [M+H] ⁺
A-109		m/z = 351.3 [M+H] ⁺

Ex.	Structure	LCMS
A-110		m/z = 331.1 [M+H] ⁺
A-111		m/z = 325.2 [M+H] ⁺
A-112		m/z = 325.2 [M+H] ⁺
A-113	 Mixture of enantiomers	m/z = 351.3 [M+H] ⁺
A-114		m/z = 365.2 [M+H] ⁺
A-115	 Mixture of enantiomers	m/z = 308.2 [M+H] ⁺
A-116		m/z = 298.1 [M+H] ⁺
A-117	 Mixture of enantiomers	m/z = 313.1 [M+H] ⁺
A-118	 Mixture of enantiomers	m/z = 312.1 [M+H] ⁺

Example A-119

***cis*-1-((2*H*-1,2,3-triazol-2-yl)methyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide**

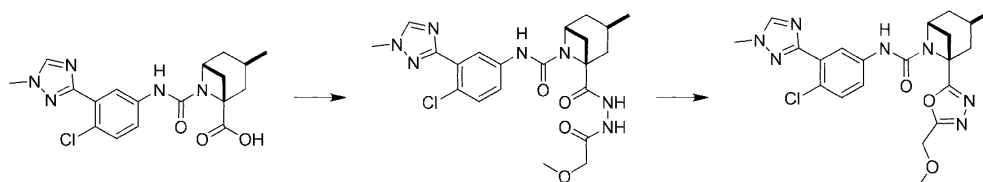
[0447] *cis*-*tert*-butyl 1-((2*H*-1,2,3-triazol-2-yl)methyl)-3-methyl-6-azabicyclo[3.1.1] heptane-6-carboxylate: To a solution of 1*H*-1,2,3-triazole (259 mg, 3.76 mmol) in DMSO (10 mL) at 0 °C was added *t*-BuONa (361 mg, 3.76 mmol) and *cis*-*tert*-butyl 1-(((methylsulfonyl)oxy)methyl)-6-azabicyclo[3.1.1] heptane-6-carboxylate (Intermediate 49) (600 mg, 1.88 mmol). The reaction mixture was heated to 120 °C and stirred for 12 h. The reaction mixture was diluted with aq. sat. NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 3:1) to give the titled compound.

[0448] *cis*-1-((2*H*-1,2,3-triazol-2-yl)methyl)-3-methyl-6-azabicyclo[3.1.1]heptane: To a solution of *cis*-*tert*-butyl 1-((2*H*-1,2,3-triazol-2-yl)methyl)-3-methyl-6-azabicyclo[3.1.1] heptane-6-carboxylate (120 mg, 0.41 mmol) and 2,6-dimethylpyridine (330 mg, 3.08 mmol) in DCM (2 mL) at 0 °C under N₂ was added dropwise a solution of TMSOTf (274 mg, 1.23 mmol) in DCM (1 mL). The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 193.4 [M+H]⁺.

[0449] *cis*-1-((2*H*-1,2,3-triazol-2-yl)methyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-119): To a solution of triphosgene (65 mg, 0.22 mmol) in THF (3 mL) at 0 °C was added a solution of 4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (100 mg, 0.48 mmol) and TEA (146 mg, 1.85 mmol) in THF (3 mL). The reaction mixture was stirred at 0 °C for 1 h. TEA (104 mg, 1.02 mmol) and *cis*-1-((2*H*-1,2,3-triazol-2-yl)methyl)-3-methyl-6-azabicyclo[3.1.1]heptane (79 mg, 0.41 mmol) were added and the reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 × 30 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 25%-60% over 8 min) to give the titled compound. LCMS: *m/z* = 427.2 [M+H]⁺.

Example A-120

***cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide**

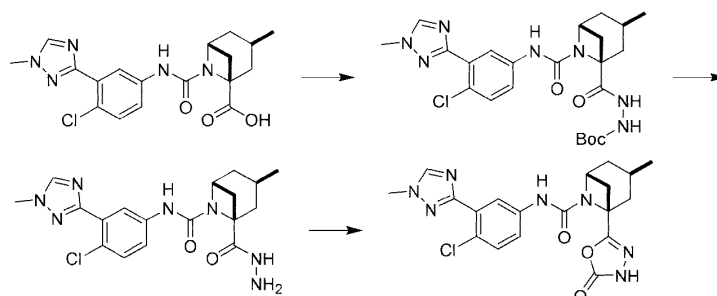


[0450] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-methoxyacetyl)hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-6-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (described in Example A-23) (450 mg, 0.92 mmol), 2-methoxyacetylhydrazine (288 mg, 2.77 mmol) in DMF (8 mL) at 20 °C under N₂ was added HATU (702 mg, 1.85 mmol) and DIEA (358 mg, 2.77 mmol) and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with DCM:MeOH = 10:1 (3 × 10 mL). The organic phases were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 476.0 [M+H]⁺.

[0451] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-120): To a solution of *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-methoxyacetyl)hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (500 mg, 1.05 mmol) in THF (10 mL) at 25 °C was added Burgess reagent (1.50 g, 6.30 mmol). The reaction mixture was heated to 60 °C and stirred for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with DCM:MeOH = 10:1 (3 × 10 mL). The organic phase was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex Gemini C18 75 × 40 mm × 5 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 15%-45% over 8 min) to give the titled compound. LCMS: *m/z* = 458.2 [M+H]⁺.

Example A-121

cis-N-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0452] *tert*-butyl 2-(*cis*-6-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carbonyl)hydrazinecarboxylate: To a solution of *cis*-6-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (described in Example A-23) (200 mg, 0.51 mmol) in DMF (5 mL) at 20 °C under N₂ was added *tert*-butyl hydrazine carboxylate (203 mg, 1.54 mmol), DIEA (199 mg, 1.54 mmol), and HATU (390 mg, 1.03 mmol). The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 1:1 to 0:1) to give the titled compound. LCMS: *m/z* = 504.0 [M+H]⁺.

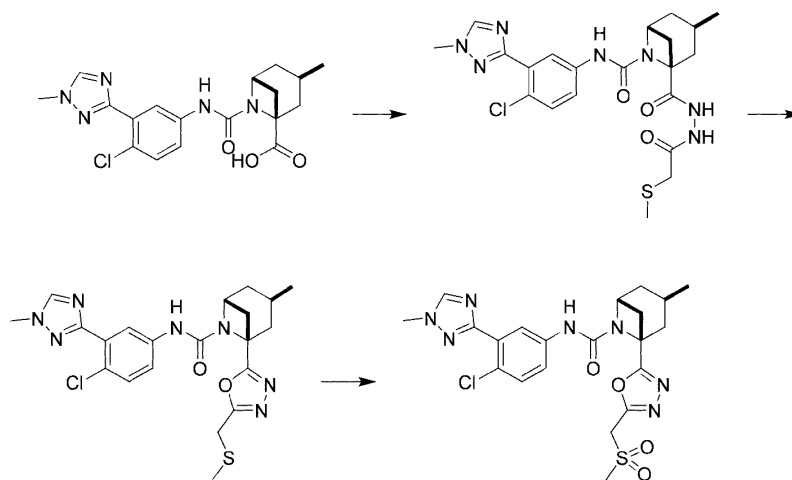
[0453] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *tert*-butyl 2-(*cis*-6-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carbonyl)hydrazinecarboxylate (550 mg, 0.43 mmol) in DCM (2 mL) at 20 °C was added TFA (307 mg, 2.69 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was adjusted to pH = 7–8 by aq. sat. NaHCO₃ at 0 °C and extracted with DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex Gemini C18 75 × 40 mm × 5 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 5%-30% over 8 min) to give the titled compound. LCMS: *m/z* = 403.9 [M+H]⁺.

[0454] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-121): To a solution of *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (38 mg, 0.09 mmol) in DCM (2 mL) at 20 °C was added CDI (23 mg, 0.14 mmol). The reaction mixture was stirred at 20 °C for 3 h and then the reaction mixture was

diluted with H₂O (2 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex Gemini C18 75 × 40 mm × 5 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 5%-30% over 8 min) and prep-TLC (DCM:MeOH = 10:1) to give the titled compound. LCMS: m/z = 430.1 [M+H]⁺.

Example A-122

***cis-N*-[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]-3-methyl-1-[5-(methylsulfonylmethyl)-1,3,4-oxadiazol-2-yl]-6-azabicyclo[3.1.1]heptane-6-carboxamide**



[0455] *cis-N*-[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]-3-methyl-1-[(2-methylsulfonylacetyl)amino]carbamoyl]-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-6-[[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]carbamoyl]-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (described in Example A-23) (300 mg, 0.76 mmol) in DMF (6 mL) at 20 °C under N₂ was added 2-methylsulfonylacetylhydrazine (277 mg, 2.31 mmol), DIEA (298 mg, 2.31 mmol) and HATU (585 mg, 1.54 mmol). The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 2:1 to 0:1) to give the titled compound. LCMS: m/z = 492.2 [M+H]⁺.

[0456] *cis-N*-[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]-3-methyl-1-[5-(methylsulfonylmethyl)-1,3,4-oxadiazol-2-yl]-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis-N*-[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]-3-methyl-1-[(2-methylsulfonylacetyl)amino]carbamoyl]-6-azabicyclo[3.1.1]heptane-6-carboxamide (110 mg, 0.22 mmol) in THF (2 mL) at 20 °C was added Burgess reagent (426 mg, 1.79 mmol). The reaction mixture was heated to 65 °C and stirred for 3 h. The reaction mixture was diluted with H₂O (6 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and

concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, DCM:MeOH = 10:1) to give the titled compound. LCMS: m/z = 474.1 [M+H]⁺.

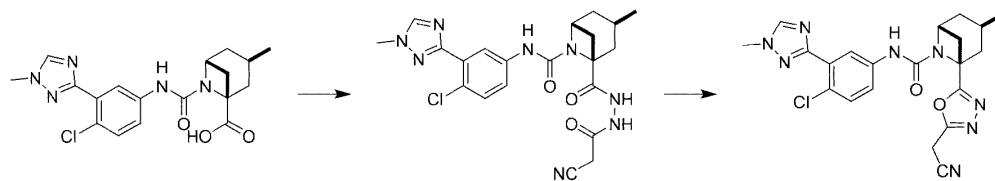
[0457] *cis-N*-[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]-3-methyl-1-[5-

(methylsulfonylmethyl)-1,3,4-oxadiazol-2-yl]-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-122):

To a solution of *cis-N*-[4-chloro-3-(1-methyl-1,2,4-triazol-3-yl)phenyl]-3-methyl-1-[5-(methylsulfonylmethyl)-1,3,4-oxadiazol-2-yl]-6-azabicyclo[3.1.1]heptane-6-carboxamide (40 mg, 0.084 mmol) in DCM (1 mL) at 0 °C was added *m*-CPBA (51 mg, 0.25 mmol, 85% w/w). The reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was quenched by addition of aq. sat. Na₂SO₃ (3 mL) and extracted with DCM (3 × 3 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex Gemini C18 75 × 40 mm × 5 μm; mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 10%-40% over 8 min) to give the titled compound. LCMS: m/z = 506.1 [M+H]⁺.

Example A-123

***cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(cyanomethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide**



[0458] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-

cyanoacetyl)hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide:

To a solution of *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-cyanoacetyl)hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (described in Example A-23) (200 mg, 0.51 mmol) and 2-cyanoacetylhydrazine (254 mg, 2.57 mmol) in DMF (4 mL) at 25 °C was added HATU (390 mg, 1.03 mmol) and DIEA (199 mg, 1.54 mmol). The reaction mixture was stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, DCM:MeOH = 10:1) to give the titled compound. LCMS: m/z = 471.1 [M+H]⁺.

[0459] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(cyanomethyl)-1,3,4-

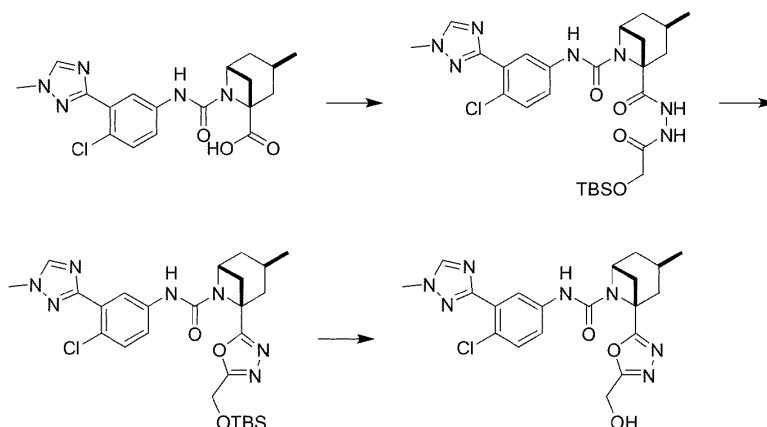
oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-123):

To a solution of *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-cyanoacetyl)hydrazinecarbonyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (100 mg, 0.10 mmol) in THF (2 mL) at 25 °C was added DMAP (65 mg, 0.53 mmol) and *p*-TsCl (24 mg, 0.12 mmol). The reaction mixture was heated to 50 °C and stirred for 12 h under N₂. The reaction mixture was diluted with H₂O (5 mL) and extracted with

DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: A: 0.2% FA in water; B: MeCN; B% in A: 10%-40% over 8 min) and further purified by prep-TLC (SiO₂, DCM:MeOH = 10:1) to give the titled compound. LCMS: m/z = 453.1 [M+H]⁺.

Example A-124

cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0460] *cis*-1-(2-(((*tert*-butyldimethylsilyl)oxy)acetyl)hydrazinecarbonyl)-*N*-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-6-((4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (described in Example A-23) (1.5 g, 2.69 mmol) in DMF (10 mL) at 25 °C under N₂ was added 2-(((*tert*-butyldimethylsilyl)oxy)acetylhydrazine (825 mg, 4.04 mmol), DIEA (1.04 g, 8.08 mmol) and HATU (2.05 g, 5.39 mmol). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with DCM:MeOH = 10:1 (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE/(EtOAc:EtOH = 3:1) = 1:0 to 1:1) to give the titled compound. LCMS: m/z = 576.1 [M+H]⁺.

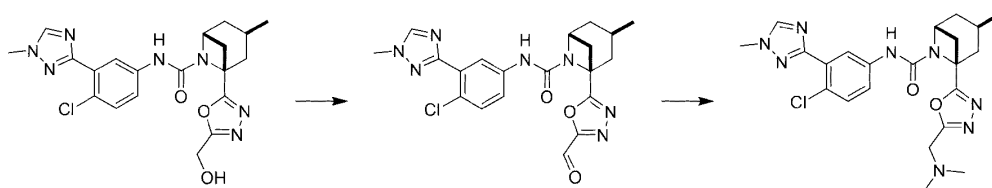
[0461] *cis*-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3,4-oxadiazol-2-yl)-*N*-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-1-(2-(((*tert*-butyldimethylsilyl)oxy)acetyl)hydrazinecarbonyl)-*N*-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (1.45 g, 2.52 mmol) in THF (30 mL) at 25 °C was added Burgess reagent (4.80 g, 20.13 mmol). The reaction mixture was heated to 60 °C and stirred for 1 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over

anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE/EtOAc = 1:0 to 1:1) to give the titled compound. LCMS: m/z = 558.1 [M+H]⁺.

[0462] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-124): To a solution of *cis*-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,3,4-oxadiazol-2-yl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (550 mg, 0.98 mmol) in MeOH (15 mL) at 25 °C was added KF (286 mg, 4.93 mmol). The reaction mixture was heated to 65 °C and stirred for 3 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The resulting residue was diluted with H₂O (10 mL) and extracted with DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, EtOAc) to give the titled compound. LCMS: m/z = 444.0 [M+H]⁺.

Example A-125

***cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-((dimethylamino)methyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide**

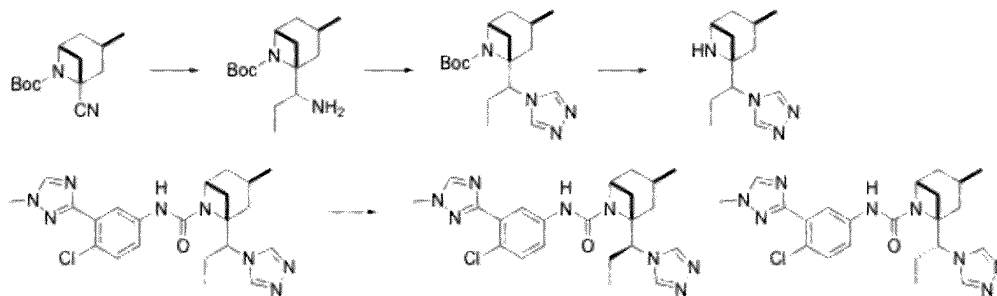


[0463] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-formyl-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide Example A-124 (95 mg, 0.21 mmol) in DCM (2 mL) at 20 °C was added DMP (145 mg, 0.34 mmol). The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was quenched by addition of aq. sat. NaHCO₃ (2 mL), filtered, and the filtrate was extracted with DCM:MeOH = 10:1 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, EtOAc) to give the titled compound.

[0464] *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-((dimethylamino)methyl)-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-125): To a solution of dimethylamine (0.54 mmol, 0.27 mL, 2M in MeOH) and *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-formyl-1,3,4-oxadiazol-2-yl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (30 mg, 0.067 mmol) in MeOH (2 mL) at 25 °C was added HOAc (6 mg, 0.10 mmol). The reaction mixture was stirred for 3 h, then NaBH₃CN (17 mg, 0.27 mmol) was added to the reaction mixture and the reaction mixture was stirred 12 h. The reaction mixture was filtered, concentrated under reduced

pressure, and the resulting residue was purified by prep-HPLC (column: Phenomenex luna C18 100 × 40 mm × 5 μm; mobile phase: A: 0.2% FA in water, B: MeCN; B% in A: 1%-35% over 8 min) to give the titled compound. LCMS: $m/z = 471.2$ $[M+H]^+$.

Example A-126 and A-127



[0465] *cis-tert-butyl 1-(1-aminopropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate*: To a solution of *cis-tert-butyl 1-cyano-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (prepared from Intermediate 44) (600 mg, 2.54 mmol) in THF (24 mL) was added dropwise EtMgBr (2.12 mL, 3 M in THF) at 0 °C under N₂. The mixture was stirred at 0 °C for 1 h and NaBH₃CN (479 mg, 7.62 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, diluted with sat.NH₄Cl (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: $m/z = 269.3$ $[M+H]^+$.

[0466] *cis-tert-butyl 1-(1-(4*H*-1,2,4-triazol-4-yl)propyl)-3-methyl-6-azabicyclo [3.1.1]heptane-6-carboxylate*: To a solution of *cis-tert-butyl 1-(1-aminopropyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxylate* (680 mg, 2.53 mmol) *N*-[(*Z*)-dimethylaminomethyleneamino]-*N,N*-dimethyl-formamidine (1.08 g, 7.60 mmol) in toluene (15 mL) was added *p*-TsOH (1.31 g, 7.60 mmol) at 25 °C under N₂. The mixture was stirred at 110 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, EtOAc:MeOH = 20:1) to give the titled compound. LCMS: $m/z = 321.3$ $[M+H]^+$.

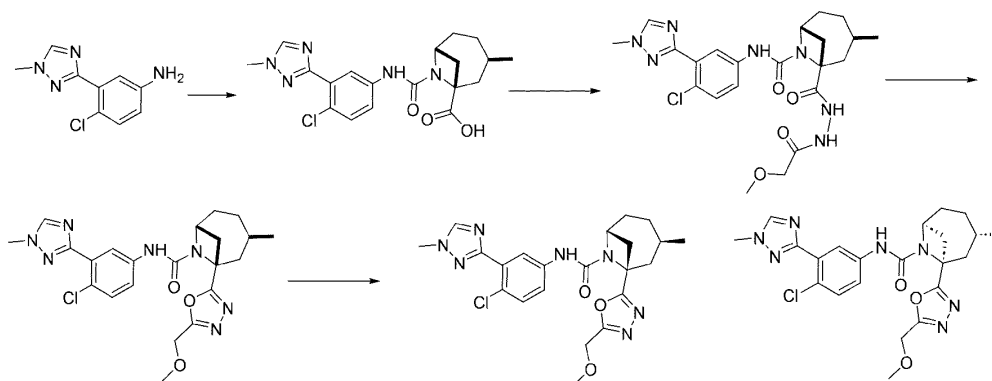
[0467] *cis-1-(1-(4*H*-1,2,4-triazol-4-yl)propyl)-3-methyl-6-azabicyclo[3.1.1]heptane trifluoroacetate*: To a solution of *cis-tert-butyl 1-(1-(4*H*-1,2,4-triazol-4-yl)propyl)-3-methyl-6-azabicyclo [3.1.1]heptane-6-carboxylate* (450 mg, 1.40 mmol) in DCM (10 mL) was added TFA (7.68 g, 67.31 mmol, 5 mL). The mixture was stirred at 20 °C for 2 h and concentrated under reduced pressure to give the titled compound. LCMS: $m/z = 221.2$ $[M+H]^+$.

[0468] *cis-1-((S)-1-(4*H*-1,2,4-triazol-4-yl)propyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-126) and *cis-1-((R)-1-(4*H*-1,2,4-triazol-4-yl)propyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (A-127)*:* To a solution of triphosgene (192 mg, 0.647 mmol) in THF (10 mL) was added a solution of 4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (300 mg, 1.44

mmol) and TEA (437 mg, 4.31 mmol) in THF (10 mL) at 0 °C under N₂. The mixture was stirred at 0 °C for 0.5 h. Then TEA (388 mg, 3.84 mmol) and *cis*-3-methyl-1-[1-(1,2,4-triazol-4-yl)propyl]-6-azabicyclo[3.1.1]heptane trifluoroacetate (449 mg, 1.34 mmol) were added to the reaction solution at 20 °C. The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Column: Phenomenex Genimi NX C18 150 × 40 mm × 5 μm; Mobile phase: A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 20% to 40% in 8 min) to give *cis*-1-(1-(4*H*-1,2,4-triazol-4-yl)propyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide as a single unknown enantiomer (first eluting diastereomer) Example A-126 LCMS: *m/z* = 455.2 [M+H]⁺ and *cis*-1-(1-(4*H*-1,2,4-triazol-4-yl)propyl)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide as a single unknown enantiomer (second eluting diastereomer) Example A-127. LCMS: *m/z* = 455.2 [M+H]⁺.

Example A-128 and A-129

cis-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide (A-128) and *cis*-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide (A-129)



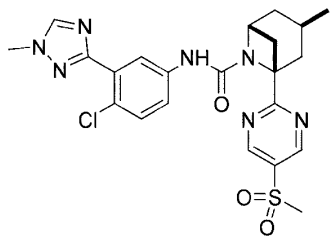
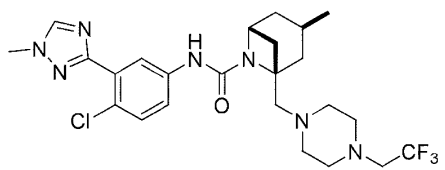
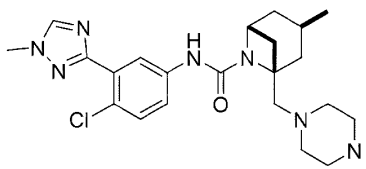
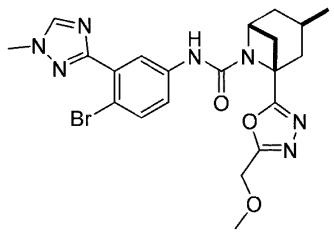
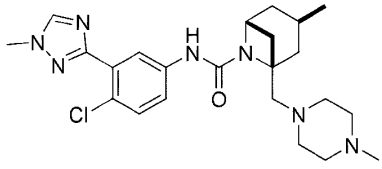
[0469] *cis*-7-((4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid: To a solution of triphosgene (569 mg, 1.92 mmol) in THF (24 mL) was added dropwise a solution of TEA (1.16 g, 11.50 mmol) and 4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (800 mg, 3.83 mmol) in THF (20 mL) at 0 °C under N₂. The reaction mixture was warmed to 20 °C and stirred for 1 h. TEA (1.94 g, 19.16 mmol) and *cis*-3-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid hydrochloride (Intermediate 50) (9.95 g, 4.60 mmol) were added to the above mixture and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with H₂O (2 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Welch Xtimate C18 250 × 70 mm × 10 μm; mobile phase: A: 10 mM NH₄HCO₃ in

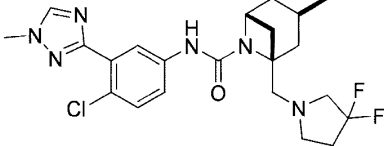
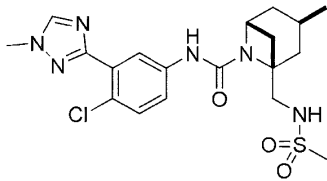
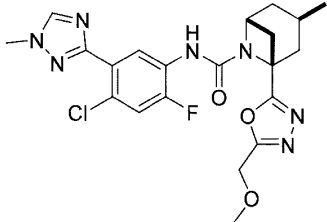
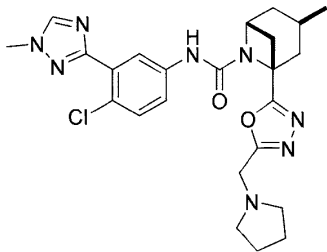
water, B: MeCN; B% in A: 5%-35% over 20 min) to give the titled compound. LCMS: $m/z = 404.2$ $[M+H]^+$.

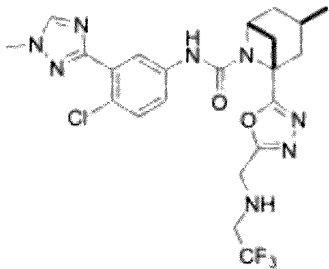
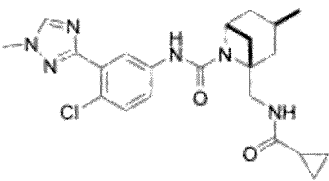
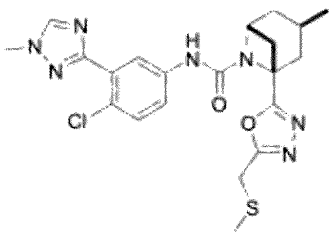
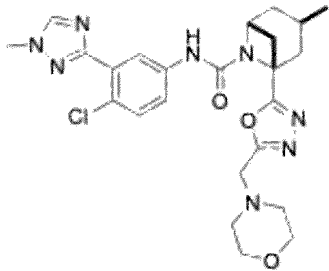
[0470] *cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-methoxyacetyl)hydrazinecarbonyl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide*: To a solution of *cis-7-((4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)carbamoyl)-3-methyl-7-azabicyclo[4.1.1]octane-1-carboxylic acid* (500 mg, 1.24 mmol) in DMF (10 mL) at 0 °C under N₂ was added 2-methoxyacetylhydrazine (644 mg, 6.19 mmol), DIEA (480 mg, 3.71 mmol) and HATU (941 mg, 2.48 mmol). The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the titled compound. LCMS: $m/z = 490.2$ $[M+H]^+$.

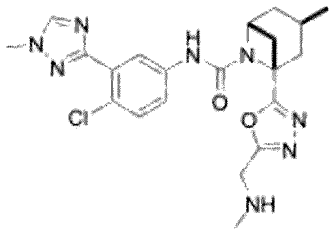
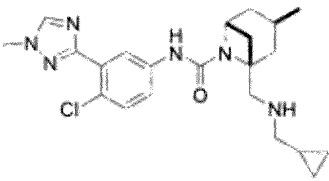
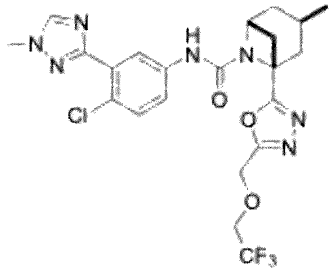
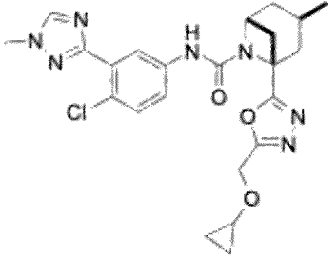
[0471] *cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide (A-128)* and *cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide (A-129)*: To a solution of *cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-methoxyacetyl)hydrazinecarbonyl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide* (2.40 g, crude) in MeCN (20 mL) at 20 °C under N₂ was added *p*-TsCl (280 mg, 1.47 mmol) and Cs₂CO₃ (1.28 g, 3.92 mmol). The reaction mixture was stirred for 12 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with DCM:MeOH = 10:1 (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:(EtOAc:EtOH = 3:1) = 1:1 to 0:1) to give the racemate. The racemate was separated by SFC (Column: DAICEL CHIRALPAK AD (250 mm × 30 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 35%-35%; Flow rate: 70.00 g/min; Monitor wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide* (peak 1 in SFC) Example **A-128** and *cis-N-(4-chloro-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-3-methyl-7-azabicyclo[4.1.1]octane-7-carboxamide* (peak 2 in SFC) Example **A-129**. LCMS: $m/z = 472.2$ $[M+H]^+$.

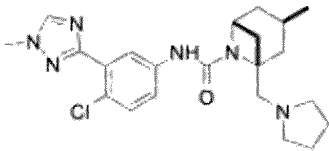
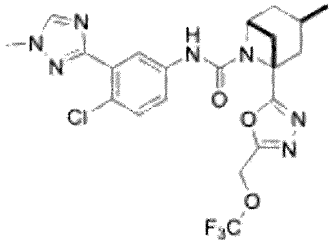
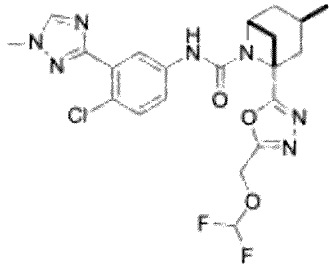
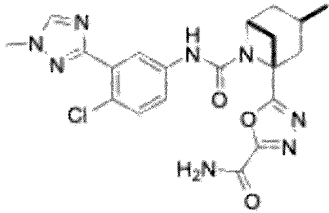
[0472] The following compounds were, or can be, made via similar procedures as those described herein.

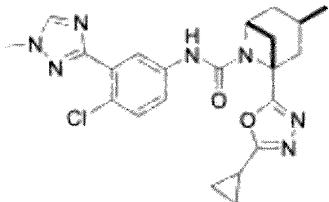
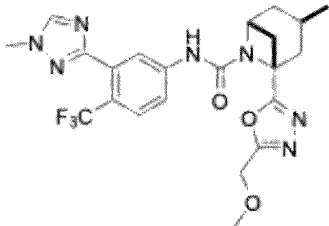
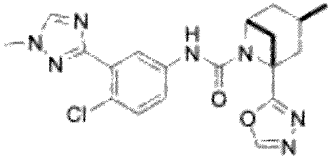
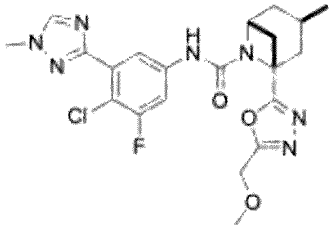
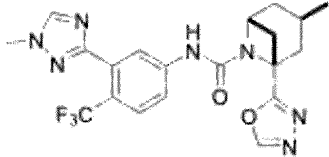
Ex.	Structure	LCMS
A-130	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 502.1 [M+H]^+$
A-131	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 526.3 [M+H]^+$
A-132	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 444.2 [M+H]^+$
A-133	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 502.0, 504.0 [M+H]^+$
A-134	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 458.2 [M+H]^+$

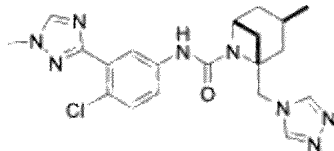
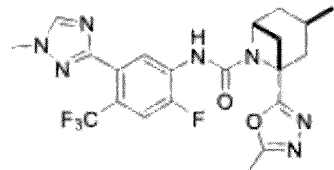
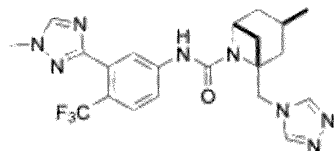
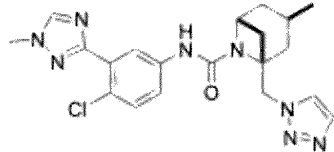
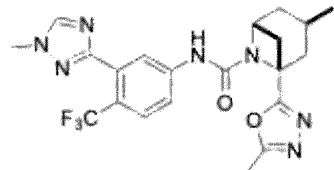
Ex.	Structure	LCMS
A-135	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 465.2 [M+H]^+$
A-136	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 453.1 [M+H]^+$
A-137	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 476.1 [M+H]^+$
A-138	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 497.1 [M+H]^+$

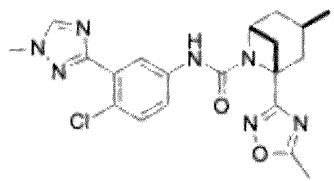
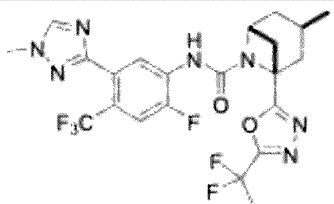
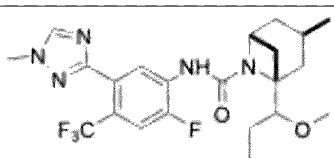
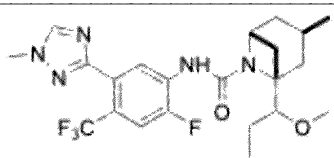
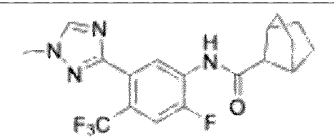
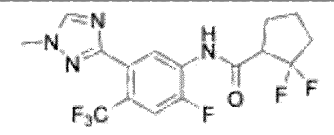
Ex.	Structure	LCMS
A-139	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 525.2 [M+H]^+$
A-140	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 443.2 [M+H]^+$
A-141	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 474.1 [M+H]^+$
A-142	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 513.2 [M+H]^+$

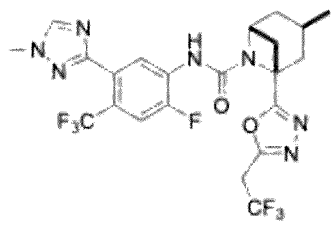
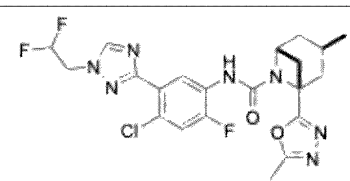
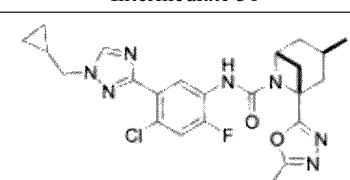
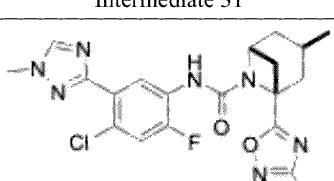
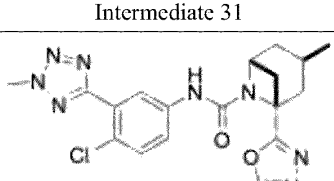
Ex.	Structure	LCMS
A-143	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 457.2 [M+H]^+$
A-144	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 429.2 [M+H]^+$
A-145	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 526.2 [M+H]^+$
A-146	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 484.2 [M+H]^+$

Ex.	Structure	LCMS
A-147	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 429.2$ $[M+H]^+$
A-148	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 512.1$ $[M+H]^+$
A-149	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 494.1$ $[M+H]^+$
A-150	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 457.1$ $[M+H]^+$

Ex.	Structure	LCMS
A-151	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 454.2 [M+H]^+$
A-152	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 492.2 [M+H]^+$
A-153	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 414.1 [M+H]^+$
A-154	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 476.2 [M+H]^+$
A-155	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 448.2 [M+H]^+$

Ex.	Structure	LCMS
A-156	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 427.2 [M+H]^+$
A-157	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 480.2 [M+H]^+$
A-158	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 461.2 [M+H]^+$
A-159	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 427.2 [M+H]^+$
A-160	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 462.2 [M+H]^+$

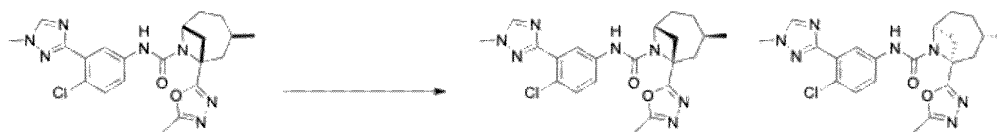
Ex.	Structure	LCMS
A-161	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 428.2 [M+H]^+$
A-162	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 530.2 [M+H]^+$
A-163	 Single unknown diastereomer, from Intermediate 47	$m/z = 470.2 [M+H]^+$
A-164	 Single unknown diastereomer, from Intermediate 48	$m/z = 470.2 [M+H]^+$
A-165		$m/z = 383.1 [M+H]^+$
A-166	 Mixture of enantiomers	$m/z = 393.1 [M+H]^+$

Ex.	Structure	LCMS
A-167	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 548.2$ $[M+H]^+$
A-168	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 496.2$ $[M+H]^+$
A-169	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 486.2$ $[M+H]^+$
A-170	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 446.2$ $[M+H]^+$
A-171	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 429.1$ $[M+H]^+$

Ex.	Structure	LCMS
A-172		$m/z = 364.1$ $[M+H]^+$
A-173	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 446.2$ $[M+H]^+$
A-174	 Single unknown enantiomer prepared from Intermediate 31	$m/z = 428.1$ $[M+H]^+$
A-175		$m/z = 331.1$ $[M+H]^+$
A-176		$m/z = 332.1$ $[M+H]^+$

SFC Separation

Example A-177 and A-178

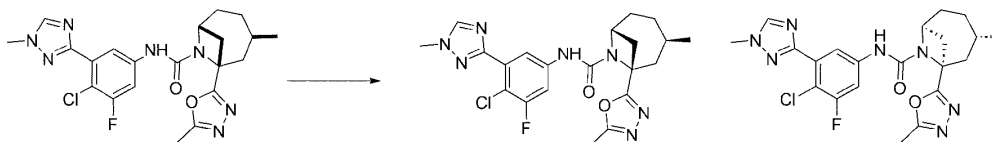


[0473] (1*S*,3*R*,6*R*)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide and (1*R*,3*S*,6*S*)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide: The mixture of enantiomers (360 mg, 0.81 mmol) was separated by SFC (DAICEL CHIRALPAK AD (250 mm×30 mm, 10 μm); Mobile phase: A: CO₂, B: MeOH; B% in A: 35%, 8 min;

Flow rate: 70.00 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) Example A-177 LCMS: $m/z = 442.2$ $[M+H]^+$ and *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC) Example A-178 LCMS: $m/z = 442.2$ $[M+H]^+$.

Example A-179 and A-180

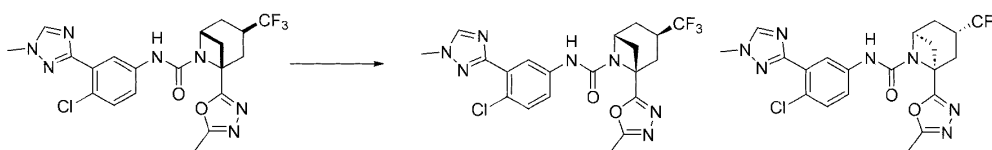
(1*S*,3*R*,6*R*)-*N*-(4-chloro-3-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide and (1*R*,3*S*,6*S*)-*N*-(4-chloro-3-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide



[0474] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK IG (250 mm × 30 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in *i*-PrOH; B% in A: 50%-50%, 7 min; Flow rate: 70.00 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis-N*-(4-chloro-3-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example A-179 and *cis-N*-(4-chloro-3-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example A-180. LCMS: $m/z = 460.1$ $[M+H]^+$.

Example A-181 and A-182

(1*S*,3*R*,5*R*)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-(trifluoromethyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,3*S*,5*S*)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-(trifluoromethyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide

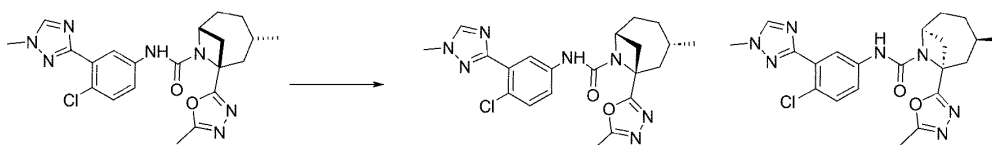


[0475] The mixture of enantiomers was separated by SFC (REGIS (s,s) WHELK-O1 (250 mm × 30 mm × 5 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 45%-45%, 12 min; Flow rate: 70.00 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis-N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-(trifluoromethyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) as a single unknown

enantiomer Example **A-181** and *cis*-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-3-(trifluoromethyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example **A-182**. LCMS: $m/z = 482.1$ $[M+H]^+$.

Example A-183 and A-184

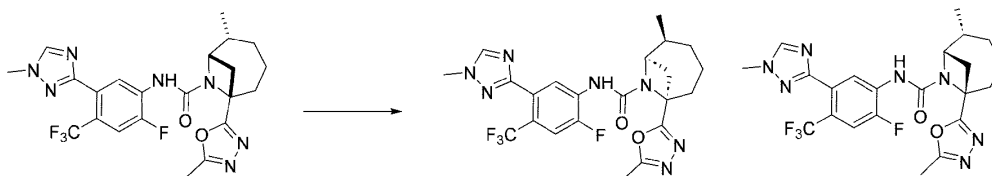
(1*S*,3*S*,6*R*)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide and (1*R*,3*R*,6*S*)-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide



[0476] The mixture of enantiomers was separated by SFC (REGIS (s, s) WHELK-O1 (250 mm × 30 mm × 5 μm), Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 50%-50%, 15 min; Flow rate: 70.00 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *trans*-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example **A-183** and *trans*-*N*-(4-chloro-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example **A-184**. LCMS: $m/z = 442.2$ $[M+H]^+$.

Example A-185 and A-186

(1*R*,5*S*,6*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide and (1*S*,5*R*,6*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide

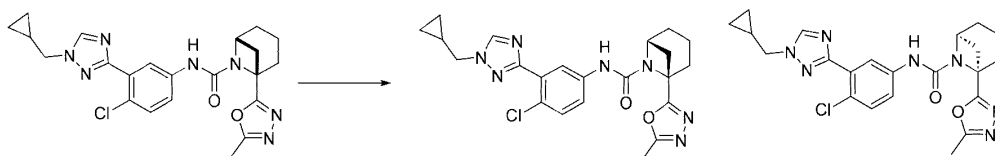


[0477] The mixture of enantiomers prepared from Intermediate 52 was separated by SFC (DAICEL CHIRALPAK AD (250 mm × 30 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 50%-50%, 12 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example **A-185** and *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example **A-186**. LCMS: $m/z = 468.2$ $[M+H]^+$.

azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example A-186. LCMS: $m/z = 494.2$ $[M+H]^+$.

Example A-187 and A-188

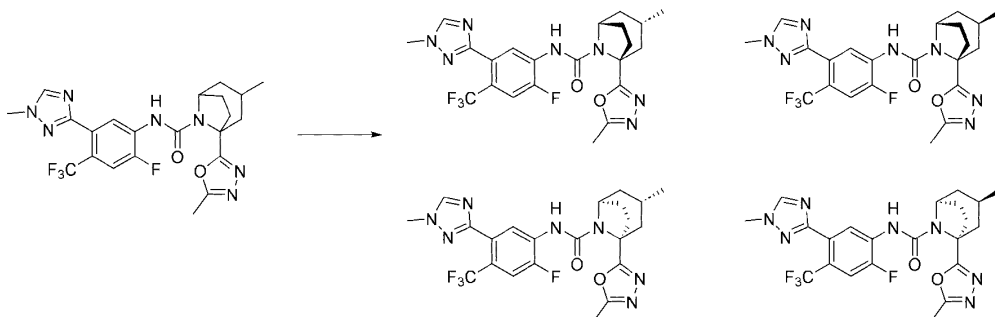
(1*S*,5*R*)-*N*-(4-chloro-3-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide and (1*R*,5*S*)-*N*-(4-chloro-3-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0478] The mixture of enantiomers was separated by SFC (ChiralPak IH, 250 × 30 mm × 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in *i*-PrOH; B% in A: 50%-50%, 17 min; Flow rate: 70 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *N*-(4-chloro-3-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example A-187 and *N*-(4-chloro-3-(1-(cyclopropylmethyl)-1*H*-1,2,4-triazol-3-yl)phenyl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example A-188. LCMS: $m/z = 454.2$ $[M+H]^+$.

Examples A-189, A-190, A-191 and A-192

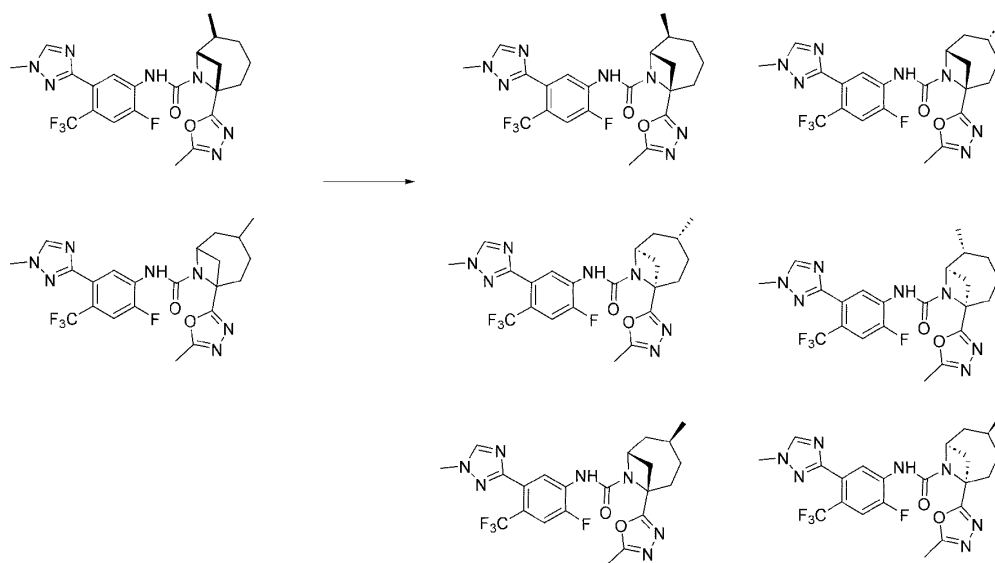
((1*R*,3*S*,5*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide, (1*R*,3*R*,5*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide, (1*S*,3*S*,5*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide and (1*S*,3*R*,5*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide



[0479] The mixture of compounds was separated by SFC (DAICEL CHIRALPAK IG (250 mm × 30mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 50%-50%, 10 min; Flow rate: 70.00 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give a mixture of *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide (example DN33665) and *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide (peak 1 and peak 2 in SFC) (example DN33685), *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide (peak 3 in SFC) as a single unknown enantiomer Example **A-189**, LCMS: *m/z* = 494.2 [M+H]⁺ and *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide (peak 4 in SFC) as a single unknown enantiomer Example **A-190**. LCMS: *m/z* = 494.2 [M+H]⁺. The mixture of compounds from peak 1 and peak 2 above was further purified by SFC (ChiralPak IH, 250 mm × 30mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 30%-30%, 7 min; Flow rate: 70.00 g/min; Wavelength: 220 & 254 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide (Peak 1 in SFC) Example **A-191** and *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-8-azabicyclo[3.2.1]octane-8-carboxamide (Peak 2 in SFC) Example **A-192**. LCMS: *m/z* = 494.3 [M+H]⁺.

Examples A-193, A-194, A-195, A-196, A-197, and A-198

(1*S*,4*S*,6*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, ((1*S*,5*S*,6*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, (1*R*,4*R*,6*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, (1*R*,4*S*,6*S*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, (1*R*,5*R*,6*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide and (1*S*,4*R*,6*R*)-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide

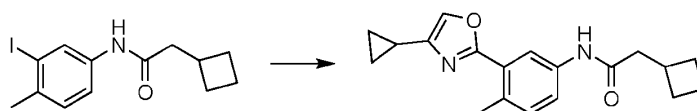


[0480] The mixture of compounds prepared from Intermediate 51 was separated by SFC (DAICEL CHIRALPAK AD (250 mm × 30 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 45%-45%, 9 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example **A-193** LCMS: *m/z* = 494.2 [M+H]⁺, *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 3 in SFC) as a single unknown enantiomer Example **A-194** LCMS: *m/z* = 494.2 [M+H]⁺, and a mixture of (*cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide, *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC). Further purification of this mixture by SFC (DAICEL CHIRALPAK IK (250 mm × 25 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 55%-55%, 6 min; Flow rate: 80 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) provided *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example **A-195** LCMS: *m/z* = 494.2 [M+H]⁺, *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 3 in SFC) as a single

unknown enantiomer Example **A-196** LCMS: $m/z = 494.2$ $[M+H]^+$, and a mixture of *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide and *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC). Further purification by SFC (DAICEL CHIRALPAK AD (250 mm $\times$ 30 mm $\times$ 10 μ m); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 50%-50%, 12 min; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) provided *trans*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-4-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 1 in SFC) as a single unknown enantiomer Example **A-197** LCMS: $m/z = 494.2$ $[M+H]^+$, and *cis*-*N*-(2-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)-4-(trifluoromethyl)phenyl)-5-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-7-azabicyclo[4.1.1]octane-7-carboxamide (peak 2 in SFC) as a single unknown enantiomer Example **A-198** LCMS: $m/z = 494.2$ $[M+H]^+$.

Example B-1

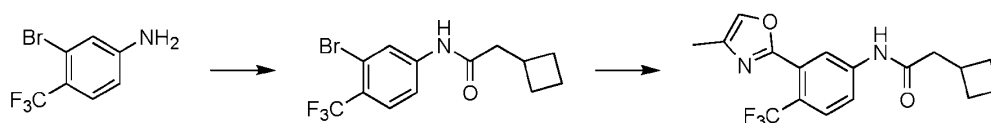
2-cyclobutyl-*N*-(3-(4-cyclopropyloxazol-2-yl)-4-methylphenyl)acetamide



[0481] To a mixture of 2-cyclobutyl-*N*-(3-iodo-4-methylphenyl)acetamide (100 mg, 0.31 mmol) and 4-cyclopropyloxazole (50 mg, 0.46 mol) in 1,4-dioxane (2 mL) at 20 °C under N₂ was added tricyclohexylphosphonium tetrafluoroborate (23 mg, 0.06 mmol), DBU (93 mg, 0.61 mmol), CuI (12 mg, 0.061 mmol) and Pd(OAc)₂ (7 mg, 0.031 mmol). The reaction mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 3:1) to give the titled compound. LCMS: $m/z = 311.2$ $[M+H]^+$.

Example B-2

2-cyclobutyl-*N*-(3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)acetamide



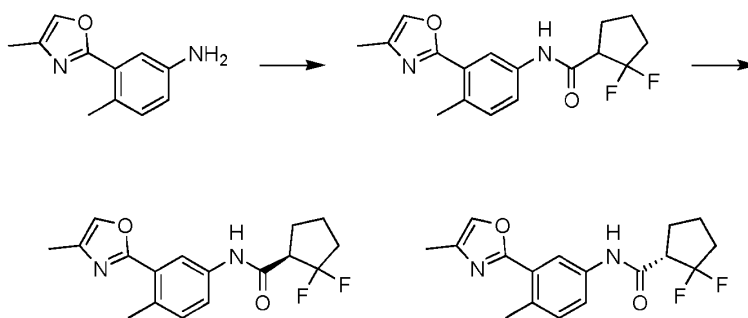
[0482] *N*-(3-bromo-4-(trifluoromethyl)phenyl)-2-cyclobutylacetamide: To a solution of 3-bromo-4-(trifluoromethyl)aniline (800 mg, 3.33 mmol) and TEA (675 mg, 6.67 mmol) in DCM (10 mL) at 0 °C under N₂ was added 2-cyclobutylacetyl chloride (530 mg, 4.00 mmol). The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE: EtOAc = 5:1 to 3:1) to give the titled compound. LCMS: m/z = 336.0, 338.0 [M+H]⁺.

[0483] 2-cyclobutyl-*N*-(3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)acetamide: To a solution of *N*-(3-bromo-4-(trifluoromethyl)phenyl)-2-cyclobutylacetamide (150 mg, 0.45 mmol) and 4-methyloxazole (56 mg, 0.67 mmol) in 1,4-dioxane (3 mL) at 20 °C under N₂ was added tricyclohexylphosphonium tetrafluoroborate (33 mg, 0.09 mmol), Pd(OAc)₂ (10 mg, 0.04 mmol), CuI (17 mg, 0.09 mmol) and DBU (136 mg, 0.09 mmol). The reaction mixture was heated to 130 °C and stirred for 3 h under microwave irradiation. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Phenomenex Luna C18 75 × 30 mm × 3 μm; A: 10 mM FA in water, B: MeCN; B% in A: 25%-55%, 8 min) to give the titled compound. LCMS: m/z = 339.0 [M+H]⁺.

Examples B-3 and B-4

(*R*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide and (*S*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide



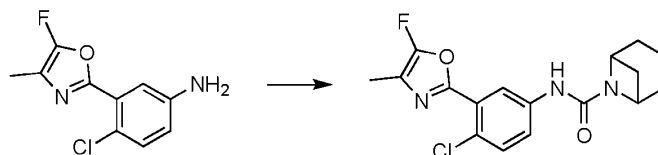
[0484] 2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide: To a solution of 4-methyl-3-(4-methyloxazol-2-yl)aniline (250 mg, 1.33 mmol) in pyridine (3 mL) at 0 °C under N₂ was added 2,2-difluorocyclopentane-1-carboxylic acid (200 mg, 1.33 mmol) and EDCI (511 mg, 2.66 mmol). The reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 100:1 to 5:1) to give the titled compound. LCMS: m/z = 320.9 [M+H]⁺.

[0485] (*R*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide and (*S*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide: The mixture of enantiomers was separated by SFC (DAICEL CHIRALCEL OD 250 mm × 30 mm × 10 μm); Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 25%-25%, 10 min; Flow rate: 60 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give 2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide (Peak 1 in SFC) Example B-3

and 2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopentane-1-carboxamide (Peak 2 in SFC) Example B-4. LCMS: $m/z = 320.9$ $[M+H]^+$.

Example B-5

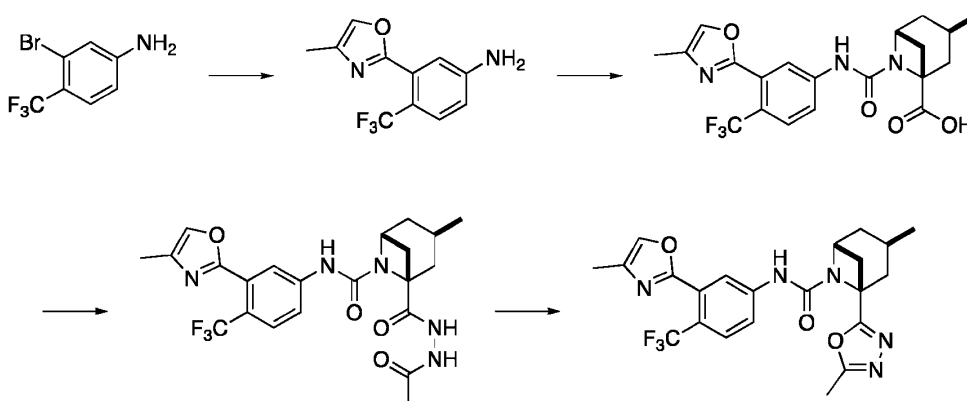
***N*-(4-chloro-3-(5-fluoro-4-methyloxazol-2-yl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide:**



[0486] To a mixture of CDI (25 mg, 0.15 mmol) in DCM (1.5 mL) at 0 °C under N_2 was added 4-chloro-3-(5-fluoro-4-methyloxazol-2-yl)aniline (30 mg, 0.13 mmol). The reaction mixture was warmed to 25 °C and stirred for 1 h. 6-Azabicyclo[3.1.1]heptane (18 mg, 0.18 mmol) and TEA (28 mg, 0.28 mmol) were added and the reaction mixture was heated to 40 °C and stirred for 12 h. 3 drops of water were added to the reaction mixture and it was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Phenomenex C18 100 × 30 mm × 10 μ m; mobile phase A: 10 mM NH_4HCO_3 in water, B: MeCN; B% in A: B%:35%-65%, 8 min) to give the titled compound. LCMS: $m/z = 350.1$ $[M+H]^+$.

Example B-6

***cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide**



[0487] 3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)aniline: To a solution of 3-bromo-4-(trifluoromethyl)aniline (1 g, 4.17 mmol) and 4-methyloxazole (950 mg, 10.84 mmol) in 1,4-dioxane (15 mL) at 20 °C under N_2 was added $Pd(OAc)_2$ (188 mg, 0.834 mmol), CuI (320 mg, 1.67 mmol), DBU (1.27 g, 8.33 mmol) and $P(Cy)_3 \cdot HBF_4$ (307 mg, 0.833 mmol). The reaction mixture was heated to 120 °C and stirred for 48 h. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: $m/z = 243.1$ $[M+H]^+$.

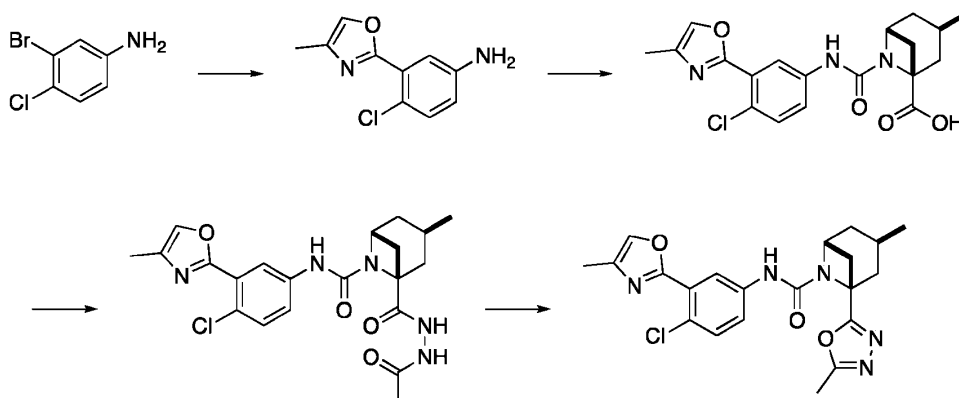
[0488] *cis*-3-methyl-6-((3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a solution of triphosgene (92 mg, 0.31 mmol) in THF (6 mL) at 0 °C under N₂ was added a solution of 3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)aniline (150 mg, 0.62 mmol) and TEA (188 mg, 1.86 mmol) in THF (6 mL). The reaction mixture was warmed to 25 °C and stirred for 1 h. Then *cis*-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid hydrochloride (643 mg, 0.67 mmol, 20% purity, Intermediate 34) and TEA (170 mg, 1.68 mmol) were added to the reaction solution and stirred for an additional 1 h. The reaction mixture was diluted with H₂O (0.5 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Welch Xtimate C18 180 × 70 mm × 10 μm; mobile phase A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 5%-55%, 20 min) to give the titled compound. LCMS: *m/z* = 424.2 [M+H]⁺.

[0489] *cis*-1-(2-acetylhydrazine-1-carbonyl)-3-methyl-*N*-(3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-3-methyl-6-((3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)carbamoyl)-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (120 mg, 0.28 mmol) and acetylhydrazine (63 mg, 0.85 mmol) in DMF (3 mL) at 0 °C under N₂ was added DIEA (110 mg, 0.85 mmol) and HATU (216 mg, 0.57 mmol). The mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the titled compound. LCMS: *m/z* = 480.1 [M+H]⁺.

[0490] *cis*-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-1-(2-acetylhydrazine-1-carbonyl)-3-methyl-*N*-(3-(4-methyloxazol-2-yl)-4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxamide (200 mg, 0.42 mmol) in MeCN (4 mL) at 20 °C under N₂ was added *p*-TsCl (119 mg, 0.63 mmol) and Cs₂CO₃ (544 mg, 1.67 mmol). The reaction mixture was stirred at 20 °C for 6 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Waters Xbridge Prep OBD C18 150 × 40 mm × 10 μm; mobile phase A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 30%-65%, 8 min) to give the titled compound. LCMS: *m/z* = 462.2 [M+H]⁺.

Example B-7

cis-N-(4-chloro-3-(4-methyloxazol-2-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide



[0491] 4-chloro-3-(4-methyloxazol-2-yl)aniline: To a solution of 3-bromo-4-chloro-aniline (1 g, 4.84 mmol) and 4-methyloxazole (1.05 g, 12.6 mmol) in 1,4-dioxane (15 mL) at 20 °C under N₂ was added P(Cy)₃•HBF₄ (714 mg, 1.94 mmol), Pd(OAc)₂ (218 mg, 0.97 mmol), CuI (370 mg, 1.94 mmol) and DBU (1.47 g, 9.69 mmol). The reaction mixture was heated to 110 °C and stirred for 16 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE:EtOAc = 5:1 to 1:1) to give the titled compound. LCMS: m/z = 209.1 [M+H]⁺.

[0492] cis-6-((4-chloro-3-(4-methyloxazol-2-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid: To a solution of triphosgene (107 mg, 0.36 mmol) in THF (6 mL) at 0 °C under N₂ was added a solution of 4-chloro-3-(4-methyloxazol-2-yl)aniline (150 mg, 0.72 mmol) and TEA (218 mg, 2.16 mmol) in THF (6 mL). The reaction mixture was warmed to 25 °C and stirred for 1 h. Then cis-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid hydrochloride (735 mg, 0.77 mmol, 20% purity, Intermediate 34) and TEA (194 mg, 1.92 mmol) were added to the reaction mixture and it was stirred for 1 h. The reaction mixture was quenched by addition of H₂O (0.5 mL) and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Welch Xtimate C18 180 × 70 mm × 10 μm; mobile phase A: 10 mM NH₄HCO₃ in water, B: MeCN; B% in A: 5%-50%, 20 min) to give the titled compound. LCMS: m/z = 390.1 [M+H]⁺.

[0493] cis-1-(2-acetylhydrazine-1-carbonyl)-N-(4-chloro-3-(4-methyloxazol-2-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of cis-6-((4-chloro-3-(4-methyloxazol-2-yl)phenyl)carbamoyl)-3-methyl-6-azabicyclo[3.1.1]heptane-1-carboxylic acid (110 mg, 0.28 mmol) and acetylhydrazine (63 mg, 0.85 mmol) in DMF (3 mL) at 0 °C under N₂ was added DIEA (109 mg, 0.85 mmol) and HATU (161 mg, 0.42 mmol). The reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined

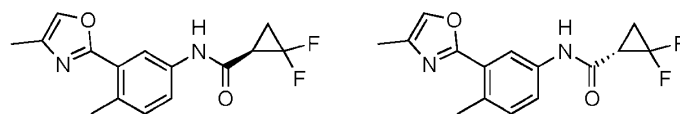
organic layers were washed with brine (2×5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the titled compound. LCMS: $m/z = 446.1$ $[\text{M}+\text{H}]^+$.

[0494] *cis*-*N*-(4-chloro-3-(4-methyloxazol-2-yl)phenyl)-3-methyl-1-(5-methyl-1,3,4-oxadiazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxamide: To a solution of *cis*-1-(2-acetylhydrazine-1-carbonyl)-*N*-(4-chloro-3-(4-methyloxazol-2-yl)phenyl)-3-methyl-6-azabicyclo[3.1.1]heptane-6-carboxamide (180 mg, 0.40 mmol) in MeCN (4 mL) at 20 °C was added *p*-TsCl (115 mg, 0.61 mmol) and Cs_2CO_3 (526 mg, 1.61 mmol). The reaction mixture was stirred at 20 °C for 6 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (Waters Xbridge Prep OBD C18 150×40 mm $\times$ 10 μm ; mobile phase A: 10 mM NH_4HCO_3 in water, B: MeCN; B% in A: 30%-60%, 8 min) to give the titled compound. LCMS: $m/z = 428.1$ $[\text{M}+\text{H}]^+$.

[0495] The following examples were prepared according to the procedures described above using the appropriate starting materials. SFC separations were performed as follows.

Examples B-8 and B-9

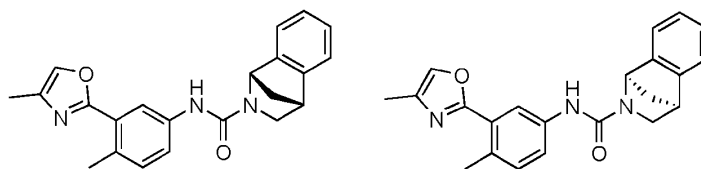
(*R*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopropane-1-carboxamide and (*S*)-2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopropane-1-carboxamide



[0496] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK AD 250 mm $\times$ 30 mm, 10 μm); Mobile phase: A: CO_2 , B: 0.1% $\text{NH}_3\text{H}_2\text{O}$ in *i*-PrOH; B% in A: 33%-33%, 10 min; Flow rate: 60 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give 2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopropane-1-carboxamide (Peak 1 in SFC) Example B-8. LCMS: $m/z = 293.1$ $[\text{M}+\text{H}]^+$ and 2,2-difluoro-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclopropane-1-carboxamide (Peak 2 in SFC) Example B-9. LCMS: $m/z = 293.1$ $[\text{M}+\text{H}]^+$.

Examples B-10 and B-11

(1*S*,4*R*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-3,4-dihydro-1,4-methanoisoquinoline-2(1*H*)-carboxamide and (1*R*,4*S*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-3,4-dihydro-1,4-methanoisoquinoline-2(1*H*)-carboxamide

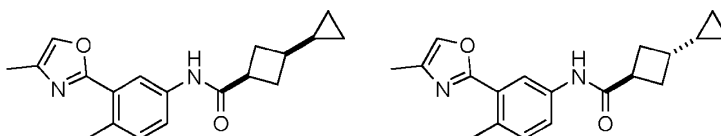


[0497] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK IG 250 mm $\times$ 30 mm, 10 μm); Mobile phase: A: CO_2 , B: 0.1% $\text{NH}_3\text{H}_2\text{O}$ in EtOH; B% in A: 60%-60%; Flow rate: 80

g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar)) to give *N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-3,4-dihydro-1,4-methanoisoquinoline-2(1*H*)-carboxamide (Peak 1 in SFC) Example B-10. LCMS: $m/z = 360.2$ $[M+H]^+$ and *N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-3,4-dihydro-1,4-methanoisoquinoline-2(1*H*)-carboxamide (Peak 2 in SFC) Example B-11. LCMS: $m/z = 360.2$ $[M+H]^+$.

Examples B-12 and B-13

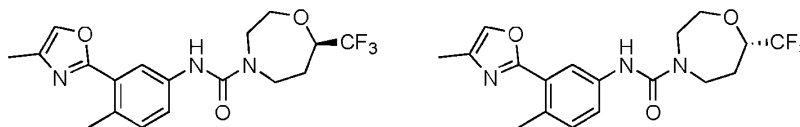
cis-3-cyclopropyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclobutane-1-carboxamide and
trans-3-cyclopropyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclobutane-1-carboxamide



[0498] The mixture of isomers was separated by SFC (DAICEL CHIRALCEL OJ 250 mm × 30 mm, 10 μm, mobile phase: A:CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 40%-40%; Flow rate: 60 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis*-3-cyclopropyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclobutane-1-carboxamide (Peak 1 in SFC) Example B-12. LCMS: $m/z = 311.2$ $[M+H]^+$ and *trans*-3-cyclopropyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)cyclobutane-1-carboxamide (Peak 2 in SFC) Example B-13. LCMS: $m/z = 311.2$ $[M+H]^+$.

Examples B-14 and B-15

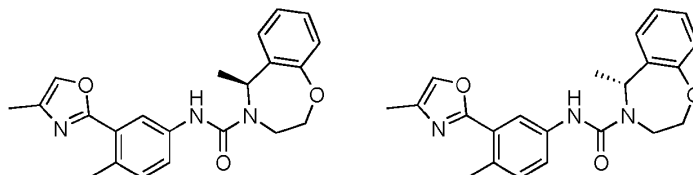
(*R*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-7-(trifluoromethyl)-1,4-oxazepane-4-carboxamide
and (*S*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-7-(trifluoromethyl)-1,4-oxazepane-4-
carboxamide



[0499] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK IG (250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 25%-25%; Flow rate: 55 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-7-(trifluoromethyl)-1,4-oxazepane-4-carboxamide (Peak 1 in SFC) Example B-14. LCMS: $m/z = 384.2$ $[M+H]^+$ and *N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-7-(trifluoromethyl)-1,4-oxazepane-4-carboxamide (Peak 2 in SFC) Example B-15. LCMS: $m/z = 384.2$ $[M+H]^+$.

Examples B-16 and B-17

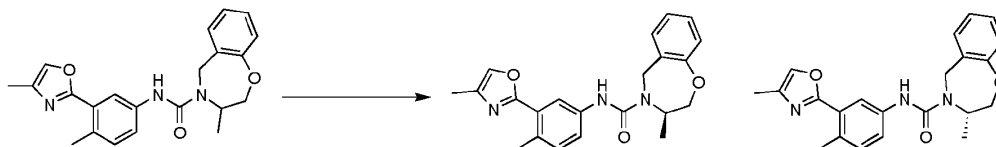
(*S*)-5-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide and (*R*)-5-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide



[0500] The mixture of enantiomers was separated by SFC (REGIS(s,s) WHELK-O1 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 50%-50%; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give 5-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide (Peak 1 in SFC) Example B-16. LCMS: *m/z* = 378.2 [M+H]⁺ and 5-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide (Peak 2 in SFC) Example B-17. LCMS: *m/z* = 378.2 [M+H]⁺.

Examples B-18 and B-19

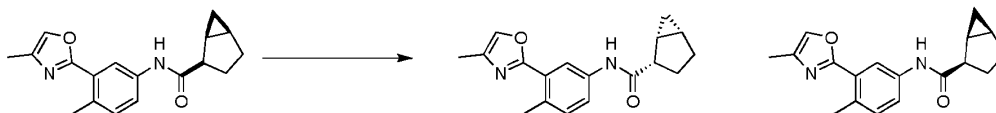
(*R*)-3-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide and (*S*)-3-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide



[0501] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK AS 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 35%-35%; Flow rate: 65 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give 3-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide (Peak 1 in SFC) Example B-18. LCMS: *m/z* = 378.2 [M+H]⁺ and 3-methyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(*5H*)-carboxamide (Peak 2 in SFC) Example B-19. LCMS: *m/z* = 378.2 [M+H]⁺.

Examples B-20 and B-21

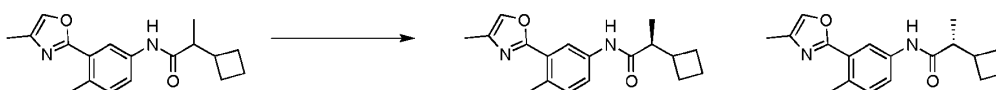
(1*R*,2*S*,5*S*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)bicyclo[3.1.0]hexane-2-carboxamide and (1*S*,2*R*,5*R*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)bicyclo[3.1.0]hexane-2-carboxamide



[0502] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK AD 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in MeOH; B% in A: 33%-33%; Flow rate: 60 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *cis*-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)bicyclo[3.1.0]hexane-2-carboxamide (Peak 1 in SFC) Example B-20. LCMS: *m/z* = 297.2 [M+H]⁺ and *cis*-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)bicyclo[3.1.0]hexane-2-carboxamide (Peak 2 in SFC) Example B-21. LCMS: *m/z* = 297.2 [M+H]⁺.

Examples B-22 and B-23

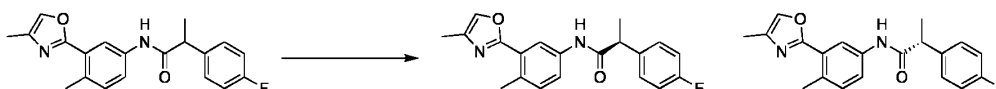
(*S*)-2-cyclobutyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide and (*R*)-2-cyclobutyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide



[0503] The mixture of enantiomers was separated by SFC (REGIS(s,s) WHELK-O1 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in *i*-PrOH; B% in A: 35%-35%; Flow rate: 65 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give 2-cyclobutyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide (Peak 1 in SFC) Example B-22. LCMS: *m/z* = 299.2 [M+H]⁺ and 2-cyclobutyl-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide (Peak 2 in SFC) Example B-23. LCMS: *m/z* = 299.2 [M+H]⁺.

Examples B-24 and B-25

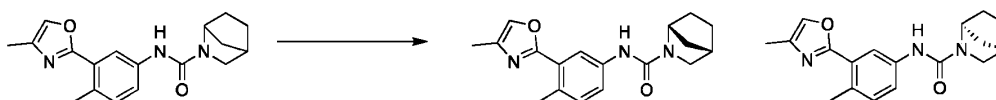
(*S*)-2-(4-fluorophenyl)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide and (*R*)-2-(4-fluorophenyl)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide



[0504] The mixture of enantiomers was separated by SFC (REGIS(s,s) WHELK-O1 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃H₂O in EtOH; B% in A: 30%-30%; Flow rate: 60 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give 2-(4-fluorophenyl)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide (Peak 1 in SFC) Example B-24. LCMS: *m/z* = 339.2 [M+H]⁺ and 2-(4-fluorophenyl)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)propanamide (Peak 2 in SFC) Example B-25. LCMS: *m/z* = 339.2 [M+H]⁺.

Examples B-26 and B-27

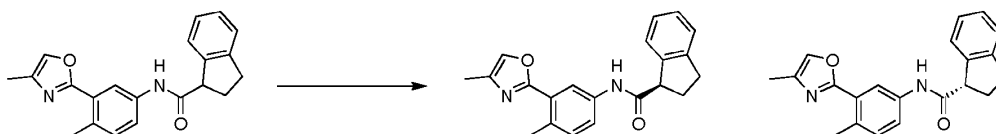
(1*R*,4*S*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide and (1*S*,4*R*)-*N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide



[0505] The mixture of enantiomers was separated by SFC (DAICEL CHIRALPAK AS 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃.H₂O in i-PrOH; B% in A: 45%-45%; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to give *cis-N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide (Peak 1 in SFC) Example B-26. LCMS: *m/z* = 312.2 [M+H]⁺ and *cis-N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxamide (Peak 2 in SFC) Example B-27. LCMS: *m/z* = 312.2 [M+H]⁺.

Examples B-28 and B-29

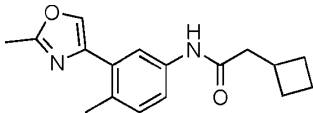
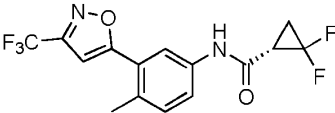
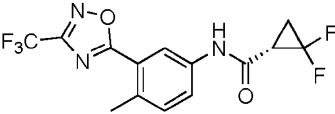
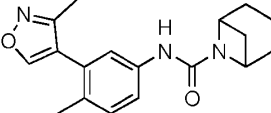
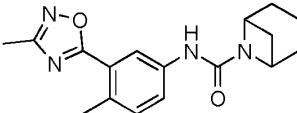
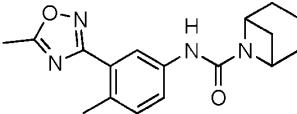
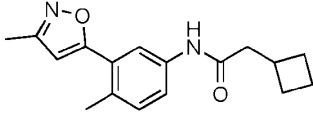
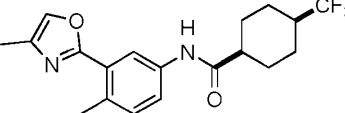
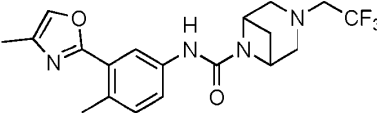
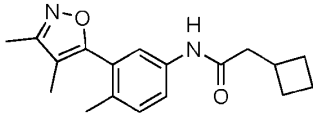
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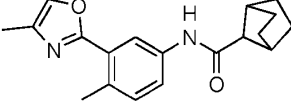
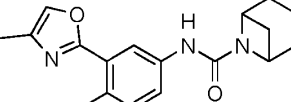
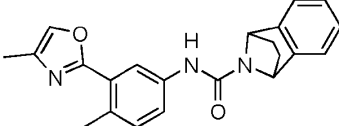
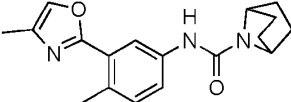
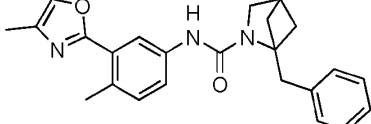
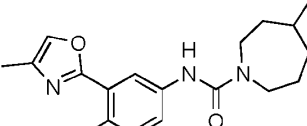
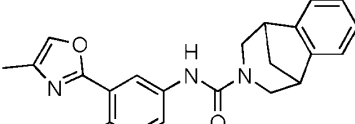
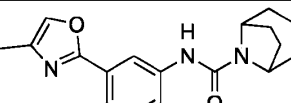
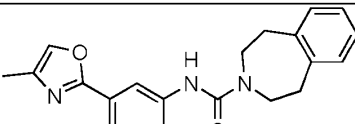


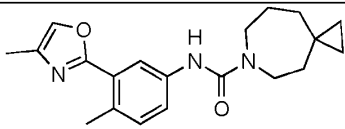
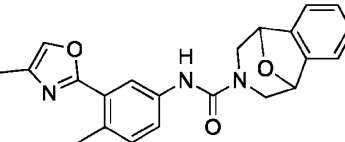
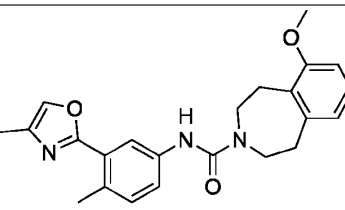
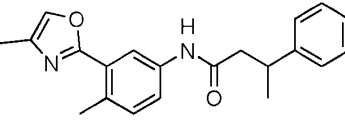
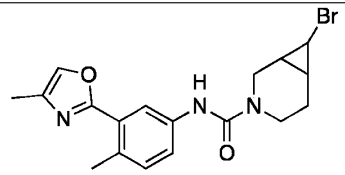
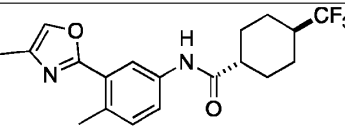
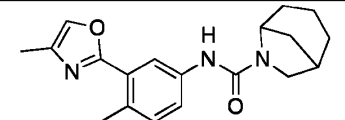
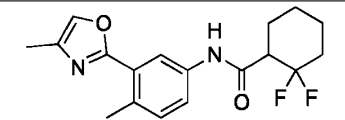
[0506] The mixture of enantiomers was separated by SFC (DAICEL CHIRALCEL OJ 250 mm × 30 mm, 10 μm; Mobile phase: A: CO₂, B: 0.1% NH₃.H₂O in EtOH; B% in A: 50%-50%; Flow rate: 70 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar) to give *N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydro-1*H*-indene-1-carboxamide (Peak 1 in SFC) Example B-28. LCMS: *m/z* = 333.2 [M+H]⁺ and *N*-(4-methyl-3-(4-methyloxazol-2-yl)phenyl)-2,3-dihydro-1*H*-indene-1-carboxamide (Peak 2 in SFC) Example B-29. LCMS: *m/z* = 333.2 [M+H]⁺.

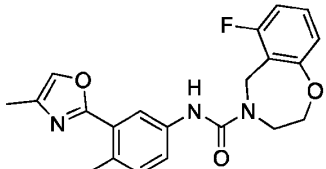
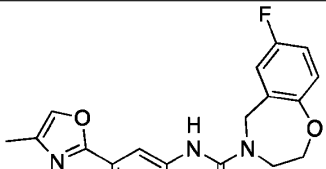
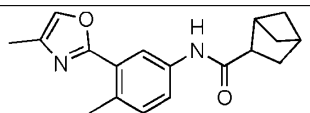
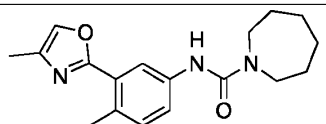
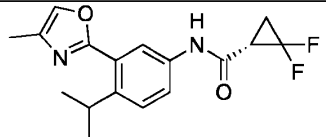
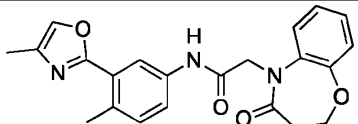
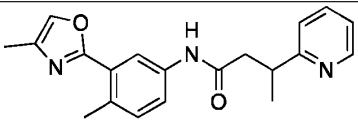
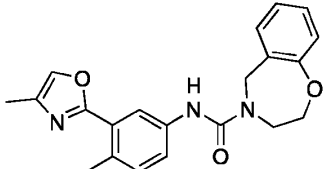
[0507] The following compounds were, or can be, made via similar procedures as those described herein.

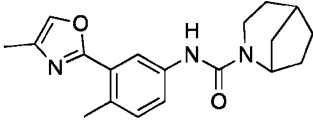
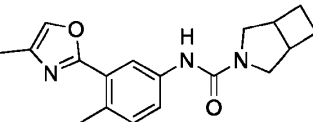
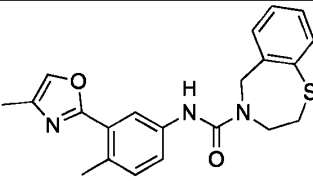
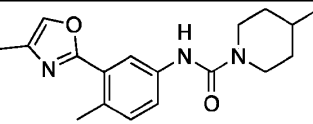
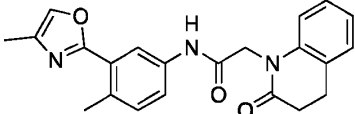
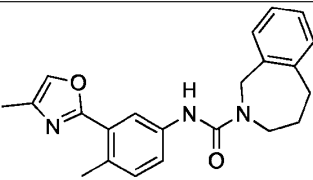
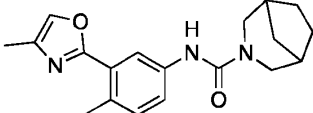
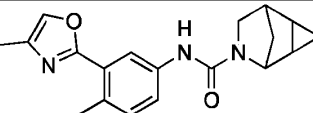
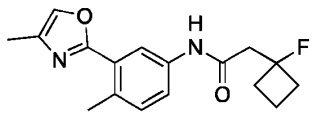
Ex.	Structure	LCMS
B-30		<i>m/z</i> = 312.9 [M+H] ⁺
B-31		<i>m/z</i> = 312.1 [M+H] ⁺
B-32		<i>m/z</i> = 312.1 [M+H] ⁺
B-33		<i>m/z</i> = 303.1 [M+H] ⁺

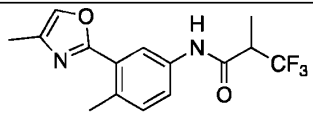
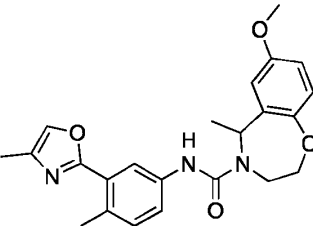
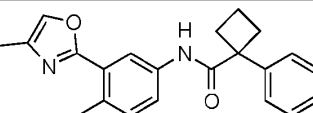
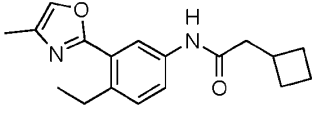
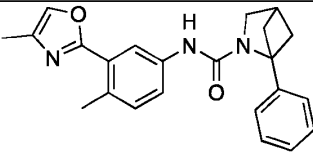
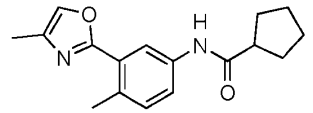
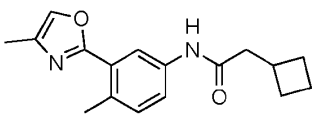
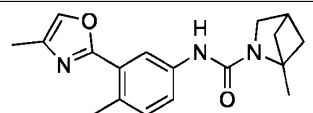
Ex.	Structure	LCMS
B-34		m/z = 285.2 [M+H] ⁺
B-35		m/z = 347.1 [M+H] ⁺
B-36		m/z = 348.1 [M+H] ⁺
B-37		m/z = 312.0 [M+H] ⁺
B-38		m/z = 313.2 [M+H] ⁺
B-39		m/z = 313.2 [M+H] ⁺
B-40		m/z = 285.1 [M+H] ⁺
B-41		m/z = 367.2 [M+H] ⁺
B-42		m/z = 395.1 [M+H] ⁺
B-43		m/z = 299.1 [M+H] ⁺

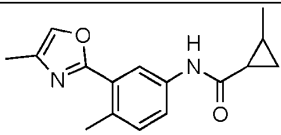
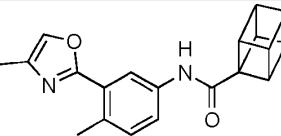
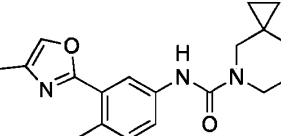
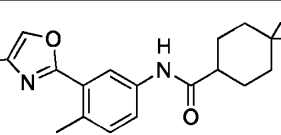
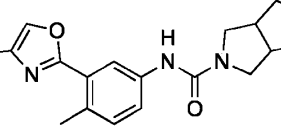
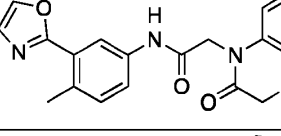
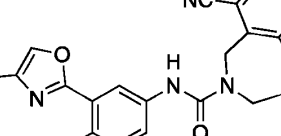
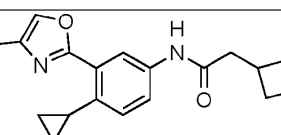
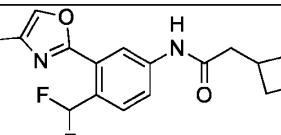
Ex.	Structure	LCMS
B-44		m/z = 311.1 [M+H] ⁺
B-45		m/z = 312.1 [M+H] ⁺
B-46		m/z = 360.1 [M+H] ⁺
B-47		m/z = 312.1 [M+H] ⁺
B-48		m/z = 388.2 [M+H] ⁺
B-49	 Mixture of enantiomers	m/z = 328.2 [M+H] ⁺
B-50		m/z = 374.2 [M+H] ⁺
B-51		m/z = 326.1 [M+H] ⁺
B-52		m/z = 362.2 [M+H] ⁺

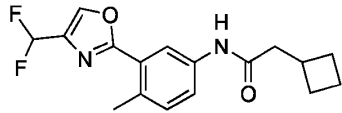
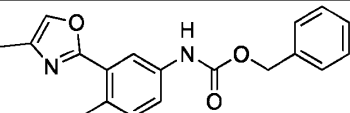
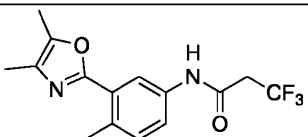
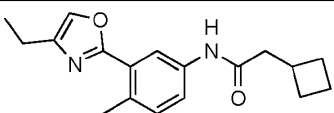
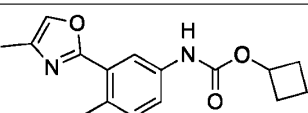
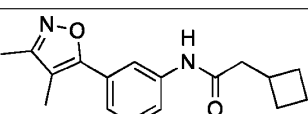
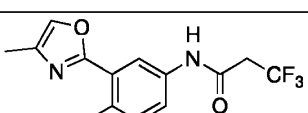
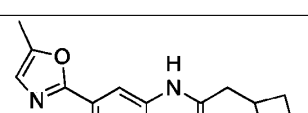
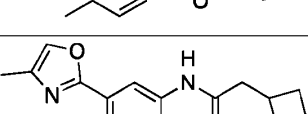
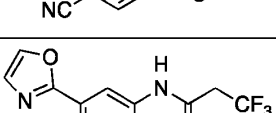
Ex.	Structure	LCMS
B-53		m/z = 340.2 [M+H] ⁺
B-54		m/z = 376.1 [M+H] ⁺
B-55		m/z = 392.2 [M+H] ⁺
B-56	 Mixture of enantiomers	m/z = 335.1 [M+H] ⁺
B-57	 Mixture of diastereomers	m/z = 392.0, 390.1 [M+H] ⁺
B-58		m/z = 367.1 [M+H] ⁺
B-59	 Mixture of enantiomers	m/z = 326.1 [M+H] ⁺
B-60	 Mixture of enantiomers	m/z = 335.1 [M+H] ⁺

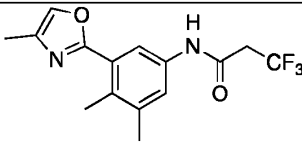
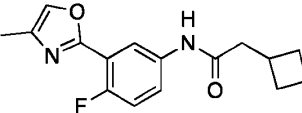
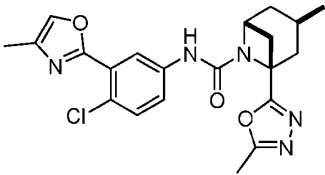
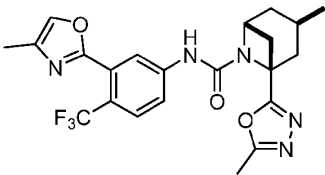
Ex.	Structure	LCMS
B-61		m/z = 382.1 [M+H] ⁺
B-62		m/z = 382.1 [M+H] ⁺
B-63	 Mixture of enantiomers	m/z = 297.1 [M+H] ⁺
B-64		m/z = 314.1 [M+H] ⁺
B-65		m/z = 321.1 [M+H] ⁺
B-66		m/z = 392.1 [M+H] ⁺
B-67	 Mixture of enantiomers	m/z = 336.1 [M+H] ⁺
B-68		m/z = 364.1 [M+H] ⁺

Ex.	Structure	LCMS
B-69	 Mixture of enantiomers	$m/z = 326.1$ $[M+H]^+$
B-70		$m/z = 312.1$ $[M+H]^+$
B-71		$m/z = 380.1$ $[M+H]^+$
B-72		$m/z = 314.1$ $[M+H]^+$
B-73		$m/z = 376.1$ $[M+H]^+$
B-74		$m/z = 362.1$ $[M+H]^+$
B-75		$m/z = 326.2$ $[M+H]^+$
B-76	 Mixture of diastereomers	$m/z = 324.1$ $[M+H]^+$
B-77		$m/z = 303.1$ $[M+H]^+$

Ex.	Structure	LCMS
B-78	 Mixture of enantiomers	$m/z = 313.1$ $[M+H]^+$
B-79	 Mixture of enantiomers	$m/z = 408.2$ $[M+H]^+$
B-80		$m/z = 347.1$ $[M+H]^+$
B-81		$m/z = 299.2$ $[M+H]^+$
B-82		$m/z = 374.2$ $[M+H]^+$
B-83		$m/z = 285.1$ $[M+H]^+$
B-84		$m/z = 285.1$ $[M+H]^+$
B-85		$m/z = 312.2$ $[M+H]^+$

Ex.	Structure	LCMS
B-86	 Mixture of diastereomers	m/z = 271.1 [M+H] ⁺
B-87		m/z = 319.1 [M+H] ⁺
B-88		m/z = 326.1 [M+H] ⁺
B-89		m/z = 335.1 [M+H] ⁺
B-90		m/z = 326.2 [M+H] ⁺
B-91		m/z = 378.1 [M+H] ⁺
B-92		m/z = 389.1 [M+H] ⁺
B-93		m/z = 311.2 [M+H] ⁺
B-94		m/z = 321.1 [M+H] ⁺

Ex.	Structure	LCMS
B-95		m/z = 321.1 [M+H] ⁺
B-96		m/z = 323.1 [M+H] ⁺
B-97		m/z = 313.1 [M+H] ⁺
B-98		m/z = 299.2 [M+H] ⁺
B-99		m/z = 287.1 [M+H] ⁺
B-100		m/z = 285.1 [M+H] ⁺
B-101		m/z = 319.0 [M+H] ⁺
B-102		m/z = 285.2 [M+H] ⁺
B-103		m/z = 296.1 [M+H] ⁺
B-104		m/z = 285.1 [M+H] ⁺

Ex.	Structure	LCMS
B-105		m/z = 313.1 [M+H] ⁺
B-106		m/z = 289.1 [M+H] ⁺
B-107	 Single unknown enantiomer prepared from Intermediate 31	m/z = 428.1 [M+H] ⁺
B-108	 Single unknown enantiomer prepared from Intermediate 31	m/z = 462.2 [M+H] ⁺

BIOLOGICAL EXAMPLE 1

Biochemical Assay of the Compounds

[0508] Preparation of full-length SARM1 (FL-SARM1) lysate: HEK293T cells (ATCC: CRL-3216) were grown on 150 mm TC-treated dishes to 80-90% confluency in complete DMEM (DMEM (Thermo Fisher: 11965175) supplemented with 10% HI-FBS (VWR: 10802-772), 1x Pen/Strep (Thermo Fisher: 15140122), 1x NEAA (Thermo Fisher: 1140050), 1x glutamax (Thermo Fisher: 35050061), and 1 mM sodium pyruvate (Thermo Fisher: 11360070)) at 37 °C and 5% CO₂. One hour prior to transfection, the media was replaced with fresh, 37 °C complete DMEM (20 mL per one 150 mm dish) supplemented with additional 10mM glucose (Alfa Aesar AAJ60067EQE). Per one 150 mm dish, 30 µg FL-SARM1 (SEQ. ID. 1; cloned in-house) plasmid was dissolved in 1 mL DMEM at ambient temperature and were mixed by inverting the tube 8-10 times. 90 µL of GenJet™ in vitro DNA transfection reagent (Ver2) was dissolved in 1 mL DMEM at ambient temperature and were mixed by inverting the tube 8-10 times. The plasmid and transfection agent solutions were combined, mixed by 8-10 inversions and incubated for 10 minutes at ambient temperature. 2 mL of this transfection mixture was added to each dish containing

HEK293T cells as prepared above followed by a gentle mixing of 4-5 horizontal rotations. The dishes were incubated at 37 °C and 5% CO₂ for 24 h. The dishes were removed from the incubator, the medium was aspirated and the cells were scraped off using cell scrapers in ice-cold 1x PBS (5 mL/dish, Thermo Fisher Scientific 10010023). The collected cells were centrifuged at 300 g for 5 minutes at 4 °C. The supernatant was aspirated and the pellet was frozen at -80 °C until needed. The cell pellet from 30 dishes was dissolved in 30 mL 1x PBS supplemented with 4 tablets of Complete. Mini EDTA-free protease inhibitor cocktail at 4 °C. This mixture was sonicated on ice for 10 minutes at 50% amplitude with a 1 second on/1 second off interval using a Model 120 sonicator (Thermo Fisher Scientific, FB120110). The lysate was centrifuged at 16000 g for 10 minutes at 4 °C. Batches with supernatant possessing NMN-dependent SARM1 activity were selected, pooled, and stored at -80 °C until used in the FL-SARM1 cellular lysate assay described below.

[0509] To a white 384-well Proxiplate (PerkinElmer, PE-6008280) was added 50 nL/well of a DMSO solution containing test compounds followed by 7.5 µL/well of a 0.067 mg/mL solution of SARM1 cellular lysate in reaction buffer (DPBS containing CHAPSO (0.1%) and fatty acid free BSA (0.032%)). The plate was centrifuged for 1 minute at 1000 RPM and then placed in an incubator at 23 °C for 15 minutes. To the wells were added 2.5 µL/well of a solution containing 40 µM NAD⁺ and 4 mM nicotinamide mononucleotide (NMN) in reaction buffer. The plate was centrifuged for 1 min at 1000 RPM, the plate was sealed and placed in an incubator at 23 °C for 3.5 hours before adding 3.5 µL/well of NAD/NADH-Glo™ solution (preparation as described by Promega using the extended detection protocol). The plate was centrifuged for 1 minute at 1000 RPM and then incubated at 23 °C for 20 minutes. 1 µL/well of a 3.625 mM solution of menadione in DMSO was added and the plate was centrifuged for 1 minute at 1000 RPM. Relative light units (RLU) were recorded using an Envision plate reader at a height of 6.5 mm. Percent inhibition was calculated as follows:

$$\% \text{ inhibition} = (\text{sample} - \text{low control}) / (\text{high control} - \text{low control}) \times 100.$$

[0510] IC₅₀ values were calculated from an 11 point curve using ½ log dilutions using a four-parameter logistic regression curve fit. Activity of the tested compounds is provided in Table 3 below as follows:
+++ = 0.0001 µM < IC₅₀ < 1 µM; ++ = IC₅₀ 1-10 µM; + = IC₅₀ > 10 µM.

Table 3

Ex.	Activity	Ex.	Activity	Ex.	Activity
A-1	+	A-8	+++	A-15	+++
A-2	+++	A-9	+++	A-16	+++
A-3	+++	A-10	++	A-17	++
A-4	++	A-11	+	A-18	+
A-5	++	A-12	++	A-19	+++
A-6	+++	A-13	++	A-20	++
A-7	+++	A-14	+++	A-21	+++

Ex.	Activity
A-22	+++
A-23	+++
A-24	+++
A-25	+
A-26	+++
A-27	++
A-28	++
A-29	++
A-30	+++
A-31	+
A-32	+
A-33	+++
A-34	++
A-35	+++
A-36	+++
A-37	+++
A-38	+
A-39	+++
A-40	+++
A-41	+++
A-42	+++
A-43	+
A-44	+++
A-45	+
A-46	++
A-47	++
A-48	+++
A-49	++
A-50	+++
A-51	+++
A-52	+++
A-53	+
A-54	++
A-55	++
A-56	++

Ex.	Activity
A-57	++
A-58	++
A-59	+++
A-60	++
A-61	++
A-62	++
A-63	++
A-64	++
A-65	++
A-66	+++
A-67	++
A-68	++
A-69	++
A-70	+++
A-71	+++
A-72	+++
A-73	+++
A-74	+
A-75	+++
A-76	++
A-77	+++
A-78	+
A-79	+
A-80	++
A-81	++
A-82	++
A-83	++
A-84	+++
A-85	++
A-86	+++
A-87	+++
A-88	+++
A-89	+++
A-90	+++
A-91	+++

Ex.	Activity
A-92	++
A-93	+++
A-94	+++
A-95	+++
A-96	+++
A-97	++
A-98	++
A-99	++
A-100	++
A-101	+++
A-102	+
A-103	+++
A-104	+++
A-105	++
A-106	++
A-107	+++
A-108	++
A-109	+++
A-110	+++
A-111	+++
A-112	+++
A-113	+++
A-114	+++
A-115	++
A-116	++
A-117	++
A-118	++
A-119	+++
A-120	+++
A-121	+++
A-122	+++
A-123	+++
A-124	+++
A-125	+++
A-126	+++

Ex.	Activity
A-127	+++
A-128	++
A-129	+++
A-130	+++
A-131	+++
A-132	+++
A-133	+++
A-134	+++
A-135	+++
A-136	+++
A-137	+++
A-138	+++
A-139	+++
A-140	+++
A-141	+++
A-142	+++
A-143	+++
A-144	+++
A-145	+++
A-146	+++
A-147	++
A-148	+++
A-149	+++
A-150	+++
A-151	+++
A-152	+++
A-153	+++
A-154	+++
A-155	+++
A-156	+++
A-157	+++
A-158	+++
A-159	+++
A-160	+++
A-161	+++

Ex.	Activity
A-162	+++
A-163	+++
A-164	+++
A-165	+++
A-166	++
A-167	+++
A-168	+++
A-169	+++
A-170	+++
A-171	+++
A-172	+++
A-173	+++
A-174	+++
A-175	+++
A-176	+++
A-177	++
A-178	+++
A-179	+
A-180	+++
A-181	+
A-182	+++
A-183	++
A-184	+++
A-185	+++
A-186	+
A-187	+
A-188	++
A-189	+++
A-190	+++
A-191	+
A-192	+
A-193	++
A-194	+
A-195	++
A-196	++

Ex.	Activity
A-197	+++
A-198	+++
B-1	++
B-2	+++
B-3	+++
B-4	+++
B-5	+++
B-6	+++
B-7	+++
B-8	++
B-9	+++
B-10	+++
B-11	+++
B-12	+++
B-13	+++
B-14	+++
B-15	+++
B-16	+++
B-17	+++
B-18	+++
B-19	+++
B-20	+++
B-21	+++
B-22	++
B-23	+++
B-24	++
B-25	+++
B-26	+++
B-27	++
B-28	+++
B-29	+++
B-30	+
B-31	++
B-32	++
B-33	++

Ex.	Activity	Ex.	Activity	Ex.	Activity
B-34	++	B-59	+++	B-84	+++
B-35	++	B-60	+++	B-85	+++
B-36	++	B-61	+++	B-86	+++
B-37	+	B-62	+++	B-87	+++
B-38	+++	B-63	+++	B-88	+++
B-39	+++	B-64	+++	B-89	+++
B-40	++	B-65	+++	B-90	+++
B-41	+++	B-66	+++	B-91	+++
B-42	+++	B-67	+++	B-92	+++
B-43	++	B-68	+++	B-93	+++
B-44	+++	B-69	+++	B-94	+++
B-45	+++	B-70	+++	B-95	++
B-46	+++	B-71	+++	B-96	++
B-47	+++	B-72	+++	B-97	++
B-48	+++	B-73	+++	B-98	++
B-49	+++	B-74	+++	B-99	++
B-50	+++	B-75	+++	B-100	++
B-51	+++	B-76	+++	B-101	++
B-52	+++	B-77	+++	B-102	++
B-53	+++	B-78	+++	B-103	++
B-54	+++	B-79	+++	B-104	++
B-55	+++	B-80	+++	B-105	+
B-56	+++	B-81	+++	B-106	+
B-57	+++	B-82	+++	B-107	+++
B-58	++	B-83	+++	B-108	+++

[0511] FL-SARM1 plasmid sequence (SEQ. ID. 1):
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[0512] In certain embodiments, provided is a method for determining modulation of Sterile alpha and Toll/interleukin-1 receptor motif-containing 1 (SARM1) by a candidate compound, said method comprising:

providing a solution comprising a SARM1 protein and the candidate compound;

adding to the solution nicotinamide mononucleotide (NMN) and nicotinamide adenine dinucleotide (NAD⁺); and

measuring the amount of NAD⁺ remaining in solution to determine modulation of SARM1 by the candidate compound.

[0513] In certain embodiments, the measuring comprises a fluorescent detection step.

[0514] In certain embodiments, the SARM1 protein is a protein comprising at least about 60%, or at least about 70%, or at least about 80%, or at least about 90%, or at least about 95%, or at least about 97%, or at least about 99% sequence homology to native SARM1 protein.

[0515] In certain embodiments, the SARM1 protein comprises a fluorescent tag.

[0516] In certain embodiments, the SARM1 protein is provided using SEQ. ID. 1, or a derivative thereof. In certain embodiments, the derivative comprises at least about 60%, or at least about 70%, or at least about 80%, or at least about 90%, or at least about 95%, or at least about 97%, or at least about 99% sequence homology to SEQ. ID. 1. In certain embodiments, the SARM1 protein is provided using SEQ. ID. 1.

[0517] In certain embodiments, the candidate compound is an inhibitor of SARM1.

[0518] 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.

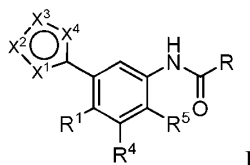
[0519] The disclosure illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claims.

[0520] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

[0521] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

What is claimed is:

1. A compound of Formula I:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^1 is N, NR^{8a} , O, S, or CR^{6a} ;

X^2 is N, NR^{8b} , O, S, or CR^{6b} ;

X^3 is N, NR^{8c} , or CR^{6c} ;

X^4 is N or CR^{6d} ;

provided that at least one of X^1 , X^2 , X^3 , and X^4 is N, and the ring containing X^1 , X^2 , X^3 , and X^4 is aromatic;

R is $-NR^2R^3$, $-OR^7$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl is optionally substituted with one to five Z^1 ;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is optionally substituted with one to five Z^1 ;

R^2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^3 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

or R^2 and R^3 together form a heterocyclyl, which may further be optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each independently hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

R⁷ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{8a}, R^{8b}, and R^{8c} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

or R^{8a} and R^{6b}, or R^{8b} and R^{6c}, or R^{6b} and R^{6c}, or R^{8c} and R^{6d}, or R^{6c} and R^{6d}, together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein

each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

with the proviso that at least one of A, B, C, D, or E occurs:

- A. X¹ is N and X² is NR^{8b}; and
- when R is C₁₋₆ alkyl; the C₁₋₆ alkyl is substituted with halo or C₃₋₁₀ cycloalkyl and optionally one to four Z¹; and/or
 - R^{8b} is other than hydrogen; and/or
 - when R is -OR⁷; then R⁷ is not methyl, ethyl, *iso*-propyl, *tert*-butyl, 2-bromoethyl, 2-methoxyethyl, 2-cyanoethyl, 2-phenylethyl, benzyl, or 9*H*-fluoren-9-ylmethyl;

and the compound is not:

- | | |
|--------------|---|
| 129628-21-3 | [2,4-dichloro-5-[4-chloro-1-methyl-5-(methylthio)-1H-pyrazol-3-yl]phenyl]-carbamic acid 2-methyl-2-propenyl ester. |
| 945236-54-4 | 1-(1,3-benzodioxol-5-yl)-N-[4-methyl-3-(1-methyl-1H-pyrazol-3-yl)phenyl]cyclopropanecarboxamide. |
| 142622-93-3 | N-[2,4-dichloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]phenyl]-2,2,2-trifluoroacetamide. |
| 142621-98-5 | N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide. |
| 2231121-13-2 | N-[4-bromo-2-fluoro-5-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2H-tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide. |

- 2231119-31-4 N-[4-bromo-3-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2H-tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide,
- 159291-92-6 1-bromo-N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorophenyl]cyclopropanecarboxamide, or
- 141576-10-5 N-[2-chloro-5-[4-chloro-1-methyl-5-(methylsulfonyl)-1H-pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide;

- B. X^2 is N or NR^{8b} ; and R is $-NR^2R^3$; and
- R^2 and R^3 are not simultaneously methyl; and/or
 - when X^1 is O; then at least one of R^{8b} , R^{8c} , R^{6c} , or R^{6d} is other than hydrogen;
- and the compound is not:

- 1150100-88-1 N'-[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-N-phenyl-N-4-piperidinylurea,
- 938467-87-9 N'-[4-chloro-3-(2-methyl-2H-tetrazol-5-yl)phenyl]-N-(3,3-diphenylpropyl)-N-[2-(4-morpholinyl)ethyl]-urea,
- 1808766-39-3 4-(3-chlorophenyl)-N-[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide,
- 1071521-28-2 4-(3-fluorobenzoyl)-N-[4-fluoro-3-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]phenyl]-1-piperazinecarboxamide,
- 1071521-22-6 4-(3-fluorobenzoyl)-N-[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide,
- 1095716-86-1 N-[4-chloro-3-ethyl-5-(1-methyl-1H-pyrazol-4-yl)phenyl]-7,8-dihydro-4-(2-methylphenyl)-2-(3-pyridinyl)pyrido[4,3-d]pyrimidine-6(5H)-carboxamide, or
- 1150100-22-3 N-[4-[[5-[[4-[[[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]amino]carbonyl]phenyl]amino]-1-piperidinyl]methyl]-6-methyl-2-pyridinyl]oxy]phenyl]methanesulfonamide;

- C. X^1 is N or CR^{6a} , X^2 is O, X^3 is N or CR^{6c} , and X^4 is N; and
- where R is C_{1-6} alkyl, the C_{1-6} alkyl is substituted with one to five Z^1 ; and/or
 - R^{6c} is not 4-amino-2-[(3,4,5-trimethoxyphenyl)amino]-5-thiazolyl, [[4-(1-pyrrolidinylmethyl)phenyl]amino]-5-thiazolyl, or [[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino]-5-thiazolyl; and/or
 - when R is $-OR^7$; then R^7 is not *iso*-butyl or *tert*-butyl;
- and the compound is not:

- 2024618-95-7 (α R,5R,8S)-N-[4-chloro-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5,6,7,8-tetrahydro- α ,2,5-trimethyl-8-quinolineacetamide;

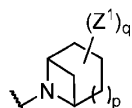
D. X^1 is O, X^2 is N or CR^{6b} , X^3 is CR^{6c} , X^4 is N, R^{6c} is other than hydrogen; and R is $-NR^2R^3$, wherein R^2 and R^3 together form a heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ; and at least one of the following a.-d. occurs:

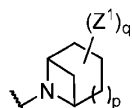
- a. X^2 is N;
- b. R^1 is other than methyl;
- c. R^2 and R^3 form an optionally substituted bridged heterocyclyl, which is optionally fused to an aryl or heteroaryl ring;
- d. R^2 and R^3 form an optionally substituted monocyclic 7-membered heterocyclyl, which is optionally fused to an aryl or heteroaryl ring;

and the compound is not:

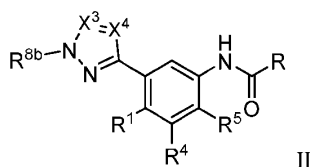
- | | |
|--------------|--|
| 2433600-20-3 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-7-azabicyclo[2.2.1]heptane-7-carboxamide, |
| 1950533-91-1 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide, |
| 1956717-19-3 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3,9-diazabicyclo[4.2.1]nonane-9-carboxamide, |
| 1951851-26-5 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-azabicyclo[3.2.1]octane-8-carboxamide, |
| 1950762-35-2 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide, |
| 1948326-39-3 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxamide, |
| 2390318-25-7 | (1S,4S)-2-thia-5-azabicyclo[2.2.1]heptane-5-carboxamide, N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-, 2-oxide, |
| 2134719-79-0 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxamide, |
| 1951235-51-0 | 1,3,3a,4,5,6,7,7a-octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-etheno-2H-isoindole-2-carboxamide, |
| 2128457-53-2 | N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4-azatricyclo[4.3.1.1 ^{3,8}]undecane-4-carboxamide, |
| 1943194-72-6 | (3aR,7aS)-1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide, |
| 1954930-48-3 | octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide, |
| 1950392-13-8 | 1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide, |

- 2127527-42-6 octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
- 2321449-65-2 rel-(3aR,4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1943187-21-0 (4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 2128457-20-3 hexahydro-2-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2129297-32-9 hexahydro-3,5-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2430356-12-8 hexahydro-4-methoxy-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2135054-93-0 hexahydro-3,3-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2130442-49-6 hexahydro-4,4-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2134261-73-5 hexahydro-2,6-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide, or
- 1944921-02-1 hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-azepine-1-carboxamide;



E. R is , wherein q is 0, 1, 2, 3, 4, or 5; and p is 0, 1, 2, or 3.

2. A compound of Formula II:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^3 is N or CR^{6c};

X^4 is N or CR^{6d};

R is -NR²R³, -OR⁷, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl; wherein the C₁₋₆ alkyl is substituted with halo or C₃₋₁₀ cycloalkyl, and optionally one to four Z¹; and wherein the C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl is optionally substituted with one to five Z¹;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R³ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

or R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R⁴ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R⁵ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6c} and R^{6d} are each independently hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

R⁷ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{8b} is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z¹;

or R^{8b} and R^{6c}, or R^{6c} and R^{6d}, together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

each Z^1 is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{12})_2$, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{S}(\text{O})\text{R}^{12}$, $-\text{S}(\text{O})_2\text{R}^{12}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{S}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{C}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{S}(\text{O})\text{N}(\text{R}^{12})_2$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{N}(\text{R}^{12})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{12})_2$, or $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} :

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{13})_2$, $-\text{OR}^{13}$, $-\text{SR}^{13}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{R}^{13}$, $-\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{13})_2$, or $-\text{NR}^{13}\text{C}(\text{O})\text{OR}^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{L}-\text{C}_{1-6}$ alkyl, $-\text{L}-\text{C}_{2-6}$ alkenyl, $-\text{L}-\text{C}_{2-6}$ alkynyl, $-\text{L}-\text{C}_{1-6}$ haloalkyl, $-\text{L}-\text{C}_{3-10}$ cycloalkyl, $-\text{L}-\text{heterocyclyl}$, $-\text{L}-\text{aryl}$, or $-\text{L}-\text{heteroaryl}$; and

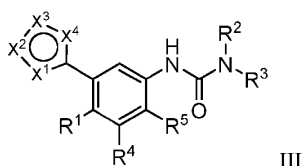
each L is independently $-\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{C}_{1-6} \text{ alkyl})-$, $-\text{N}(\text{C}_{2-6} \text{ alkenyl})-$, $-\text{N}(\text{C}_{2-6} \text{ alkynyl})-$, $-\text{N}(\text{C}_{1-6} \text{ haloalkyl})-$, $-\text{N}(\text{C}_{3-10} \text{ cycloalkyl})-$, $-\text{N}(\text{heterocyclyl})-$, $-\text{N}(\text{aryl})-$, $-\text{N}(\text{heteroaryl})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6} \text{ alkenyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6} \text{ alkynyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ haloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{3-10} \text{ cycloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{heterocyclyl})-$, $-\text{C}(\text{O})\text{N}(\text{aryl})-$, $-\text{C}(\text{O})\text{N}(\text{heteroaryl})-$, $-\text{NHC}(\text{O})-$, $-\text{NHC}(\text{O})\text{O}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NHS}(\text{O})-$, or $-\text{S}(\text{O})_2\text{NH}-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{SF}_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl;

provided that:

- when R is -OR⁷; then R⁷ is not methyl, ethyl, *iso*-propyl, *tert*-butyl, 2-bromoethyl, 2-methoxyethyl, 2-cyanoethyl, 2-phenylethyl, benzyl, or 9*H*-fluoren-9-ylmethyl; and the compound is not:
- | | |
|--------------|--|
| 129628-21-3 | [2,4-dichloro-5-[4-chloro-1-methyl-5-(methylthio)-1 <i>H</i> -pyrazol-3-yl]phenyl]-carbamic acid 2-methyl-2-propenyl ester. |
| 945236-54-4 | 1-(1,3-benzodioxol-5-yl)-N-[4-methyl-3-(1-methyl-1 <i>H</i> -pyrazol-3-yl)phenyl]cyclopropanecarboxamide. |
| 142622-93-3 | N-[2,4-dichloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-3-yl]phenyl]-2,2,2-trifluoroacetamide. |
| 142621-98-5 | N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide. |
| 2231121-13-2 | N-[4-bromo-2-fluoro-5-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2 <i>H</i> -tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide. |
| 2231119-31-4 | N-[4-bromo-3-[2-[[2-(trimethylsilyl)ethoxy]methyl]-2 <i>H</i> -tetrazol-5-yl]phenyl]-1-(3-chlorophenyl)cyclopropanecarboxamide. |
| 159291-92-6 | 1-bromo-N-[2-chloro-5-[4-chloro-1-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-3-yl]-4-fluorophenyl]cyclopropanecarboxamide, or |
| 141576-10-5 | N-[2-chloro-5-[4-chloro-1-methyl-5-(methylsulfonyl)-1 <i>H</i> -pyrazol-3-yl]-4-fluorophenyl]-2,2,2-trifluoroacetamide. |

3. A compound of Formula III:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N, NR^{8a}, O, S, or CR^{6a};

X² is N or NR^{8b};

X³ is N, NR^{8c}, or CR^{6c};

X⁴ is N or CR^{6d};

provided that the ring containing X¹, X², X³, and X⁴ is aromatic;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^3 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^2 and R^3 together form a heterocyclyl, which may further be optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{6a} and R^{8b} , R^{8b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{13})_2$, $-\text{OR}^{13}$, $-\text{SR}^{13}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{R}^{13}$, $-\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{13})_2$, or $-\text{NR}^{13}\text{C}(\text{O})\text{OR}^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{L}-C_{1-6}$ alkyl, $-\text{L}-C_{2-6}$ alkenyl, $-\text{L}-C_{2-6}$ alkynyl, $-\text{L}-C_{1-6}$ haloalkyl, $-\text{L}-C_{3-10}$ cycloalkyl, $-\text{L}-\text{heterocyclyl}$, $-\text{L}-\text{aryl}$, or $-\text{L}-\text{heteroaryl}$; and

each L is independently $-\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{C}_{1-6}\text{ alkyl})-$, $-\text{N}(\text{C}_{2-6}\text{ alkenyl})-$, $-\text{N}(\text{C}_{2-6}\text{ alkynyl})-$, $-\text{N}(\text{C}_{1-6}\text{ haloalkyl})-$, $-\text{N}(\text{C}_{3-10}\text{ cycloalkyl})-$, $-\text{N}(\text{heterocyclyl})-$, $-\text{N}(\text{aryl})-$, $-\text{N}(\text{heteroaryl})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6}\text{ alkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6}\text{ alkenyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6}\text{ alkynyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6}\text{ haloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{3-10}\text{ cycloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{heterocyclyl})-$, $-\text{C}(\text{O})\text{N}(\text{aryl})-$, $-\text{C}(\text{O})\text{N}(\text{heteroaryl})-$, $-\text{NHC}(\text{O})-$, $-\text{NHC}(\text{O})\text{O}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NHS}(\text{O})-$, or $-\text{S}(\text{O})_2\text{NH}-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{SF}_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl;

provided that:

R^2 and R^3 are not simultaneously methyl;

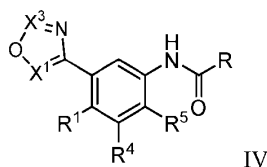
when X^1 is O: then at least one of R^{8b} , R^{8c} , R^{6c} , or R^{6d} is other than hydrogen; and

the compound is not:

1150100-88-1 $\text{N}'-[2,4\text{-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl}]-\text{N-phenyl-N-4-piperidinylurea}$,

- 938467-87-9 N'-[4-chloro-3-(2-methyl-2H-tetrazol-5-yl)phenyl]-N-(3,3-diphenylpropyl)-N-[2-(4-morpholinyl)ethyl]-urea,
- 1808766-39-3 4-(3-chlorophenyl)-N-[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide,
- 1071521-28-2 4-(3-fluorobenzoyl)-N-[4-fluoro-3-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]phenyl]-1-piperazinecarboxamide,
- 1071521-22-6 4-(3-fluorobenzoyl)-N-[4-fluoro-3-(1H-1,2,4-triazol-5-yl)phenyl]-1-piperazinecarboxamide,
- 1095716-86-1 N-[4-chloro-3-ethyl-5-(1-methyl-1H-pyrazol-4-yl)phenyl]-7,8-dihydro-4-(2-methylphenyl)-2-(3-pyridinyl)pyrido[4,3-d]pyrimidine-6(5H)-carboxamide, or
- 1150100-22-3 N-[4-[[5-[[4-[[[2,4-difluoro-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]amino]carbonyl]phenylamino]-1-piperidinyl]methyl]-6-methyl-2-pyridinyl]oxy]phenyl]methanesulfonamide.

4. A compound of Formula IV:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N or CR^{6a};

X³ is N or CR^{6c};

R is -NR²R³, -OR⁷, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl; wherein the C₁₋₆ alkyl is substituted with one to five Z¹; and wherein the C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl is optionally substituted with one to five Z¹;

R¹ is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R³ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

or R² and R³ together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

R^{6a} and R^{6c} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^7 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{10} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a} ;

each R^{12} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1a} is independently halo, cyano, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{N}(\text{R}^{13})_2$, $-\text{OR}^{13}$, $-\text{SR}^{13}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{R}^{13}$, $-\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{C}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})\text{N}(\text{R}^{13})_2$, $-\text{NR}^{13}\text{S}(\text{O})_2\text{N}(\text{R}^{13})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{13})_2$, or $-\text{NR}^{13}\text{C}(\text{O})\text{OR}^{13}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b} ;

each Z^{1b} is independently halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-\text{L}-\text{C}_{1-6}$ alkyl, $-\text{L}-\text{C}_{2-6}$ alkenyl, $-\text{L}-\text{C}_{2-6}$ alkynyl, $-\text{L}-\text{C}_{1-6}$ haloalkyl, $-\text{L}-\text{C}_{3-10}$ cycloalkyl, $-\text{L}-\text{heterocyclyl}$, $-\text{L}-\text{aryl}$, or $-\text{L}-\text{heteroaryl}$; and

each L is independently $-\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{C}_{1-6} \text{ alkyl})-$, $-\text{N}(\text{C}_{2-6} \text{ alkenyl})-$, $-\text{N}(\text{C}_{2-6} \text{ alkynyl})-$, $-\text{N}(\text{C}_{1-6} \text{ haloalkyl})-$, $-\text{N}(\text{C}_{3-10} \text{ cycloalkyl})-$, $-\text{N}(\text{heterocyclyl})-$, $-\text{N}(\text{aryl})-$, $-\text{N}(\text{heteroaryl})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6} \text{ alkenyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{2-6} \text{ alkynyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ haloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{C}_{3-10} \text{ cycloalkyl})-$, $-\text{C}(\text{O})\text{N}(\text{heterocyclyl})-$, $-\text{C}(\text{O})\text{N}(\text{aryl})-$, $-\text{C}(\text{O})\text{N}(\text{heteroaryl})-$, $-\text{NHC}(\text{O})-$, $-\text{NHC}(\text{O})\text{O}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NHS}(\text{O})-$, or $-\text{S}(\text{O})_2\text{NH}-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{SF}_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, and heteroaryl;

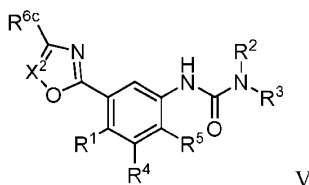
provided that:

R^{6c} is not 4-amino-2-[(3,4,5-trimethoxyphenyl)amino]-5-thiazolyl, [[4-(1-pyrrolidinylmethyl)phenyl]amino]-5-thiazolyl, or [[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino]-5-thiazolyl; and

when R is $-\text{OR}^7$; then R^7 is not *iso*-butyl or *tert*-butyl; and the compound is not:

2024618-95-7 ($\alpha\text{R},5\text{R},8\text{S}$)-N-[4-chloro-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5,6,7,8-tetrahydro- $\alpha,2,5$ -trimethyl-8-quinolineacetamide.

5. A compound of Formula V:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X^2 is N or CR^{6b};

R^1 is halo, cyano, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₁₀ cycloalkyl, is optionally substituted with one to five Z¹;

R^2 and R^3 together form a heterocyclyl, which may further be optionally substituted with one to five Z¹;

R^4 is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^5 is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -SR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z¹;

R^{6b} is hydrogen, halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

R^{6c} is halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -C(O)R¹¹, -C(O)OR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -NR¹¹S(O)R¹¹, -NR¹¹S(O)₂R¹¹, -S(O)N(R¹¹)₂, -S(O)₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹S(O)N(R¹¹)₂, -NR¹¹S(O)₂N(R¹¹)₂, -OC(O)N(R¹¹)₂, or -NR¹¹C(O)OR¹¹; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z¹;

or R^{6b} and R^{6c} together form a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z¹;

each Z¹ is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹²)₂, -OR¹², -SR¹², -C(O)R¹², -C(O)OR¹², -S(O)R¹², -S(O)₂R¹², -C(O)N(R¹²)₂, -NR¹²C(O)R¹², -NR¹²S(O)R¹², -NR¹²S(O)₂R¹², -S(O)N(R¹²)₂, -S(O)₂N(R¹²)₂, -NR¹²C(O)N(R¹²)₂, -NR¹²S(O)N(R¹²)₂, -NR¹²S(O)₂N(R¹²)₂, -OC(O)N(R¹²)₂, or -NR¹²C(O)OR¹²; wherein

each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl;

provided that at least one of the following occurs:

X² is N; or

R¹ is other than methyl; or

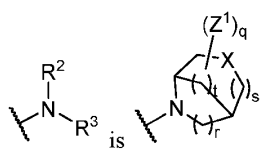
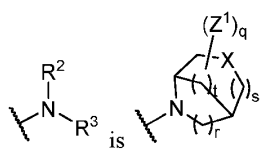
R² and R³ form an optionally substituted bridged heterocyclyl, which is optionally fused to an aryl or heteroaryl ring; or

R² and R³ form an optionally substituted monocyclic 7-membered heterocyclyl, which is optionally fused to an aryl or heteroaryl ring;

and the compound is not:

- 2433600-20-3 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-7-azabicyclo[2.2.1]heptane-7-carboxamide,
- 1950533-91-1 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2,5-diazabicyclo[2.2.2]octane-2-carboxamide,
- 1956717-19-3 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3,9-diazabicyclo[4.2.1]nonane-9-carboxamide,
- 1951851-26-5 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-azabicyclo[3.2.1]octane-8-carboxamide,
- 1950762-35-2 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxa-8-azabicyclo[3.2.1]octane-8-carboxamide
- 1948326-39-3 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxamide,
- 2390318-25-7 (1S,4S)-2-thia-5-azabicyclo[2.2.1]heptane-5-carboxamide, N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-, 2-oxide,
- 2134719-79-0 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxamide,
- 1951235-51-0 1,3,3a,4,5,6,7,7a-octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-etheno-2H-isoindole-2-carboxamide,
- 2128457-53-2 N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4-azatricyclo[4.3.1.1^{3,8}]undecane-4-carboxamide,
- 1943194-72-6 (3aR,7aS)-1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1954930-48-3 octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1950392-13-8 1,3,3a,4,7,7a-hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
- 2127527-42-6 octahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-epoxy-2H-isoindole-2-carboxamide,
- 2321449-65-2 rel-(3aR,4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,
- 1943187-21-0 (4S,7R)-octahydro-3a-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-4,7-methano-2H-isoindole-2-carboxamide,

- 2128457-20-3 hexahydro-2-methyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2129297-32-9 hexahydro-3,5-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2430356-12-8 hexahydro-4-methoxy-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2135054-93-0 hexahydro-3,3-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2130442-49-6 hexahydro-4,4-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide,
- 2134261-73-5 hexahydro-2,6-dimethyl-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-1H-azepine-1-carboxamide, or
- 1944921-02-1 hexahydro-N-[4-methyl-3-(4-methyl-2-oxazolyl)phenyl]-2-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-azepine-1-carboxamide.

6. The compound of any one of claims 1-5, wherein R or the moiety  is , which may optionally be fused to a C₆ aryl; wherein:

q is 0, 1, 2, or 3;

r is 0 or 1;

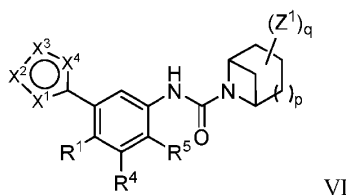
s is 0, 1, or 2;

t is 1 or 2;

X is CH₂, CHZ¹, C(Z¹)₂, NR⁹, O, or S; and

R⁹ is H or Z¹.

7. A compound of Formula VI:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers thereof, wherein:

X¹ is N, NR^{8a}, O, S, or CR^{6a},

X² is N, NR^{8b}, O, S, or CR^{6b},

X³ is N, NR^{8c}, or CR^{6c};

X^4 is N or CR^{6d} ;

provided that at least one of X^1 , X^2 , X^3 , and X^4 is N, and the ring containing X^1 , X^2 , X^3 , and X^4 is aromatic;

q is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, or 3;

R^1 is halo, cyano, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{3-6} cycloalkyl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-10} cycloalkyl, is independently optionally substituted with one to five Z^1 ;

R^4 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

R^5 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{11}$, $-SR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-NR^{11}S(O)R^{11}$, $-NR^{11}S(O)_2R^{11}$, $-S(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-NR^{11}C(O)N(R^{11})_2$, $-NR^{11}S(O)N(R^{11})_2$, $-NR^{11}S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, or $-NR^{11}C(O)OR^{11}$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, is independently optionally substituted with one to five Z^1 ;

R^{8a} , R^{8b} , and R^{8c} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^1 ;

or R^{8a} and R^{6b} , or R^{8b} and R^{6c} , or R^{6b} and R^{6c} , or R^{8c} and R^{6d} , or R^{6c} and R^{6d} , together form a 5-membered cycloalkyl or a 5-membered heterocyclyl, which may further be independently optionally substituted with one to five Z^1 ;

each Z^1 is independently halo, cyano, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-N(R^{12})_2$, $-OR^{12}$, $-SR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}S(O)R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-S(O)N(R^{12})_2$, $-S(O)_2N(R^{12})_2$, $-NR^{12}C(O)N(R^{12})_2$, $-NR^{12}S(O)N(R^{12})_2$, $-NR^{12}S(O)_2N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-NR^{12}C(O)OR^{12}$; wherein

each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹⁰ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R¹² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

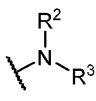
each Z^{1a} is independently halo, cyano, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -SR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -NR¹³S(O)R¹³, -NR¹³S(O)₂R¹³, -S(O)N(R¹³)₂, -S(O)₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -NR¹³S(O)N(R¹³)₂, -NR¹³S(O)₂N(R¹³)₂, -OC(O)N(R¹³)₂, or -NR¹³C(O)OR¹³; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

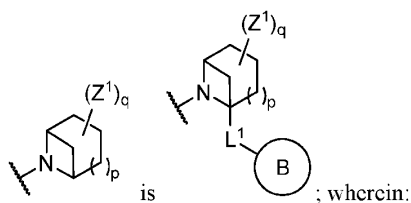
each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C₁₋₆ alkyl, -L-C₂₋₆ alkenyl, -L-C₂₋₆ alkynyl, -L-C₁₋₆ haloalkyl, -L-C₃₋₁₀ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -N(C₁₋₆ alkyl)-, -N(C₂₋₆ alkenyl)-, -N(C₂₋₆ alkynyl)-, -N(C₁₋₆ haloalkyl)-, -N(C₃₋₁₀ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C₁₋₆ alkyl)-, -C(O)N(C₂₋₆ alkenyl)-, -C(O)N(C₂₋₆ alkynyl)-, -C(O)N(C₁₋₆ haloalkyl)-, -C(O)N(C₃₋₁₀ cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -NHC(O)-, -NHC(O)O-, -NHC(O)NH-, -NHS(O)-, or -S(O)₂NH-;

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five substituents independently selected from halo, cyano, -OH, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl.

8. The compound of any one of claims 1-5 or 7, wherein R, the moiety , or the moiety



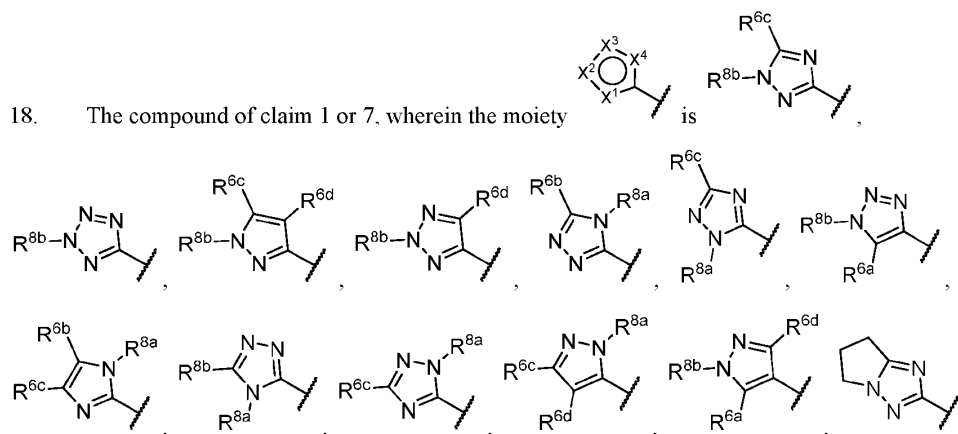
q is 0, 1, 2, 3, or 4;

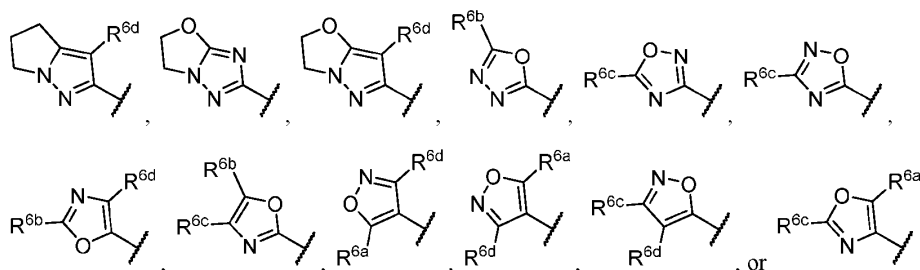
p is 0, 1, 2, or 3;

Ring B is C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^{1b}, and

L¹ is a bond, C₁₋₄ alkylene, C₂₋₄ alkenylene, or C₂₋₄ alkynylene.

9. The compound of claim 7 or 8, wherein p is 1.
10. The compound of claim 6, 7, or 8, wherein q is 1 or 2.
11. The compound of any preceding claim, wherein R¹ is halo, cyano, C₁₋₃ alkyl, C₁₋₃ haloalkyl, or C₃₋₆ cycloalkyl optionally substituted with cyano or methyl.
12. The compound of any preceding claim, wherein R¹ is fluoro, chloro, cyano, methyl, ethyl, isopropyl, difluoromethyl, trifluoromethyl, cyclobutyl, or cyclopropyl optionally substituted with cyano or methyl.
13. The compound of any preceding claim, wherein R¹ is chloro, cyano, or trifluoromethyl.
14. The compound of any preceding claim, wherein R⁴ is hydrogen or C₁₋₆ alkyl.
15. The compound of any preceding claim, wherein R⁴ is hydrogen or methyl.
16. The compound of any preceding claim, wherein R⁵ is hydrogen or halo.
17. The compound of any preceding claim, wherein R⁵ is hydrogen or fluoro.





19. A compound selected from Table 1, or a pharmaceutically acceptable salt thereof.
20. A compound selected from Table 2, or a pharmaceutically acceptable salt thereof.
21. A pharmaceutical composition comprising a compound of any preceding claim, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, and a pharmaceutically acceptable carrier.
22. A method for inhibiting SARM1 activity, the method comprising contacting a cell with an effective amount of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, the pharmaceutical composition of claim 21.
23. The method of claim 22, wherein the contacting is *in vivo*.
24. A method for treating a disease or condition mediated, at least in part, by SARM1, the method comprising administering to a subject in need thereof, an effective amount of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21.
25. A method for inhibiting axon degeneration, the method comprising administering to a subject in need thereof, an effective amount of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21.
26. A method for treating a neurodegenerative or neurological disease or disorder, the method comprising administering an effective amount of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21, to a subject in need thereof.
27. The method of claim 26, wherein the neurodegenerative or neurological disease or disorder is associated with axonal degeneration, axonal damage, axonopathy, a demyelinating disease, a central pontine myelinolysis, a nerve injury disease or disorder, a metabolic disease, a mitochondrial disease, metabolic axonal degeneration, axonal damage resulting from traumatic axonal injury (TAI), a leukoencephalopathy or a leukodystrophy.
28. The method of claim 24, wherein the disease or condition is a spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, osmotic hyponatremia, hypoxic

demyelination, ischemic demyelination, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury (TBI), traumatic axonal injury (TAI), post radiation injury, neurologic complications of chemotherapy (chemotherapy induced peripheral neuropathy, CIPN), neuropathy, acute ischemic optic neuropathy, vitamin B₁₂ deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, retinal degeneration, retinitis pigmentosa, glaucoma, retinitis pigmentosa, traumatic optic injury, Leber's hereditary optic atrophy (neuropathy), Leber congenital amaurosis, neuromyelitis optica, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, west Nile virus encephalopathy, La Crosse virus encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, essential tremor, Charcot-Marie-Tooth disease, motoneuron disease, spinal muscular atrophy (SMA), hereditary sensory and autonomic neuropathy (HSAN), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, hereditary ataxias, noise induced hearing loss, congenital hearing loss, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, HIV neuropathy, enteric neuropathies and axonopathies, Guillain-Barre syndrome, or severe acute motor axonal neuropathy (AMAN).

29. A method for treating chemotherapy induced peripheral neuropathy (CIPN), the method comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21.

30. Use of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21, for treating a disease or condition mediated, at least in part, by SARM1.

31. The use of claim 29, wherein the disease or condition is a spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, osmotic hyponatremia, hypoxic demyelination, ischemic demyelination, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury (TBI), traumatic axonal injury (TAI), post radiation injury, neurologic complications of chemotherapy (chemotherapy induced peripheral neuropathy, CIPN), neuropathy, acute ischemic optic neuropathy, vitamin B₁₂ deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, retinal degeneration, retinitis

pigmentosa, glaucoma, traumatic optic injury, Leber's hereditary optic atrophy (neuropathy), Leber congenital amaurosis, neuromyelitis optica, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, west Nile virus encephalopathy, La Crosse virus encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, essential tremor, Charcot-Marie-Tooth disease, motoneuron disease, spinal muscular atrophy (SMA), hereditary sensory and autonomic neuropathy (HSAN), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Fredrich's ataxia, hereditary ataxias, noise induced hearing loss, congenital hearing loss, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, HIV neuropathy, enteric neuropathies and axonopathies, Guillain-Barre syndrome, or severe acute motor axonal neuropathy (AMAN).

32. A compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21, for use in therapy.

33. A compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21, for use in treating a spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, osmotic hyponatremia, hypoxic demyelination, ischemic demyelination, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury (TBI), traumatic axonal injury (TAI), post radiation injury, neurologic complications of chemotherapy (chemotherapy induced peripheral neuropathy, CIPN), neuropathy, acute ischemic optic neuropathy, vitamin B₁₂ deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, retinal degeneration, retinitis pigmentosa, glaucoma, traumatic optic injury, Leber's hereditary optic atrophy (neuropathy), Leber congenital amaurosis, neuromyelitis optica, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, west Nile virus encephalopathy, La Crosse virus encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, essential tremor, Charcot-Marie-Tooth disease, motoneuron disease, spinal muscular atrophy (SMA), hereditary sensory and autonomic neuropathy (HSAN), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Fredrich's ataxia, hereditary ataxias, noise induced hearing loss, congenital hearing loss, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, HIV neuropathy,

enteric neuropathies and axonopathies, Guillain-Barre syndrome, or severe acute motor axonal neuropathy (AMAN).

34. The use of a compound of any one of claims 1-20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, tautomer, or mixture of stereoisomers thereof, or the pharmaceutical composition of claim 21, for the manufacture of a medicament for treating a spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, osmotic hyponatremia, hypoxic demyelination, ischemic demyelination, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury (TBI), traumatic axonal injury (TAI), post radiation injury, neurologic complications of chemotherapy (chemotherapy induced peripheral neuropathy, CIPN), neuropathy, acute ischemic optic neuropathy, vitamin B₁₂ deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, retinal degeneration, retinitis pigmentosa, glaucoma, traumatic optic injury, Leber's hereditary optic atrophy (neuropathy), Leber congenital amaurosis, neuromyelitis optica, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, west Nile virus encephalopathy, La Crosse virus encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, essential tremor, Charcot-Marie-Tooth disease, motoneuron disease, spinal muscular atrophy (SMA), hereditary sensory and autonomic neuropathy (HSAN), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Fredrich's ataxia, hereditary ataxias, noise induced hearing loss, congenital hearing loss, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, HIV neuropathy, enteric neuropathies and axonopathies, Guillain-Barre syndrome, or severe acute motor axonal neuropathy (AMAN).