

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 63/325,577, filed March 30, 2022, and United States Provisional Application Serial Number 63/346,203, filed May 26, 2022, the contents of which are hereby incorporated by reference in their entirety.

FIELD

[0002] The present disclosure relates generally to small molecule modulators of NLR Family Pyrin Domain Containing 3 (NLRP3), and their use as therapeutic agents.

BACKGROUND

[0003] Inhibition of NLRP3 activation has been shown to result in potent therapeutic effects in animal models of inflammatory diseases. Modulators of NLRP3, inhibitors in particular, have broad therapeutic potential in a wide array of auto-inflammatory and chronic inflammatory diseases that either require better treatment options or for which no adequate therapies exist. Therapies targeting NLRP3-dependent cytokines are already approved for therapeutic use; however, they have notable disadvantages relative to direct NLRP3 antagonists. There remains a strong impetus for the discovery and clinical development of molecules that antagonize NLRP3.

DESCRIPTION

[0004] 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 NLRP3.

[0005] In some embodiments, provided are compounds that modulate the activity of NLRP3. In some embodiments, the compounds inhibit the activation of NLRP3.

[0006] 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.

[0007] In another embodiment, provided is a method for treating a disease or condition mediated, at least in part, by NLRP3, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0008] In another embodiment, provided is a method for treating a disease or condition mediated, at least in part, by TNF- α , the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof. In some embodiments the administration is to a subject resistant to treatment with an anti-TNF- α agent. In some

embodiments, the disease is a gut disease or condition. In some embodiments, the disease or condition is inflammatory bowel disease, Crohn's disease, or ulcerative colitis.

[0009] 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.

[0010] 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 NLRP3.

[0011] 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 NLRP3.

[0012] 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

[0013] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[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, " C_{1-6} 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., -(CH₂)₃CH₃), sec-butyl (i.e., -CH(CH₃)CH₂CH₃), isobutyl (i.e., -CH₂CH(CH₃)₂), and tert-butyl (i.e., -C(CH₃)₃), and “propyl” includes n-propyl (i.e., -(CH₂)₂CH₃), and isopropyl (i.e., -CH(CH₃)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 quinolinylenyl 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., C₂₋₂₀ alkenyl), 2 to 12 carbon atoms (i.e., C₂₋₁₂ alkenyl), 2 to 8 carbon atoms (i.e., C₂₋₈ alkenyl), 2 to 6 carbon atoms (i.e., C₂₋₆ alkenyl), or 2 to 4 carbon atoms (i.e., C₂₋₄ 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., C₂₋₂₀ alkynyl), 2 to 12 carbon atoms (i.e., C₂₋₁₂ alkynyl), 2 to 8 carbon atoms (i.e., C₂₋₈ alkynyl), 2 to 6 carbon atoms (i.e., C₂₋₆ alkynyl), or 2 to 4 carbon atoms (i.e., C₂₋₄ 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] “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.

[0023] “Acyl” refers to a group -C(O)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.

[0024] “Amido” refers to both a “C-amido” group which refers to the group -C(O)NR^yR^z and an “N-amido” group which refers to the group -NR^yC(O)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.

[0025] “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.

[0026] “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.

[0027] “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.

[0028] “Arylalkyl” or “Aralkyl” refers to the group “aryl-alkyl”.

[0029] “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.

[0030] “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.

[0031] “Cyanoalkyl” 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.

[0032] “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, decalinyl, 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.

[0033] “Cycloalkylalkyl” refers to the group “cycloalkyl-alkyl-”.

[0034] “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.

[0035] “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.

[0036] “Halogen” or “halo” refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0037] “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.

[0038] “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.

[0039] “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.

[0040] “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.

[0041] “Heteroaryl” refers to an aromatic group having a single ring 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, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, 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, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, thiophenyl (i.e., thienyl), triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, 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.

[0042] “Heteroarylalkyl” refers to the group “heteroaryl-alkyl”.

[0043] “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, decahydroisoquinoly, 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, tetrahydrofuryl, tetrahydropyrany, trithianyl, tetrahydroquinoliny, 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.

[0044] “Heterocyclylalkyl” refers to the group “heterocyclyl-alkyl-.”

[0045] “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.

[0046] “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.

[0047] “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.

[0048] “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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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 labelled 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.

[0055] 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.

[0056] 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 , ^{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.

[0057] 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.

[0058] 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.

[0059] Provided are also or 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.

[0060] 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 an organic acid. 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] “Diastereomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

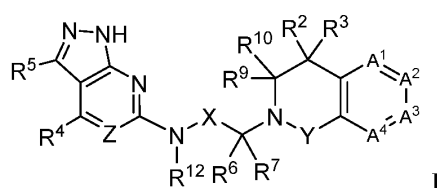
[0065] Relative centers of the compounds as depicted herein are indicated graphically using the “thick bond” style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[0066] “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

[0067] Provided herein are compounds that are modulators of NLRP3. In certain embodiments, provided is a compound of Formula I:



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

X is C(X¹), NR¹⁶, S(O)₂, or S(O)(NR¹⁸);

Y is C(Y¹), O, NR¹⁷, S(O)₂, or S(O)(NR¹⁹);

Z is CR⁸ or N;

X¹ is O, NR¹⁸, or S;

Y¹ is O, NR¹⁹, or S;

A¹, A², A³, and A⁴ are each independently N, CH, or CR¹; provided at least one of A¹, A², A³, and A⁴ is CR¹;

each R¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 eight Z¹; or

any two adjacent R¹ together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO₂, -SF₅, -OR¹¹, -N(R¹¹)₂, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹C(O)OR¹¹, -NR¹¹C(O)R¹¹, -OC(O)R¹¹, -OC(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, halo, or cyano; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z¹;

R³ is hydrogen, halo, cyano, 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 eight Z¹; or

R² and R³ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

R⁴ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁵ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl; or

R⁴ and R⁵ together form a heterocyclyl or heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁶ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl may further be optionally substituted with one to five Z^{1b};

R⁷ is hydrogen, halo, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl, or may further be optionally substituted with one to five Z^{1b};

or R⁶ and R⁷ join to form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl ring may further be optionally substituted with one to five Z^{1b};

R⁸ is hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

R⁹ and R¹⁰ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl, wherein each C₁₋₆ alkyl or C₁₋₆ haloalkyl is independently optionally substituted with one to five Z¹; or

R⁹ and R¹⁰ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

each Z¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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};

R¹² 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 optionally substituted with one to eight Z¹;

each Z^{1a} is independently hydroxy, halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)₀₋₂R¹³, -NR¹³S(O)₀₋₂R¹³, -S(O)₀₋₂N(R¹³)₂, -NR¹³S(O)₀₋₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -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, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

each R¹⁴ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R¹⁶ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

R¹⁷ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

R¹⁸ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

R¹⁹ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

each Z^{1b} is independently halo, cyano, hydroxy, -SH, -NH₂, -NO₂, -SF₅, 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-;

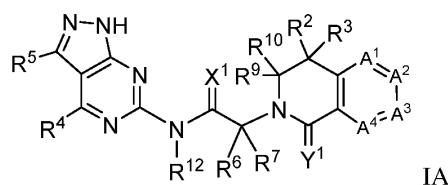
wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five hydroxy, halo, cyano, hydroxy, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆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

[0068] In certain embodiments, X is C(X¹). In certain embodiments, X is NR¹⁶. In certain embodiments, X is S(O)₂.

[0069] In certain embodiments, Y is C(X¹). In certain embodiments, Y is O. In certain embodiments, Y is NR¹⁶. In certain embodiments, Y is S(O)₂.

[0070] In certain embodiments, Z is CR⁸. In certain embodiments, Z is N.

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



IA

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

X¹ is O or S;

Y¹ is O or S;

A¹, A², A³, and A⁴ are each independently N, CH, or CR¹; provided at least one of A¹, A², A³, and A⁴ is CR¹;

each R¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)_{0.2}R¹¹, -NR¹¹S(O)_{0.2}R¹¹, -S(O)_{0.2}N(R¹¹)₂, -NR¹¹S(O)_{0.2}N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 eight Z¹; or

any two adjacent R¹ together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO₂, -SF₅, -OR¹¹, -N(R¹¹)₂, -C(O)R¹¹, -C(O)OR¹¹, -S(O)_{0.2}R¹¹, -NR¹¹S(O)_{0.2}R¹¹, -S(O)_{0.2}N(R¹¹)₂, -NR¹¹S(O)_{0.2}N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹C(O)OR¹¹, -NR¹¹C(O)R¹¹, -OC(O)R¹¹, -OC(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, halo, or cyano; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z¹;

R³ is hydrogen, halo, cyano, 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 eight Z¹; or

R² and R³ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

R⁴ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁵ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl; or

R⁴ and R⁵ together form a heterocyclyl or heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁶ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl may further be optionally substituted with one to five Z^{1b};

R⁷ is hydrogen, halo, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl, or may further be optionally substituted with one to five Z^{1b};

or R⁶ and R⁷ join to form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl ring may further be optionally substituted with one to five Z^{1b};

R⁹ and R¹⁰ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl, wherein each C₁₋₆ alkyl or C₁₋₆ haloalkyl is independently optionally substituted with one to five Z¹; or

R⁹ and R¹⁰ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

each Z¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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};

R¹² 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 optionally substituted with one to eight Z¹;

each Z^{1a} is independently hydroxy, halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)₀₋₂R¹³, -NR¹³S(O)₀₋₂R¹³, -S(O)₀₋₂N(R¹³)₂, -NR¹³S(O)₀₋₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -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, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

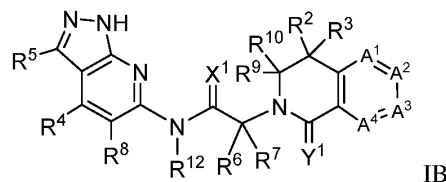
each R¹⁴ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

each Z^{1b} is independently halo, cyano, hydroxy, -SH, -NH₂, -NO₂, -SF₅, 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 hydroxy, halo, cyano, hydroxy, -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.

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



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

X¹ is O or S;

Y¹ is O or S;

A¹, A², A³, and A⁴ are each independently N, CH, or CR¹; provided at least one of A¹, A², A³, and A⁴ is CR¹;

each R¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 eight Z¹; or

any two adjacent R¹ together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO₂, -SF₅, -OR¹¹, -N(R¹¹)₂, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹C(O)OR¹¹, -NR¹¹C(O)R¹¹, -OC(O)R¹¹, -OC(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, halo, or cyano; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z¹;

R³ is hydrogen, halo, cyano, 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 eight Z¹; or

R² and R³ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

R⁴ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁵ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl; or

R⁴ and R⁵ together form a heterocyclyl or heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁶ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl may further be optionally substituted with one to five Z^{1b};

R⁷ is hydrogen, halo, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl, or may further be optionally substituted with one to five Z^{1b};

or R⁶ and R⁷ join to form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl ring may further be optionally substituted with one to five Z^{1b};

R⁸ is hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

R⁹ and R¹⁰ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl, wherein each C₁₋₆ alkyl or C₁₋₆ haloalkyl is independently optionally substituted with one to five Z¹; or

R⁹ and R¹⁰ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

each Z¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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};

R¹² 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 optionally substituted with one to eight Z¹;

each Z^{1a} is independently hydroxy, halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)₀₋₂R¹³, -NR¹³S(O)₀₋₂R¹³, -S(O)₀₋₂N(R¹³)₂, -NR¹³S(O)₀₋₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -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, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

each R¹⁴ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

each Z^{1b} is independently halo, cyano, hydroxy, -SH, -NH₂, -NO₂, -SF₅, 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 hydroxy, halo, cyano, hydroxy, -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.

[0073] In certain embodiments, A², A³ and A⁴ are each independently N, CH, or CR¹; and A¹ is CR¹.

[0074] In certain embodiments, A¹, A³ and A⁴ are each independently N, CH, or CR¹; and A² is CR¹.

[0075] In certain embodiments, A¹, A², and A⁴ are each independently N, CH, or CR¹; and A³ is CR¹.

[0076] In certain embodiments, A¹, A², and A³ are each independently N, CH, or CR¹; and A⁴ is CR¹.

[0077] In certain embodiments, at least one of A¹, A², A³, and A⁴ is N.

[0078] In certain embodiments, A¹, A², A³, and A⁴ are each independently CH or CR¹.

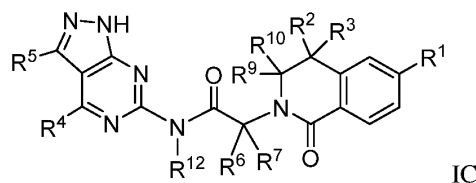
[0079] In certain embodiments, A², A³, and A⁴ are each independently CH or CR¹; and A¹ is CR¹.

[0080] In certain embodiments, A¹, A³, and A⁴ are each independently CH or CR¹; and A² is CR¹.

[0081] In certain embodiments, A¹, A², and A⁴ are each independently CH or CR¹; and A³ is CR¹.

[0082] In certain embodiments, A¹, A², and A³ are each independently CH or CR¹; and A⁴ is CR¹.

[0083] In certain embodiments, provided is a compound represented by Formula IC:

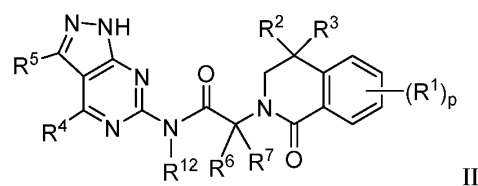


or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁹, R¹⁰, and R¹² are each independently as defined herein.

[0084] In certain embodiments, R^{12} is hydrogen or C_{1-6} alkyl. In certain embodiments, R^{12} is hydrogen or methyl. In certain embodiments, R^{12} is hydrogen. In certain embodiments, R^{12} is C_{1-6} alkyl. In certain embodiments, R^{12} is methyl.

[0085] In certain embodiments, R^9 is hydrogen or C_{1-6} alkyl. In certain embodiments, R^9 is hydrogen or methyl and R^{10} is hydrogen. In certain embodiments, R^9 is hydrogen. In certain embodiments, R^{10} is hydrogen. In certain embodiments, R^9 and R^{10} are hydrogen. In certain embodiments, R^9 is methyl and R^{10} is hydrogen.

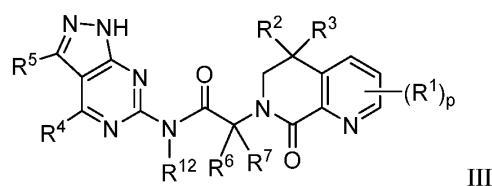
[0086] In certain embodiments, provided is a compound represented by Formula II:



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

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^{12} are each independently as defined herein; and
p is 1, 2, 3, or 4.

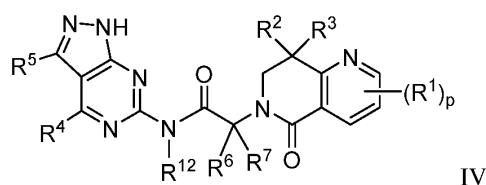
[0087] In certain embodiments, provided is a compound represented by Formula III:



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

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^{12} are each independently as defined herein; and
p is 1, 2, 3, or 4.

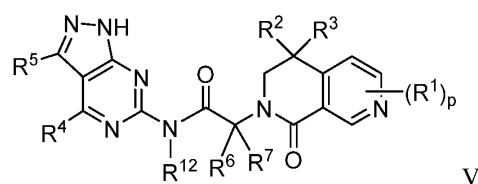
[0088] In certain embodiments, provided is a compound represented by Formula IV:



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

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^{12} are each independently as defined herein; and
p is 1, 2, 3, or 4.

[0089] In certain embodiments, provided is a compound represented by Formula V:



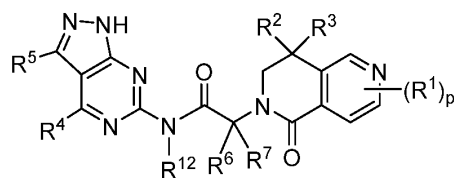
V

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

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^{12} are each independently as defined herein; and

p is 1, 2, 3, or 4.

[0090] In certain embodiments, provided is a compound represented by Formula VI:



VI

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

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^{12} are each independently as defined herein; and

p is 1, 2, 3, or 4.

[0091] In certain embodiments, R^6 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} heteroalkyl, C_{3-10} cycloalkyl, or heterocyclyl. In certain embodiments, R^6 is hydrogen.

[0092] In certain embodiments, R^7 is hydrogen, halo, cyano, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} heteroalkyl, C_{3-10} cycloalkyl, or heterocyclyl. In certain embodiments, R^7 is hydrogen.

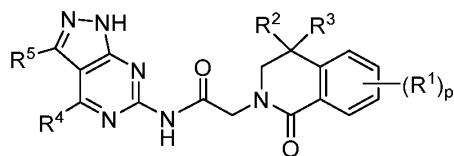
[0093] In certain embodiments, R^6 and R^7 are hydrogen.

[0094] In certain embodiments, R^6 and R^7 join to form a C_{3-10} cycloalkyl.

[0095] In certain embodiments, R^8 is hydrogen, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl. In certain embodiments, R^8 is hydrogen or halo. In certain embodiments, R^8 is hydrogen or fluoro.

[0096] In certain embodiments, R^{12} is hydrogen; R^6 is hydrogen; and R^7 is hydrogen.

[0097] In certain embodiments, provided is a compound represented by Formula VII:



VII

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

R^1 , R^2 , R^3 , R^4 , and R^5 are each independently as defined herein; and

p is 1, 2, 3, or 4.

[0098] In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 1 or 2. In certain embodiments, p is 3. In certain embodiments, p is 4.

[0099] In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₁₀ cycloalkyl, or heterocyclyl, wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₃₋₁₀ cycloalkyl are independently optionally substituted with one to eight Z¹; or any two adjacent R¹ together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring.

[0100] In certain embodiments, each R¹ is independently fluoro, bromo, chloro, iodo, cyano, ethyl, vinyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, methoxy, fluoromethoxy, difluoromethoxy, cyclopropyl, cyclobutyl, cyclopropylmethyl, oxetan-3-yl, 2,2-difluorocycloprop-1-yl, 1-cyanocyclopropyl, 1-methylcyclopropyl, 1-fluoro-2-(trifluoromethyl)cyclopropyl, ethynyl, 1-fluorovinyl, 1-fluorocyclopropyl, 2-fluorocyclopropyl, or 1,2-difluorocyclopropyl; or two adjacent R¹ together with the atoms to which they are attached form a thiophene.

[0101] In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or C₃₋₁₀ cycloalkyl, wherein the C₂₋₆ alkenyl or C₃₋₁₀ cycloalkyl is independently optionally substituted with one to eight Z¹. In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or C₃₋₁₀ cycloalkyl, wherein the C₃₋₁₀ cycloalkyl is independently optionally substituted with one to eight Z¹. In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or C₃₋₁₀ cycloalkyl, wherein the C₂₋₆ alkenyl or C₃₋₁₀ cycloalkyl is independently optionally substituted with one to eight Z¹, wherein each is independently selected from halo, cyano and C₁₋₆ alkyl.

[0102] In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ haloalkyl, or C₃₋₁₀ cycloalkyl. In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ haloalkoxy, C₁₋₆ haloalkyl, or C₃₋₁₀ cycloalkyl. In certain embodiments, each R¹ is independently halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl. In certain embodiments, each R¹ is independently halo or C₁₋₆ alkyl.

[0103] In certain embodiments, each R¹ is independently fluoro, bromo, chloro, iodo, cyano, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, methoxy, fluoromethoxy, difluoromethoxy, cyclopropyl, cyclobutyl, 2,2-difluorocycloprop-1-yl, 1-cyanocyclopropyl, and 1-methylcyclopropyl, ethynyl, 1-fluorovinyl, 1-fluorocyclopropyl, or 1,2-difluorocyclopropyl. In certain embodiments, each R¹ is independently fluoro, bromo, chloro, iodo, cyano, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, methoxy, fluoromethoxy, difluoromethoxy, cyclopropyl, cyclobutyl, 2,2-difluorocycloprop-1-yl, 1-cyanocyclopropyl, and 1-methylcyclopropyl. In certain embodiments, each R¹ is independently fluoro, bromo, -CH₃, -OCHF₂, -CF₃, or cyclopropyl. In certain embodiments, each R¹ is independently fluoro, bromo, or -CH₃. In certain embodiments, each R¹ is independently halo. In certain embodiments, each R¹ is independently bromo. In certain embodiments, each R¹ is independently halo or -CF₃.

[0104] In certain embodiments, p is 1; and each R^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl. In certain embodiments, p is 2; and each R^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl. In certain embodiments, p is 1 or 2; and each R^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl.

[0105] In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl or heterocyclyl ring; wherein the C_{3-10} cycloalkyl or heterocyclyl is independently optionally substituted with one to eight Z^1 . In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl ring optionally substituted with one to eight Z^1 . In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl optionally substituted with halo, cyano, C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl optionally substituted with halo, C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl optionally substituted with fluoro, methyl or trifluoromethyl. In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl ring optionally substituted with C_{1-6} alkyl. In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl ring optionally substituted with methyl. In certain embodiments, R^2 and R^3 together form a heterocyclyl ring optionally substituted with one to eight Z^1 . In certain embodiments, R^2 and R^3 together form a C_{3-10} cycloalkyl or heterocyclyl ring. In certain embodiments, R^2 and R^3 together form an unsubstituted C_{3-10} cycloalkyl ring. In certain embodiments, R^2 and R^3 together form an unsubstituted cyclopropyl ring. In certain embodiments, R^2 and R^3 together form an unsubstituted heterocyclyl ring.

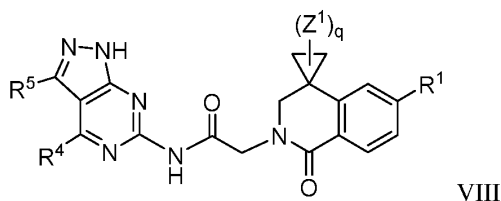
[0106] In certain embodiments, R^2 is C_{1-6} alkyl, C_{1-6} haloalkyl, or $-OR^{11}$, wherein R^{11} is C_{1-6} alkyl optionally substituted with one to five Z^{1a} . In certain embodiments, R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^3 is hydrogen or C_{1-6} alkyl. In certain embodiments, R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^2 is C_{1-6} alkyl. In certain embodiments, R^2 is methyl or ethyl.

[0107] In certain embodiments, R^2 is $-C(R^{24})_2R^{25}$; each R^{24} and R^{25} are independently hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^2 is $-C(R^{24})_2R^{25}$; each R^{24} is independently hydrogen, halo, C_{1-4} alkyl, or C_{1-4} haloalkyl, and R^{25} is hydrogen.

[0108] In certain embodiments, R^3 is hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^3 is hydrogen or C_{1-6} alkyl. In certain embodiments, R^3 is C_{1-6} alkyl. In certain embodiments, R^3 is hydrogen or methyl. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is methyl.

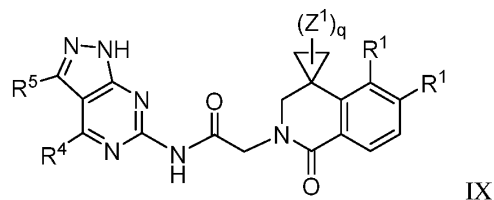
[0109] In certain embodiments, R^2 is C_{1-6} alkyl; R^3 is hydrogen, or C_{1-6} alkyl; or R^2 and R^3 together form a C_{3-10} cycloalkyl ring optionally substituted with C_{1-6} alkyl. In certain embodiments, R^2 and R^3 are C_{1-6} alkyl.

[0110] In certain embodiments, provided is a compound represented by Formula VIII:



or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, or 4; and Z^1 , R^1 , R^4 , and R^5 are each independently as defined herein.

[0111] In certain embodiments, provided is a compound represented by Formula IX:

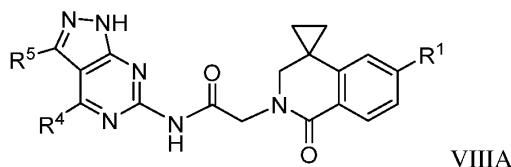


or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein q is 0, 1, 2, 3, or 4; and Z^1 , R^1 , R^4 , and R^5 are each independently as defined herein.

[0112] In certain embodiments, q is 1. In certain embodiments, q is 2. In certain embodiments, q is 3. In certain embodiments, q is 4. In certain embodiments, each Z^1 is independently halo, cyano, C_{1-6} alkyl, or C_{1-6} haloalkyl. In certain embodiments, q is 1 or 2; and each Z^1 is independently halo, cyano, C_{1-6} alkyl, or C_{1-6} haloalkyl.

[0113] In certain embodiments, each R^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl; q is 1 or 2; and each Z^1 is independently halo, cyano, C_{1-6} alkyl, or C_{1-6} haloalkyl.

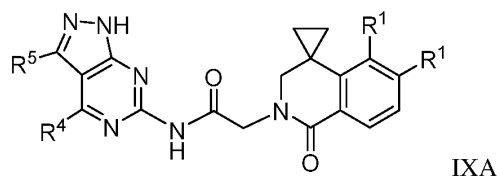
[0114] In certain embodiments, provided is a compound represented by Formula VIIIA:



or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein R^1 , R^4 , and R^5 are each independently as defined herein.

[0115] In certain embodiments, R^1 is halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl. In certain embodiments, R^1 is halo. In certain embodiments, R^1 is bromo. In certain embodiments, R^1 is $-CF_3$.

[0116] In certain embodiments, provided is a compound represented by Formula IXA:



or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein R^1 , R^4 , and R^5 are each independently as defined herein.

[0117] In certain embodiments, each R^1 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl. In certain embodiments, each R^1 is independently fluoro, chloro, bromo, $-CH_3$, or $-CF_3$. In certain embodiments, each R^1 is independently fluoro, bromo, $-CH_3$, or $-CF_3$. In certain embodiments,

each R¹ is independently halo. In certain embodiments, each R¹ is independently bromo. In certain embodiments, each R¹ is independently halo or -CF₃.

[0118] In certain embodiments, R⁵ is hydrogen or C₁₋₆ haloalkyl. In certain embodiments, R⁵ is hydrogen or -CF₃. In certain embodiments, R⁵ is hydrogen. In certain embodiments, R⁵ is C₁₋₆ haloalkyl. In certain embodiments, R⁵ is -CF₃.

[0119] In certain embodiments, R⁴ is hydrogen.

[0120] In certain embodiments, R⁴ is hydrogen; and R⁵ is hydrogen or C₁₋₆ haloalkyl. In certain embodiments, R⁴ is hydrogen; and R⁵ is hydrogen or -CF₃. In certain embodiments, R⁴ is hydrogen; and R⁵ is hydrogen. In certain embodiments, R⁴ is hydrogen; and R⁵ is C₁₋₆ haloalkyl. In certain embodiments, R⁴ is hydrogen; and R⁵ is -CF₃.

[0121] In certain embodiments, each Z^{1a} is independently halo.

[0122] In certain embodiments, each Z¹ is independently halo, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, or -C(O)OR¹¹.

[0123] In certain embodiments, each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0124] In certain embodiments, each R¹¹ is independently hydrogen or C₁₋₆ alkyl. In certain embodiments, each R¹¹ is hydrogen.

[0125] In certain embodiments, R¹² is hydrogen or C₁₋₆ alkyl. In certain embodiments, R¹² is hydrogen.

[0126] In certain embodiments, each R¹³ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl. In certain embodiments, each R¹³ is independently hydrogen or C₁₋₆ alkyl.

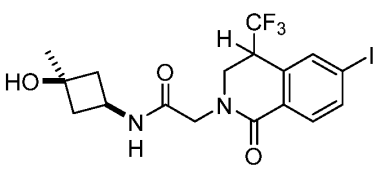
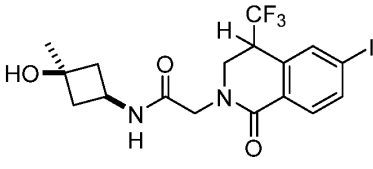
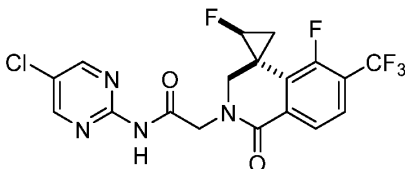
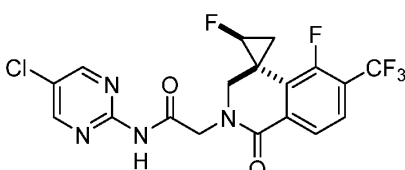
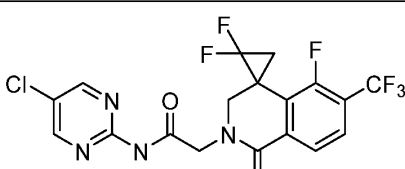
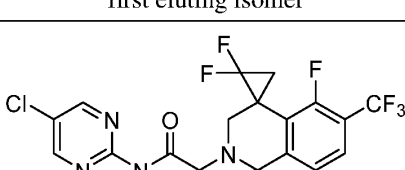
[0127] In certain embodiments, each R¹⁴ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, or C₃₋₆ cycloalkyl. In certain embodiments, each R¹⁴ is independently hydrogen or C₁₋₆ alkyl. In certain embodiments, each R¹⁴ is hydrogen.

[0128] 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

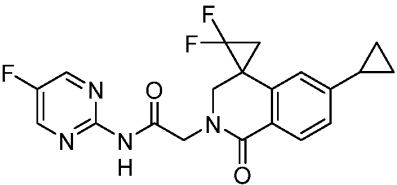
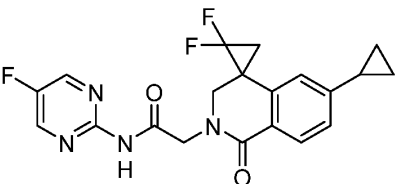
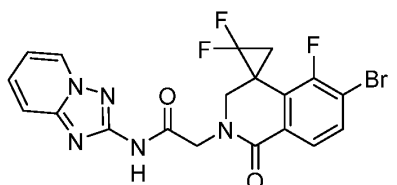
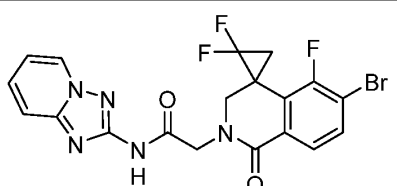
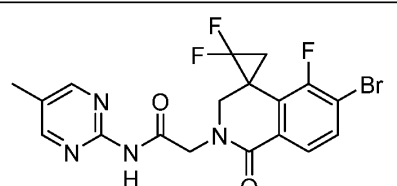
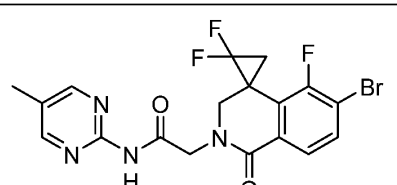
Ex. No.	Structure
1	

Ex. No.	Structure
2	
3	
4	
5	
6	
7	
8	
9	

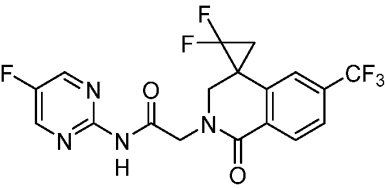
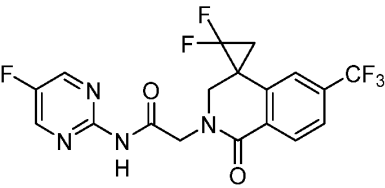
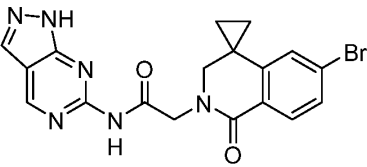
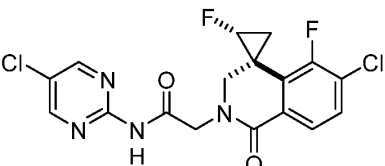
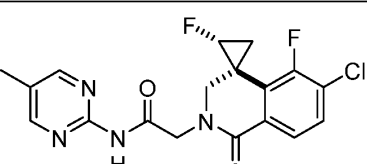
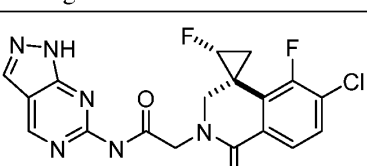
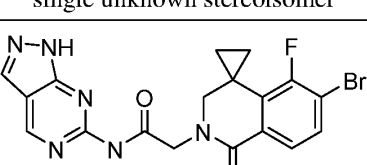
Ex. No.	Structure
10	 first eluting isomer
11	 second eluting isomer
12	 first eluting isomer
13	 second eluting isomer
14	 first eluting isomer
15	 second eluting isomer

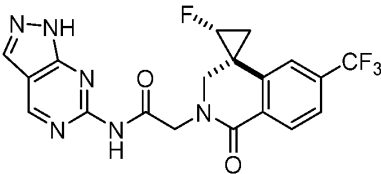
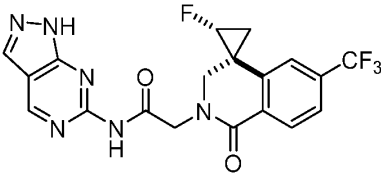
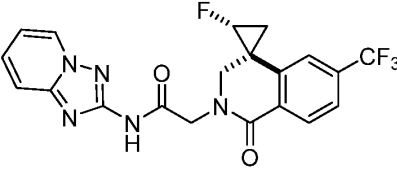
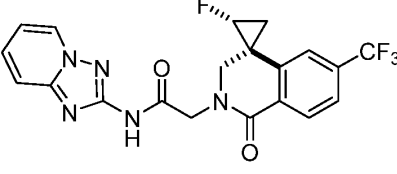
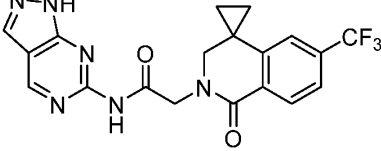
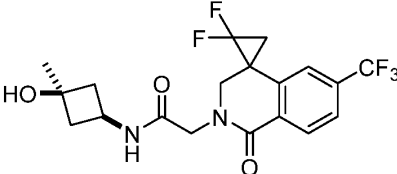
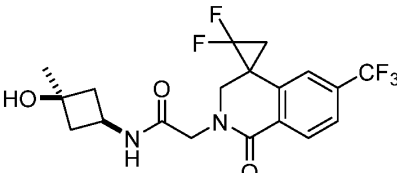
Ex. No.	Structure
16	first eluting isomer
17	second eluting isomer
18	first eluting isomer
19	second eluting isomer
20	first eluting isomer
21	second eluting isomer

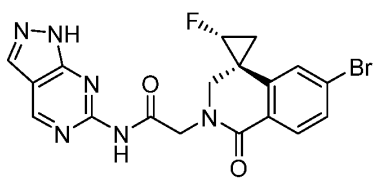
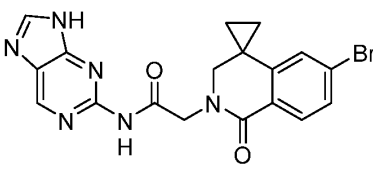
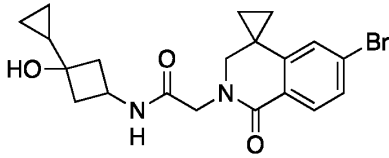
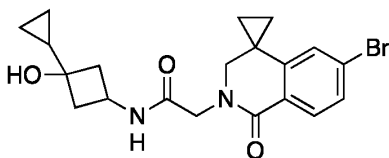
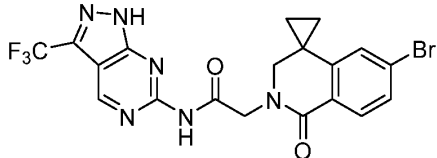
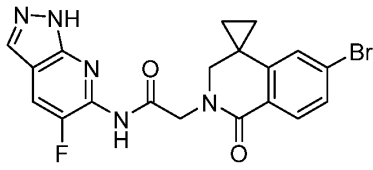
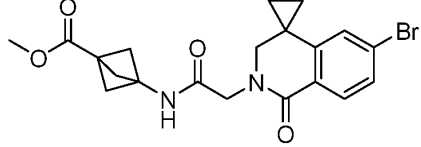
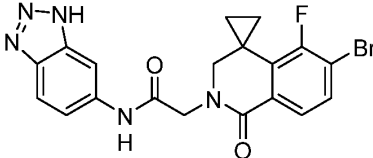
Ex. No.	Structure
22	 first eluting isomer
23	 second eluting isomer
24	 first eluting isomer
25	 second eluting isomer
26	 first eluting isomer
27	 second eluting isomer

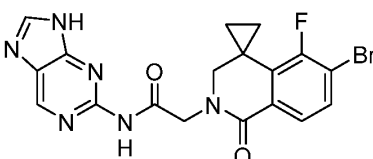
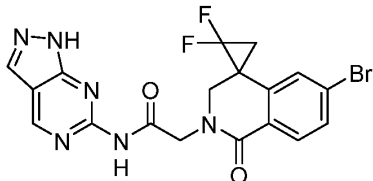
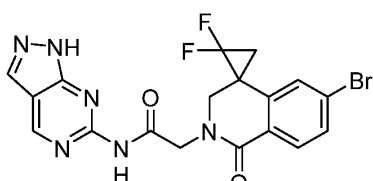
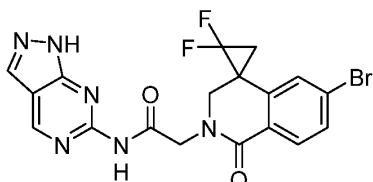
Ex. No.	Structure
28	 first eluting isomer
29	 second eluting isomer
30	 first eluting isomer
31	 second eluting isomer
32	 first eluting isomer
33	 second eluting isomer

Ex. No.	Structure
34	first eluting isomer
35	second eluting isomer
36	first eluting isomer
37	second eluting isomer
38	first eluting isomer
39	second eluting isomer

Ex. No.	Structure
40	 first eluting isomer
41	 second eluting isomer
42	
43	 single unknown stereoisomer
44	 single unknown stereoisomer
45	 single unknown stereoisomer
46	

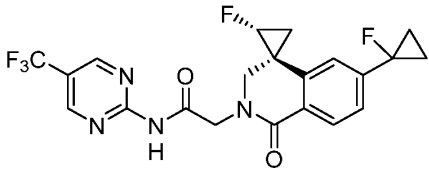
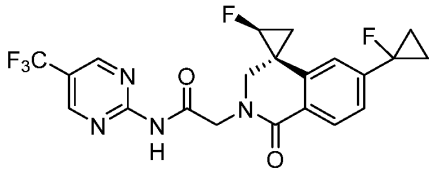
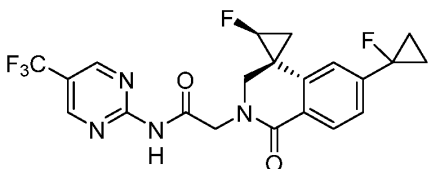
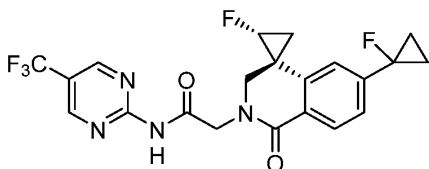
Ex. No.	Structure
47	 first eluting isomer
48	 second eluting isomer
49	 first eluting isomer
50	 second eluting isomer
51	 first eluting isomer
52	 first eluting isomer
53	 second eluting isomer

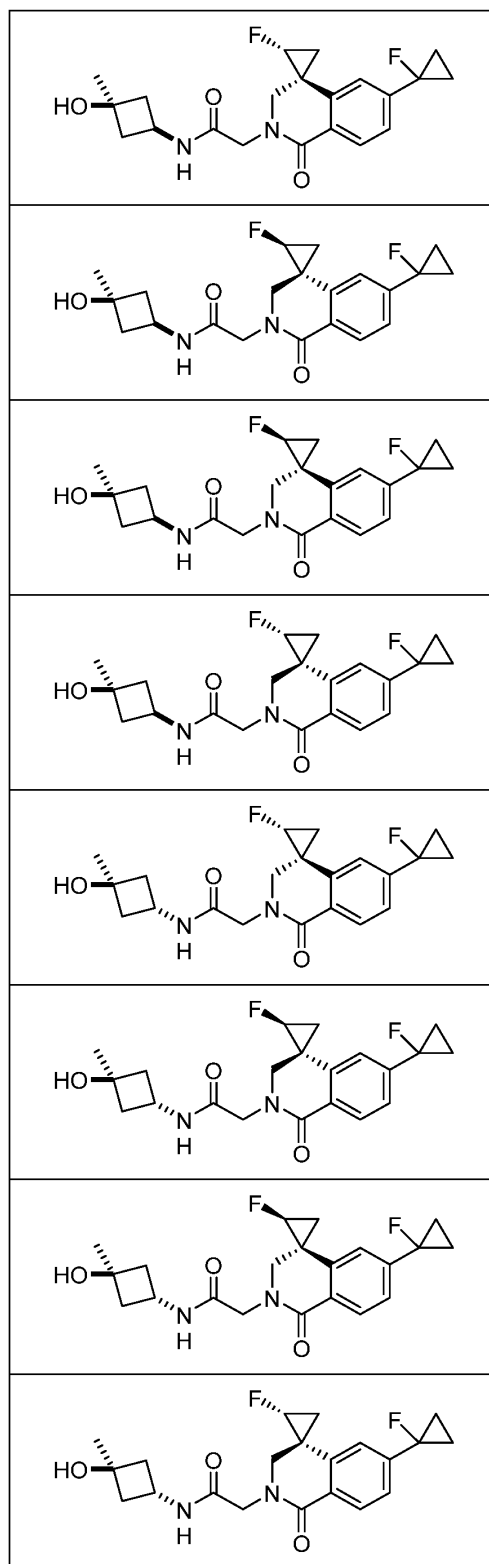
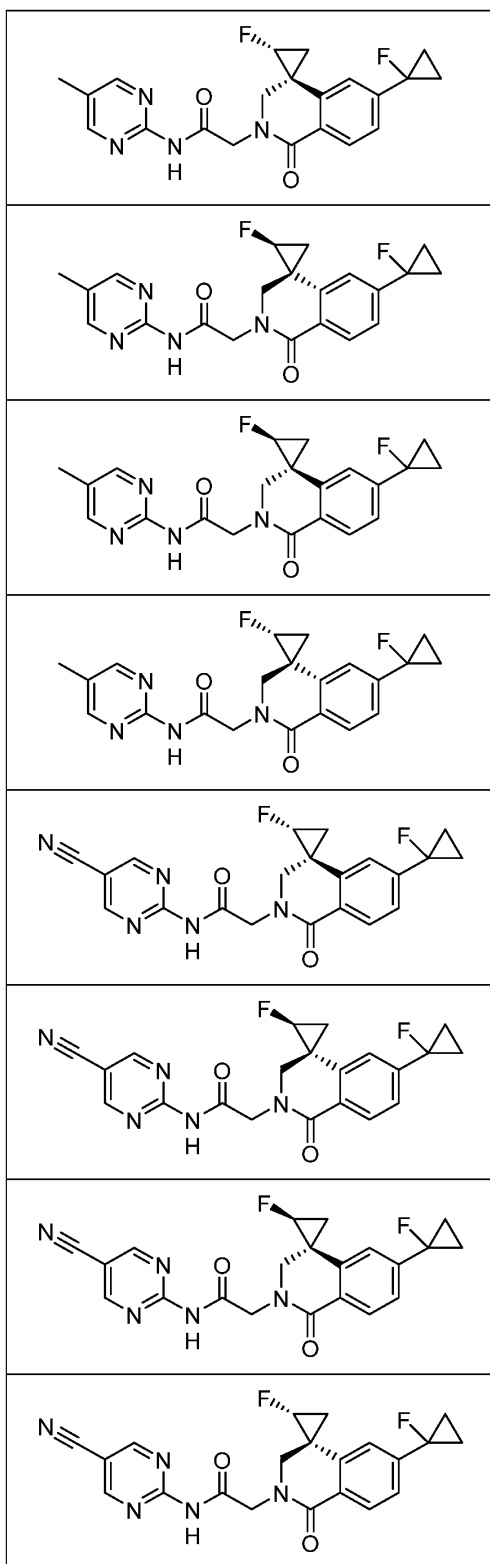
Ex. No.	Structure
54	 single known stereoisomer
55	
56	 first eluting isomer
57	 second eluting isomer
58	
59	
60	
61	

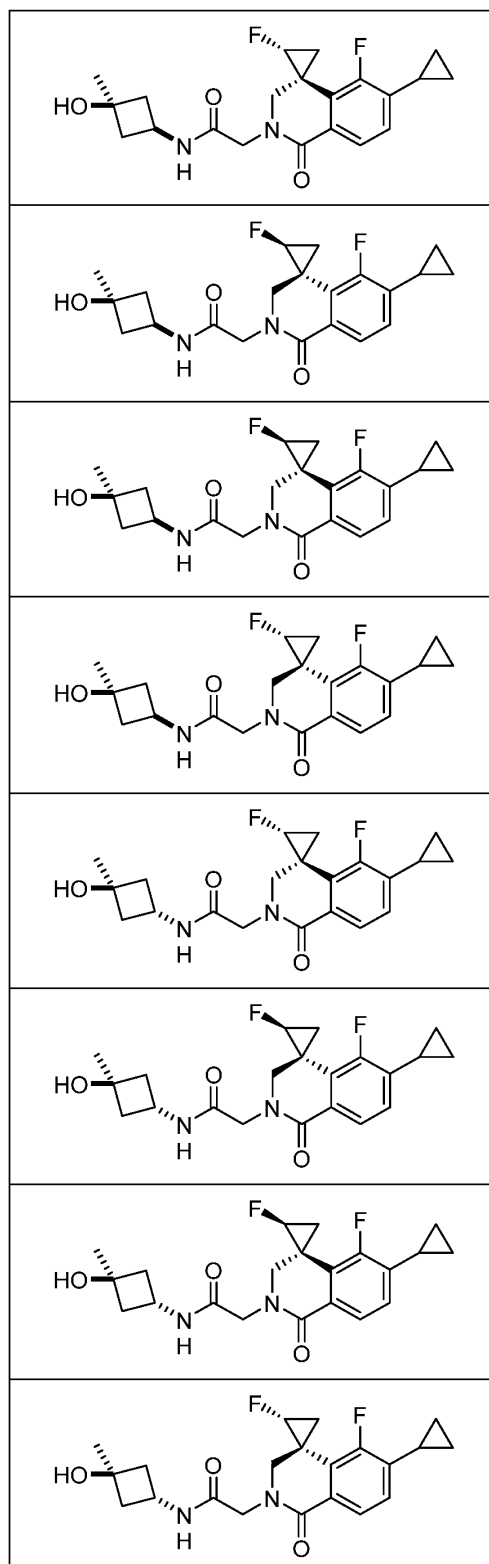
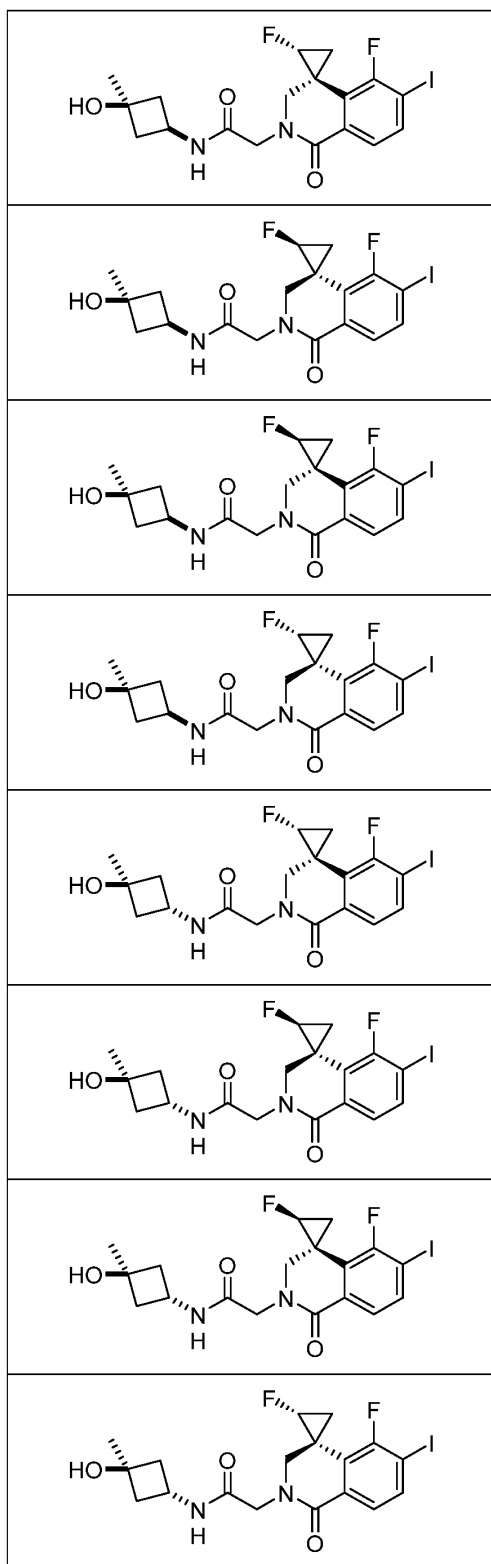
Ex. No.	Structure
62	
63	 mixture of enantiomers
64	 first eluting isomer
65	 second eluting isomer

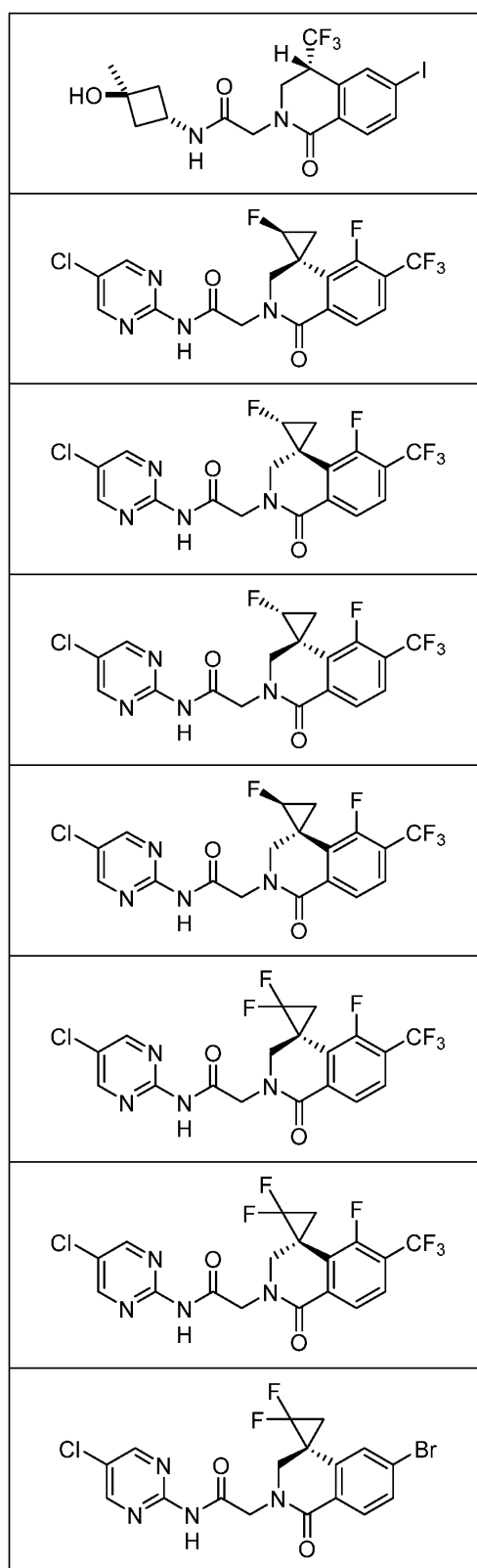
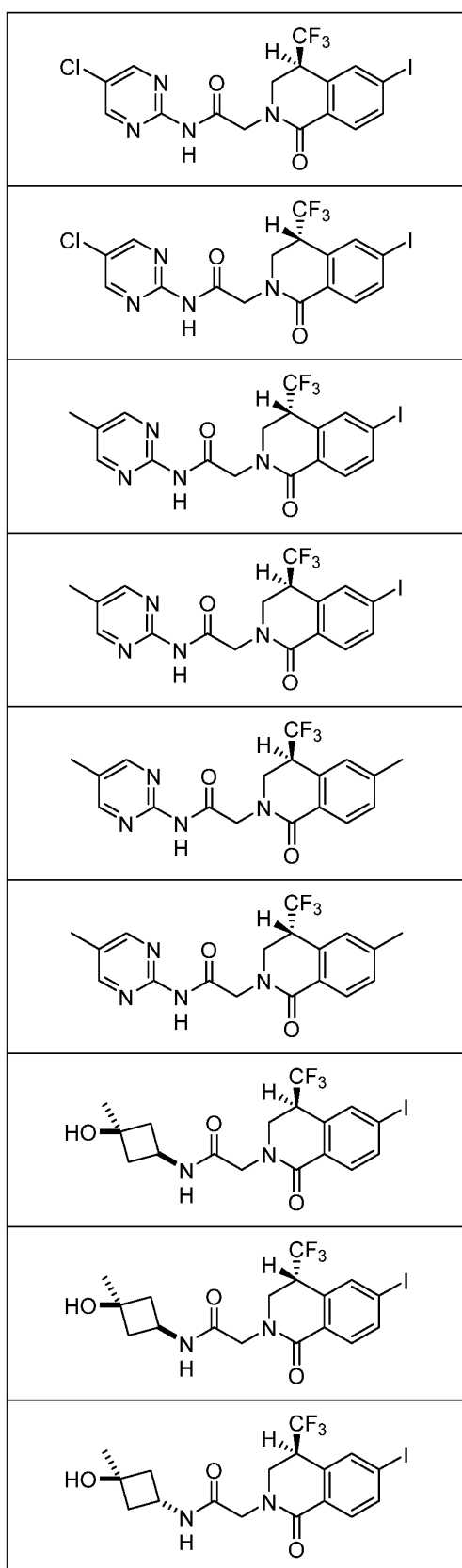
[0129] In certain embodiments, provided is a compound selected from Table 2 or a pharmaceutically acceptable salt, isotopically enriched analog, prodrug, stereoisomer, or a mixture of stereoisomers thereof:

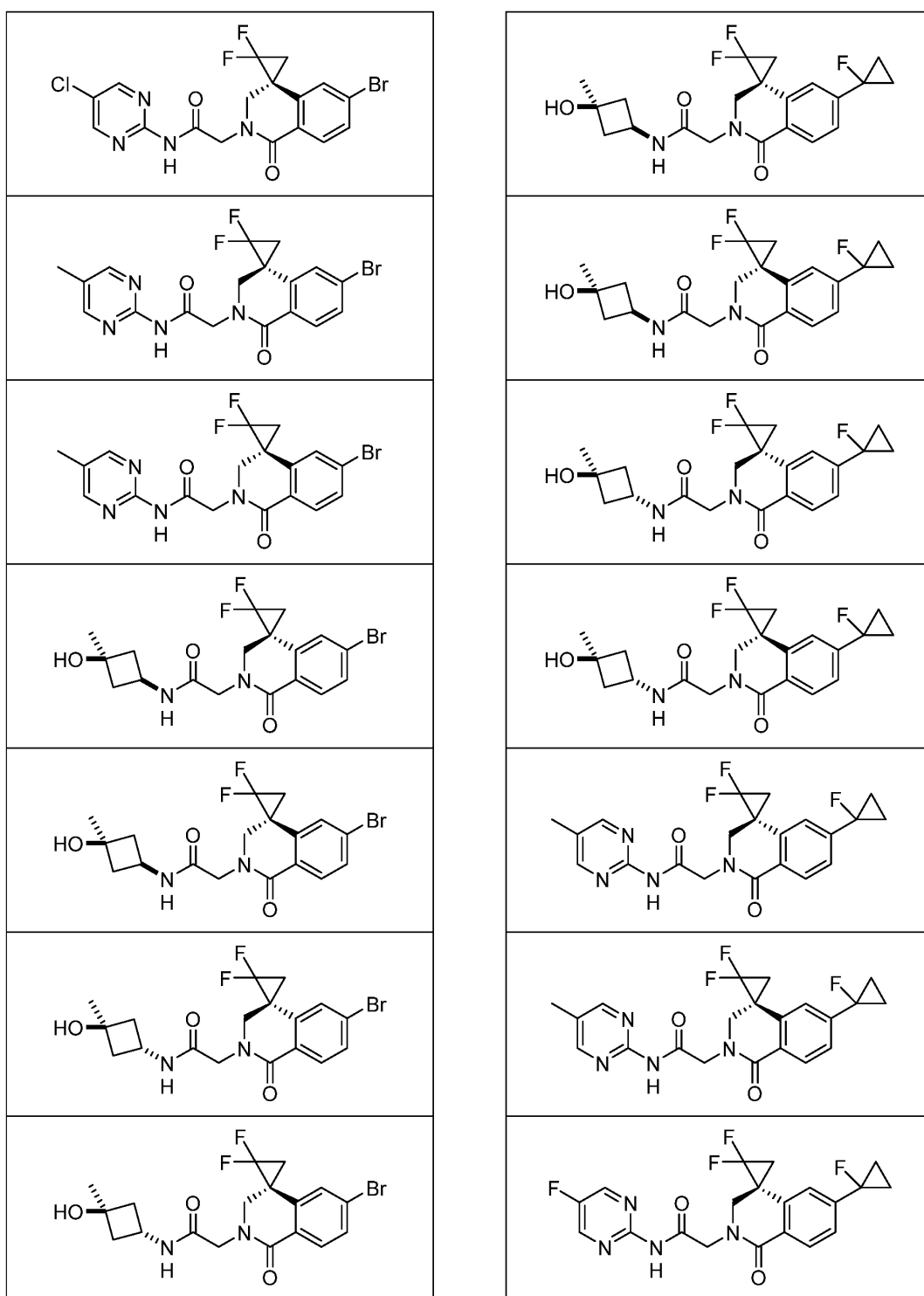
Table 2

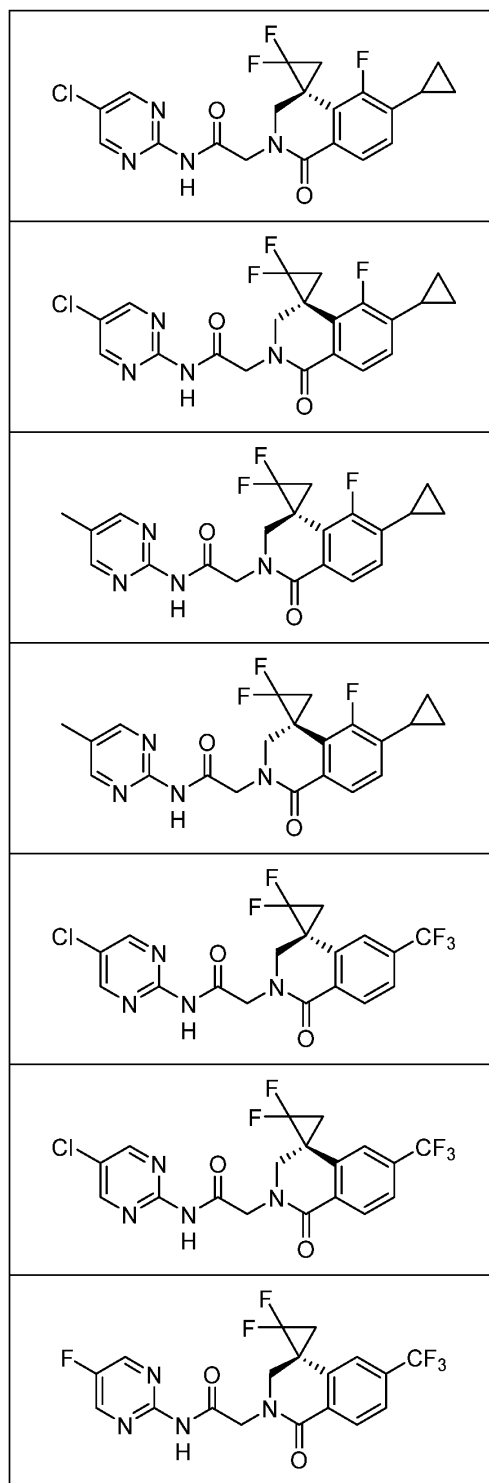
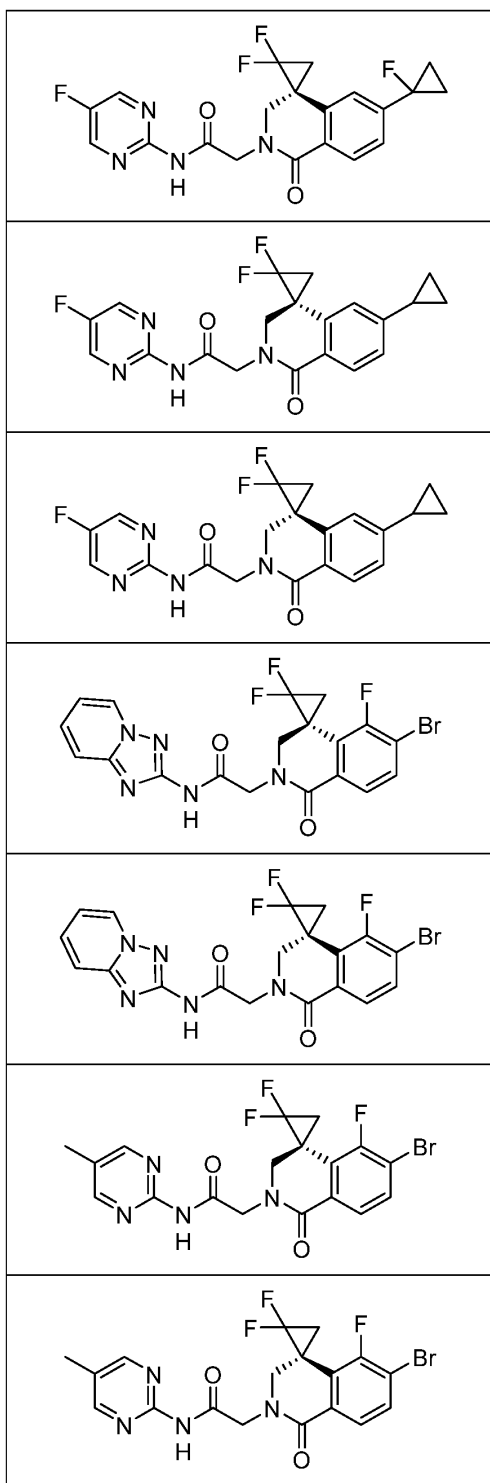
	
	

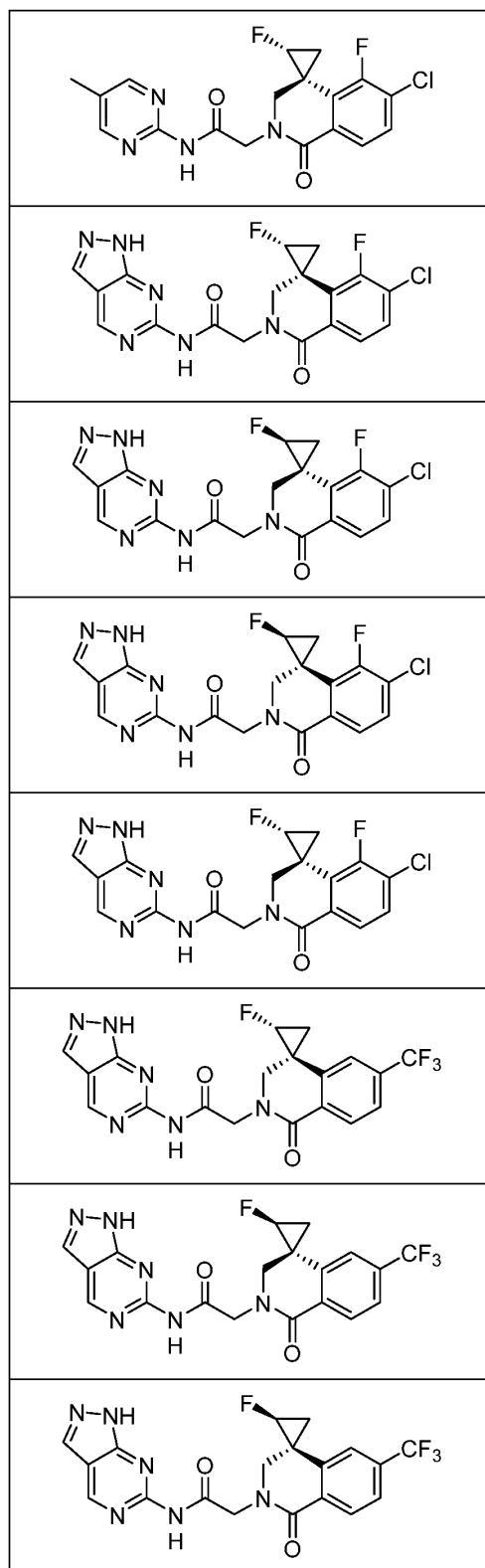
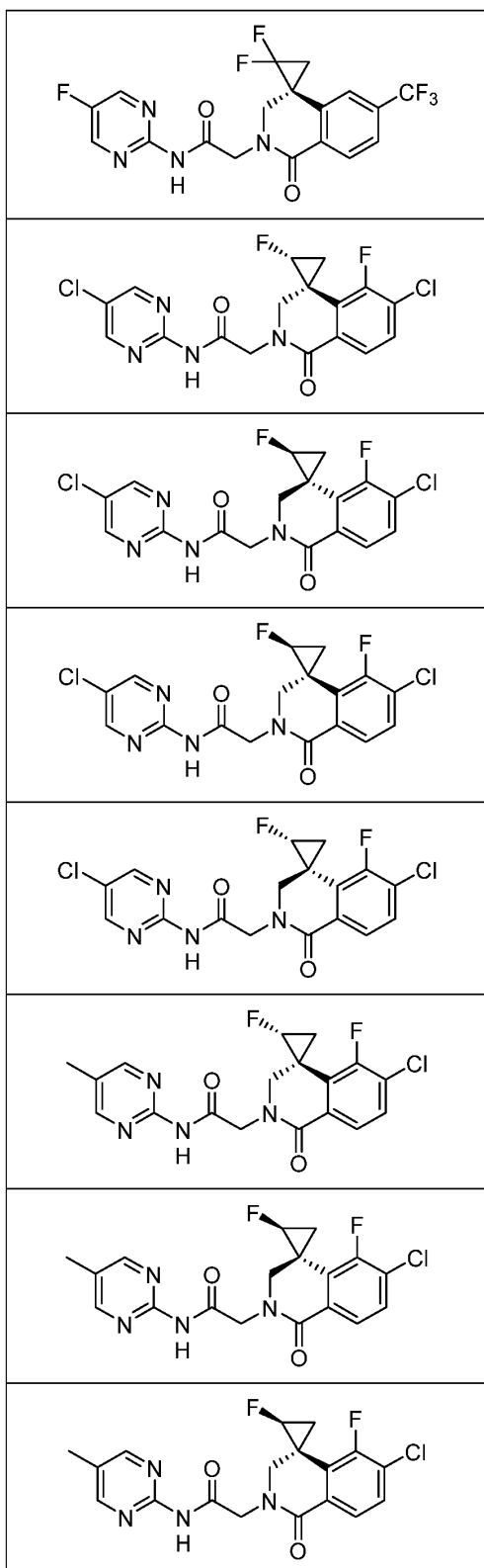


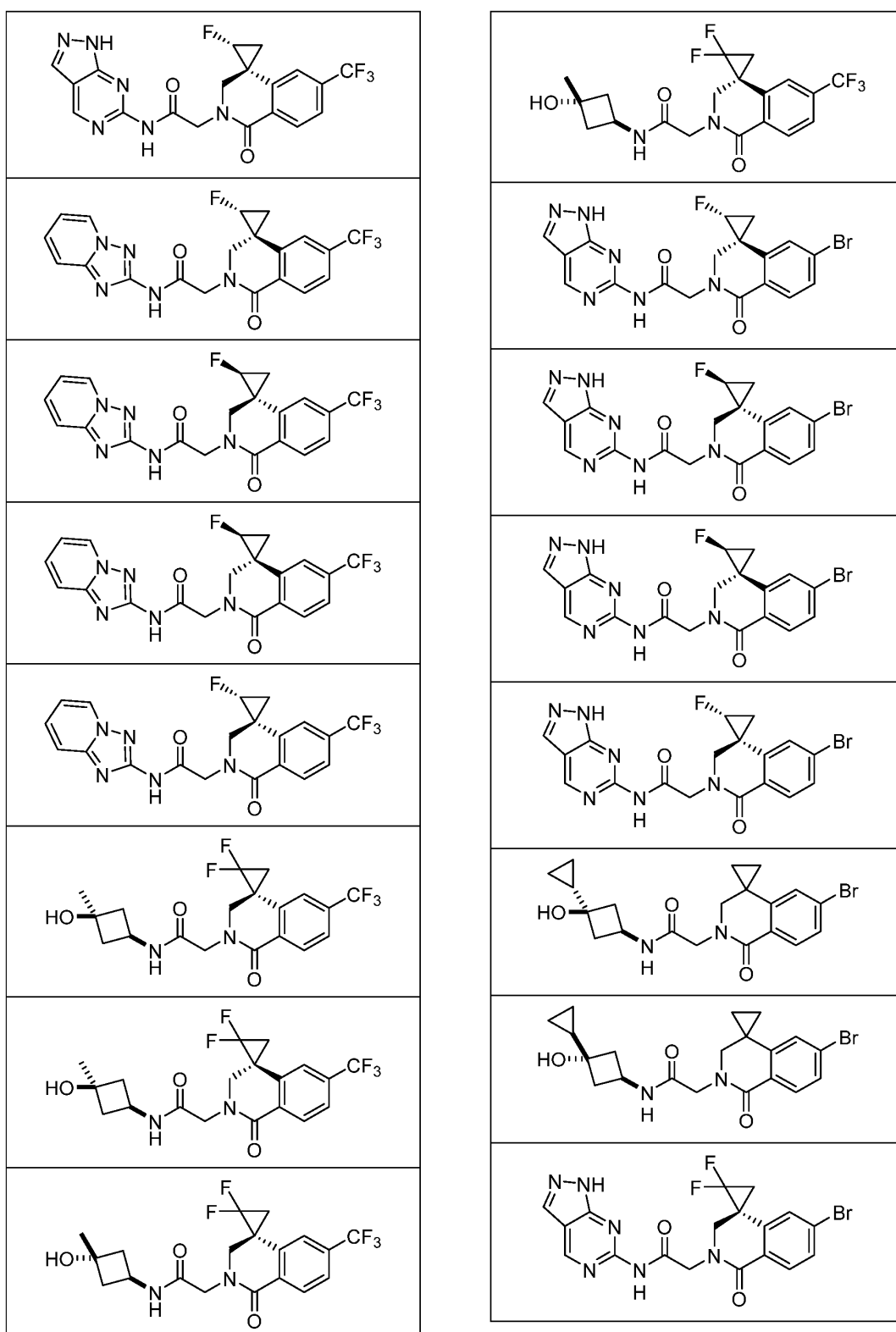


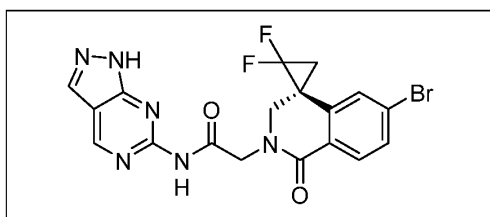












3. Methods

[0130] “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.

[0131] “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 some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0132] “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 some embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[0133] 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.

[0134] 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.

[0135] In certain embodiments, provided are compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, that modulate the activity of NLR Family Pyrin Domain Containing 3 (NLRP3). In certain embodiments, the compounds provided herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, inhibit the activation of NLRP3.

[0136] NLR proteins are involved in the immune system, helping to start and regulate the immune system's response to injury, toxins, or invasion by microorganisms. NLRP3 (also known as cryopyrin, NALP3, LRR and PYD domains-containing protein 3), is a protein encoded by the NLRP3 gene (also known as CIAS1). Once activated, NLRP3 molecules assemble, along with other proteins, into inflammasomes. The activation of NLRP3 by cellular stress leads to inflammasome activation and downstream proteolytic events, including the formation of active proinflammatory cytokines such as interleukin (IL)-1 β and IL-18 which are then secreted. Among other cytokines, IL-1 β and IL-18 are known mediators of inflammation, e.g., artery wall inflammation, atherosclerosis and the aging process.

[0137] In certain embodiments, provided is a method of inhibiting inflammasome (e.g., the NLRP3 inflammasome) 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*.

[0138] 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 inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[0139] 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 inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[0140] Chronic inflammation responses have been associated with various types of cancer. During malignant transformation or cancer therapy, inflammasomes may become activated in response to certain

signals; and IL-1 β expression is elevated in a variety of cancers (e.g., breast, prostate, colon, lung, head and neck cancers, melanomas, etc.), where patients with IL-1 β producing tumors generally have a worse prognosis.

[0141] In certain embodiments, provided is a method for treating a disease or condition mediated, at least in part, by NLRP3, comprising administering an 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.

[0142] In certain embodiments, provided is a method for treating a disease or condition selected from an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease or cancer, 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.

[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 use in treating an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease or cancer in a subject in need thereof.

[0144] 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 or preventing an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease or cancer in a subject in need thereof.

[0145] In certain embodiments, provided is a method for treating inflammation, an auto-immune disease, cancer, an infection, a central nervous system disease, a metabolic disease, a cardiovascular disease, a respiratory disease, a liver disease, a renal disease, an ocular disease, a skin disease, a lymphatic condition, a psychological disorder, graft versus host disease, allodynia, and any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3, 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.

[0146] In certain embodiments, the disease or condition may be a disease or condition of the immune system, the cardiovascular system, the endocrine system, the gastrointestinal tract, the renal system, the hepatic system, the metabolic system, the respiratory system, the central nervous system, may be a cancer or other malignancy, and/or may be caused by or associated with a pathogen. It will be appreciated that these general embodiments defined according to broad categories of diseases, disorders and conditions are not mutually exclusive.

[0147] In certain embodiments, the disease or condition includes, inflammation, including inflammation occurring as a result of an inflammatory disorder, e.g. an autoinflammatory disease, inflammation occurring as a symptom of a non-inflammatory disorder, inflammation occurring as a result of infection,

or inflammation secondary to trauma, injury or autoimmunity; auto-immune diseases such as acute disseminated encephalitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS), anti-synthetase syndrome, aplastic anemia, autoimmune adrenalitis, autoimmune hepatitis, autoimmune oophoritis, autoimmune polyglandular failure, autoimmune thyroiditis, Coeliac disease, Crohn's disease, type 1 diabetes (T1D), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, Kawasaki's disease, lupus erythematosus including systemic lupus erythematosus (SLE), multiple sclerosis (MS) including primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, pemphigus, pernicious anemia, polyarthritis, primary biliary cirrhosis, rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis or Still's disease, refractory gouty arthritis, Reiter's syndrome, Sjögren's syndrome, systemic sclerosis a systemic connective tissue disorder, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Behçet's disease, Chagas' disease, dysautonomia, endometriosis, hidradenitis suppurativa (HS), interstitial cystitis, neuromyotonia, psoriasis, sarcoidosis, scleroderma, ulcerative colitis, Schnitzler syndrome, macrophage activation syndrome, Blau syndrome, vitiligo or vulvodinia; cancer including lung cancer, pancreatic cancer, gastric cancer, myelodysplastic syndrome, leukemia including acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML), adrenal cancer, anal cancer, basal and squamous cell skin cancer, bile duct cancer, bladder cancer, bone cancer, brain and spinal cord tumors, breast cancer, cervical cancer, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), colorectal cancer, endometrial cancer, oesophagus cancer, Ewing family of tumors, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumor (GIST), gestational trophoblastic disease, glioma, Hodgkin lymphoma, Kaposi sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, liver cancer, lung carcinoid tumor, lymphoma including cutaneous T cell lymphoma, malignant mesothelioma, melanoma skin cancer, Merkel cell skin cancer, multiple myeloma, nasal cavity and paranasal sinuses cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thymus cancer, thyroid cancer including anaplastic thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor; infections including viral infections (e.g. from influenza virus, human immunodeficiency virus (HIV), alphavirus (such as Chikungunya and Ross River virus), flaviviruses (such as Dengue virus and Zika virus), herpes viruses (such as Epstein Barr Virus, cytomegalovirus, Varicella-zoster virus, and KSHV), poxviruses (such as vaccinia virus (Modified vaccinia virus Ankara) and Myxoma virus), adenoviruses (such as Adenovirus 5), or papillomavirus), bacterial infections (e.g. from Staphylococcus aureus, Helicobacter pylori, Bacillus anthracis, Bordetella pertussis, Burkholderia pseudomallei, Corynebacterium diphtheriae, Clostridium tetani, Clostridium

botulinum, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Listeria monocytogenes*, *Hemophilus influenzae*, *Pasteurella multocida*, *Shigella dysenteriae*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Rickettsia rickettsii*, *Legionella pneumophila*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Propionibacterium acnes*, *Treponema pallidum*, *Chlamydia trachomatis*, *Vibrio cholerae*, *Salmonella typhimurium*, *Salmonella typhi*, *Borrelia burgdorferi* or *Yersinia pestis*), fungal infections (e.g. from *Candida* or *Aspergillus* species), protozoan infections (e.g. from *Plasmodium*, *Babesia*, *Giardia*, *Entamoeba*, *Leishmania* or *Trypanosomes*), helminth infections (e.g. from *schistosoma*, roundworms, tapeworms or flukes) and prion infections; central nervous system diseases such as Parkinson's disease, Alzheimer's disease, dementia, motor neuron disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, intracranial aneurysms, traumatic brain injury, and amyotrophic lateral sclerosis; metabolic diseases such as type 2 diabetes (T2D), atherosclerosis, obesity, gout, and pseudo-gout; cardiovascular diseases such as hypertension, ischemia, reperfusion injury including post-MI ischemic reperfusion injury, stroke including ischemic stroke, transient ischemic attack, myocardial infarction including recurrent myocardial infarction, heart failure including congestive heart failure and heart failure with preserved ejection fraction, embolism, aneurysms including abdominal aortic aneurysm, and pericarditis including Dressler's syndrome; respiratory diseases including chronic obstructive pulmonary disorder (COPD), asthma such as allergic asthma and steroid-resistant asthma, asbestosis, silicosis, nanoparticle induced inflammation, cystic fibrosis and idiopathic pulmonary fibrosis; liver diseases including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) including advanced fibrosis stages F3 and F4; alcoholic fatty liver disease (AFLD), and alcoholic steatohepatitis (ASH); renal diseases including chronic kidney disease, oxalate nephropathy, nephrocalcinosis, glomerulonephritis, and diabetic nephropathy; ocular diseases including those of the ocular epithelium, age-related macular degeneration (AMD) (dry and wet), uveitis, corneal infection, diabetic retinopathy, optic nerve damage, dry eye, and glaucoma; skin diseases including dermatitis such as contact dermatitis and atopic dermatitis, contact hypersensitivity, sunburn, skin lesions, hidradenitis suppurativa (HS), other cyst-causing skin diseases, and acne conglobata; lymphatic conditions such as lymphangitis and Castleman's disease; psychological disorders such as depression and psychological stress; graft versus host disease; allodynia including mechanical allodynia; and any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

[0148] In certain embodiments, the disease, disorder or condition is an autoinflammatory disease such as cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), tumor Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor antagonist (DIRA), Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), adult-onset Still's disease (AOSD), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation

(PLAID), PLCG2- associated autoinflammatory, antibody deficiency and immune dysregulation (APLAID), or sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD).

[0149] In certain embodiments, provided is a method for treating a disease or condition selected from an autoinflammatory disorder and/or an autoimmune disorder selected from cryopyrin-associated autoinflammatory syndrome (CAPS; e.g., familial cold autoinflammatory syndrome (FCAS)), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome, neonatal-onset multisystem inflammatory disease (NOMID), familial Mediterranean fever and nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, and multiple sclerosis and neuroinflammation occurring in protein misfolding diseases (e.g., Prion diseases) 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.

[0150] In certain embodiments, provided is a method for treating a disease or condition selected from cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID), familial Mediterranean fever (FMF), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA); hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), Tumor Necrosis Factor (TNF), Receptor-Associated Periodic Syndrome (TRAPS), systemic juvenile idiopathic arthritis, adult-onset Still's disease (AOSD), relapsing polychondritis, Schnitzler's syndrome, Sweet's syndrome, Behcet's disease, anti-synthetase syndrome, deficiency of interleukin 1 receptor antagonist (DIRA), and haploinsufficiency of A20 (HA20) 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 disease or condition selected from Alzheimer's disease, atherosclerosis, asthma, allergic airway inflammation, cryopyrin-associated periodic syndromes, gout, inflammatory bowel disease and related disorders, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hypertension, myocardial infarction, multiple sclerosis, experimental autoimmune encephalitis, oxalate-induced nephropathy, hyperinflammation following influenza infection, graft-versus-host disease, stroke, silicosis, type 1 diabetes, obesity-induced inflammation or insulin resistance, rheumatoid arthritis, myelodysplastic syndrome, contact hypersensitivity, joint inflammation triggered by chikungunya virus, or traumatic brain injury 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 disease or condition that is mediated, at least in part, by TNF- α . In certain embodiments, the disease or condition is resistant to treatment with

an anti-TNF- α agent. In some embodiments, the disease is a gut disease or condition. In some embodiments the disease or condition is inflammatory bowel disease, Crohn's disease, or ulcerative colitis. In some embodiments, a compound disclosed herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof is administered in combination with an anti-TNF- α agent. In some embodiments, the anti-TNF- α agent is infliximab, etanercept, certolizumab pegol, golimumab, or adalimumab.

[0153] In certain embodiments, the disease or condition is an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or cancer.

[0154] In certain embodiments, the disease or condition is an autoinflammatory disorder and/or an autoimmune disorder.

[0155] In certain embodiments, the disease or condition is a neurodegenerative disease.

[0156] In certain embodiments, the disease or condition is Parkinson's disease or Alzheimer's disease.

[0157] In certain embodiments, provided is a method for treating cancer, comprising administering an 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.

[0158] In certain embodiments, the cancer is metastasizing cancer, gastrointestinal cancer, skin cancer, non-small-cell lung carcinoma, or colorectal adenocarcinoma.

[0159] 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 neurodegenerative disease (e.g., Parkinson's disease or Alzheimer's disease) in a subject in need thereof.

[0160] 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 cancer in a subject in need thereof.

[0161] In certain embodiments, a compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, may be administered alone as a sole therapy or can be administered in addition with one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

[0162] For example, therapeutic effectiveness may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the individual is enhanced). Alternatively, by way of example only, the benefit experienced by an individual may be increased by administering compound as disclosed herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[0163] Other embodiments include use of the presently disclosed compounds in therapy.

4. Kits

[0164] 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.

[0165] 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

[0166] 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.).

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] 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 some 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, orally or nasally, from devices that deliver the formulation in an appropriate manner.

6. Dosing

[0175] 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 some 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 some 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

[0176] 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.

[0177] It will be appreciated that where typical 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.

[0178] 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.

[0179] 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.

[0180] 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).

EXAMPLES

[0181] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill 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 for 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

[0182] 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.

[0183] **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 Avance 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.

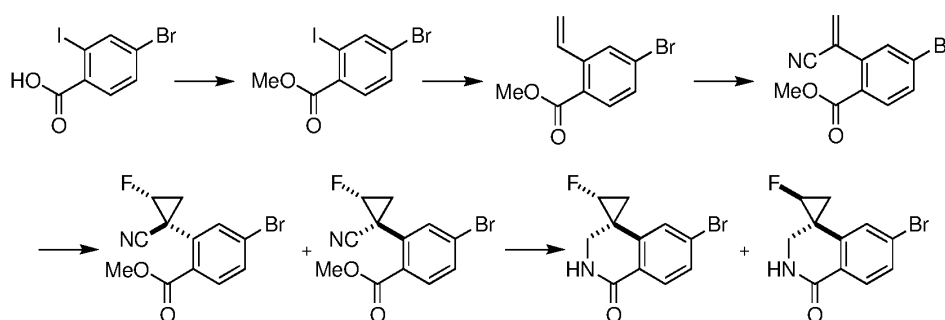
[0184] **Thin Layer Chromatography:** Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel F254 (Merck) plates, R_f is the distance travelled by the compound divided by the distance travelled by the solvent on a TLC plate. Column chromatography was performed 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 I₂ to 10 g silica gel and thoroughly mixing), ninhydrin (available commercially from Aldrich), or Magic Stain (generated by thoroughly mixing 25 g (NH₄)₆Mo₇O₂₄·4H₂O, 5 g (NH₄)₂Ce(IV)(NO₃)₆ in 450 mL water and 50 mL concentrated H₂SO₄) to visualize the compound.

[0185] **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,

H₂O+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: HCl/H₂O=0.04%, or formic acid/H₂O=0.2% (v/v); MPB: ACN. Neutral: Waters Xbridge 150 × 25, 5 μm; MPA: 10 mM NH₄HCO₃ in H₂O; 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) IPAm) (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 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 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.

Intermediates 1 and 2

(2's,4r)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one and (2'r,4r)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one



[0186] methyl 4-bromo-2-iodobenzoate: To a solution of 4-bromo-2-iodobenzoic acid (10.0 g, 30.6 mmol) in MeOH (100 mL) at 0 °C was added conc. H₂SO₄ (15 g, 153 mmol). The reaction mixture was stirred at 80 °C for 5 h. The reaction mixture was poured into water (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (3 × 50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide a crude residue that was

used directly. ¹H NMR (400 MHz, CDCl₃): δ 8.18 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 0.8, 8.0 Hz, 1H), 3.93 (s, 3H).

[0187] methyl 4-bromo-2-vinylbenzoate: To a mixture of methyl 4-bromo-2-iodo-benzoate (6.0 g, 17.6 mmol), potassium vinyltrifluoroborate (2.4 g, 17.6 mmol), and CsF (8.0 g, 52.8 mmol) in 1,4-dioxane (100 mL) was added Pd(dppf)Cl₂ (1.3 g, 1.76 mmol). The reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography. ¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.49-7.37 (m, 2H), 5.66 (d, *J* = 17.2 Hz, 1H), 5.41 (d, *J* = 10.8 Hz, 1H), 3.90 (s, 3H).

[0188] methyl 4-bromo-2-(1-cyanovinyl)benzoate: To a mixture of Cu₂O (345 mg, 2.41 mmol), 6,6'-dimethyl-2,2'-bipyridine (444 mg, 2.41 mmol), and Selectfluor (6.4 g, 18 mmol) in acetone (20 mL) and water (10 mL) were added methyl 4-bromo-2-vinyl-benzoate (2.9 g, 12 mmol) and TMSCN (2.4 g, 24.1 mmol). The reaction mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into aq. NaHCO₃ (1 M, 30 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 residue was purified by silica gel column chromatography. ¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 6.24 (s, 1H), 6.01 (s, 1H), 3.96 (s, 3H).

[0189] methyl 4-bromo-2-((1*r*,2*r*)-1-cyano-2-fluorocyclopropyl)benzoate and methyl 4-bromo-2-((1*r*,2*s*)-1-cyano-2-fluorocyclopropyl)benzoate: To a solution of methyl 4-bromo-2-(1-cyanovinyl)benzoate (800 mg, 3.01 mmol) in THF (30 mL) at 0 °C were added (fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (2.3 g, 6.0 mmol) and NaH (1.2 g, 30.1 mmol, 60% purity in mineral oil). The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (50 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 residue was purified by silica gel column chromatography to provide the title products as a 3:2 mixture. LCMS: *m/z* = 298.0, 300.0 [M+H]⁺.

[0190] (2'*s*,4*r*)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one and (2'*r*,4*r*)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: To a solution of methyl 4-bromo-2-((1*r*,2*r*)-1-cyano-2-fluorocyclopropyl)benzoate and methyl 4-bromo-2-((1*r*,2*s*)-1-cyano-2-fluorocyclopropyl)benzoate (0.92 g, 3.09 mmol, 3:2 mixture) and dichlorocobalt (401 mg, 3.09 mmol) in MeOH (10 mL) at 0 °C was added NaBH₄ (350 mg, 9.26 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into sat. aq. NH₄Cl (20 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 residue was purified by silica gel column chromatography to provide:

[0191] (2'*s*,4*r*)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (Int. 1): ¹H NMR (400 MHz, CDCl₃): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.85 (d, *J* = 2.0

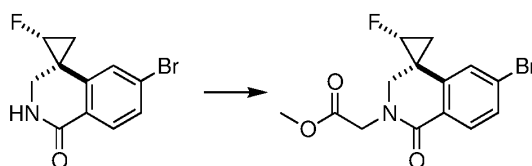
Hz, 1H), 6.12 (br s, 1H), 4.70-4.50 (m, 1H), 3.87 (d, $J = 12.4$ Hz, 1H), 3.51 (dd, $J = 4.4, 12.8$ Hz, 1H), 1.62-1.54 (m, 1H), 1.42-1.24 (m, 1H).

[0192] (2'r,4r)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (Int. 2):

^1H NMR (400 MHz, CDCl_3): δ 8.02 (d, $J = 8.4$ Hz, 1H), 7.55 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.28 (d, $J = 2.0$ Hz, 1H), 6.56 (br s, 1H), 4.81-4.59 (m, 1H), 3.78 (dd, $J = 7.6, 12.4$ Hz, 1H), 2.74 (dd, $J = 4.4, 12.8$ Hz, 1H), 1.83-1.73 (m, 1H), 1.21-1.15 (m, 1H).

Intermediate 3

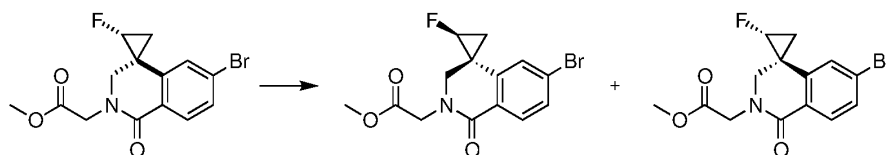
methyl 2-[(2's,4r)-6-bromo-2'-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate



[0193] To a solution of (2's,4r)-6-bromo-2'-fluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (200 mg, 0.74 mmol, Int. 1) in DMF (2.0 mL) at 0 °C was added NaH (45 mg, 1.11 mmol, 60% purity in mineral oil). The reaction mixture was stirred at 20 °C for 0.5 h followed by the addition of methyl 2-bromoacetate (227 mg, 1.48 mmol). The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was poured into sat. aq. NH_4Cl and ice water mixture (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 residue was purified by silica gel column chromatography. LCMS: $m/z = 342.0, 344.0$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.03 (d, $J = 4.4$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 6.83 (s, 1H), 4.73-4.54 (m, 2H), 4.13-4.08 (m, 1H), 4.03-3.94 (m, 1H), 3.77 (s, 3H), 3.44 (m, 1H), 1.63-1.55 (m, 1H), 1.44-1.33 (m, 1H).

Intermediates 4 and 5

methyl 2-((1R,2S)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate & methyl 2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate



[0194] methyl 2-[(2's,4r)-6-bromo-2'-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (Int. 3) could be further separated by chiral SFC (Column: Daicel Chiralpak AD (250mm x 30mm, 10 μm particle size); Mobile Phase: A: CO_2 , B: 0.1% NH_4OH in $i\text{-PrOH}$; Gradient: 38% B isocratic; Flow Rate: 64 g/min; Detection Wavelength: 220 nm; Column Temperature: 40 °C; System Back Pressure: 100 bar) to provide:

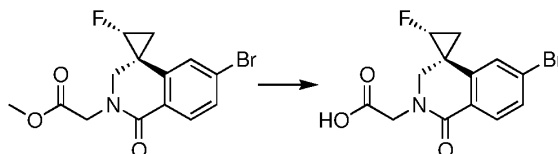
[0195] methyl 2-((1R,2S)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (first eluting isomer, Int. 4): ^1H NMR (400 MHz, CDCl_3): δ 8.02 (d, $J = 8.0$ Hz, 1H), 7.51 (dd, $J = 1.6, 8.4$ Hz, 1H), 6.83 (d, $J = 1.6$ Hz, 1H), 4.73-4.54 (m, 2H), 4.10 (dd, $J = 2.0, 12.4$ Hz,

1H), 4.00 (d, $J = 17.2$ Hz, 1H), 3.77 (s, 3H), 3.44 (d, $J = 12.4$ Hz, 1H), 1.60-1.57 (m, 1H), 1.44-1.33 (m, 1H).

[0196] methyl 2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (second eluting isomer, Int. 5): ^1H NMR (400 MHz, CDCl_3): δ 8.02 (d, $J = 8.0$ Hz, 1H), 7.51 (dd, $J = 1.6, 8.4$ Hz, 1H), 6.83 (d, $J = 1.6$ Hz, 1H), 4.73-4.54 (m, 2H), 4.10 (dd, $J = 2.0, 12.4$ Hz, 1H), 4.00 (d, $J = 17.2$ Hz, 1H), 3.77 (s, 3H), 3.44 (d, $J = 12.4$ Hz, 1H), 1.60-1.57 (m, 1H), 1.44-1.33 (m, 1H).

Intermediate 6

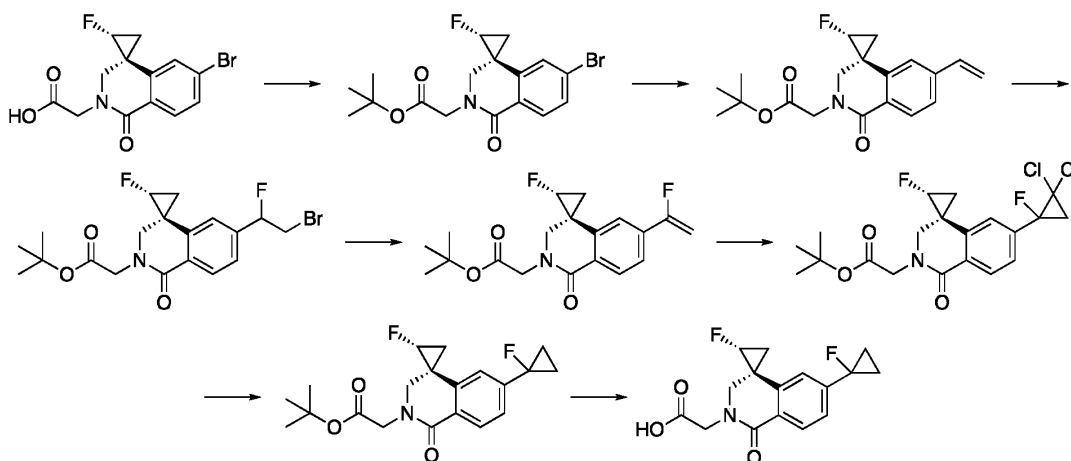
2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid



[0197] To a solution of methyl 2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (150 mg, 0.44 mmol, Int. 5) in THF (2.0 mL) and water (2.0 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (46 mg, 1.10 mmol). The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with water (5 mL), extracted with MTBE (3 mL), and the organics were discarded. The aqueous was adjusted pH = 3 by the addition of aq. HCl (3 M) and extracted with EtOAc (3×2 mL). The combined organics were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: $m/z = 328.0$, 330.0 $[\text{M}+\text{H}]^+$.

Intermediate 7

2-((1S,2R)-2-fluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid



[0198] tert-butyl 2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate: To a solution of 2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid (1.25 g, 3.81 mmol, Int. 6) in DCM (20 mL) at 0 °C were added

DMAP (465 mg, 3.81 mmol), DCC (865 mg, 4.19 mmol), and *t*-BuOH (424 mg, 5.71 mmol). The mixture was stirred at 20 °C for 16 h. The mixture was filtered and the filtrate was washed with aq. sat. Na₂CO₃ (3 × 200 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 4.73-4.51 (m, 2H), 4.07 (dd, *J* = 1.6, 12.4 Hz, 1H), 3.85 (d, *J* = 17.2 Hz, 1H), 3.43 (d, *J* = 12.4 Hz, 1H), 1.58-1.54 (m, 1H), 1.48 (s, 9H), 1.44-1.33 (m, 1H).

[0199] *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-vinyl-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate:

To a solution of *tert*-butyl 2-((1S,2R)-6'-bromo-2-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (500 mg, 1.30 mmol), potassium trifluoro(vinyl)borate (436 mg, 3.25 mmol) in 1,4-dioxane (10 mL) were added CsF (593 mg, 3.90 mmol) and Pd(dppf)Cl₂ (95 mg, 0.13 mmol). The mixture was stirred at 90 °C for 3 h. The reaction mixture was poured into H₂O (20 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: *m/z* = 276.2 [M-*t*Bu+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.75-6.68 (m, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.37 (d, *J* = 11.2 Hz, 1H), 4.75-4.53 (m, 2H), 4.07 (dd, *J* = 2.0, 12.8 Hz, 1H), 3.87 (d, *J* = 17.2 Hz, 1H), 3.44 (d, *J* = 12.8 Hz, 1H), 1.64-1.60 (m, 1H), 1.48 (s, 9H), 1.42-1.31 (m, 1H).

[0200] *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(2-bromo-1-fluoroethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate:

To a solution of *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-vinyl-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (1.04 g, 3.14 mmol) in DCM (20 mL) at 0 °C were added NBS (614 mg, 3.45 mmol) and triethylamine tris(hydrogen fluoride) (759 mg, 4.71 mmol). The mixture was stirred at 0 °C for 15 min then stirred at 20 °C for 16 h. The mixture was poured into H₂O (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: *m/z* = 374.0, 376.0 [M-*t*Bu+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.31 (br d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 5.73-5.55 (m, 1H), 4.75-4.52 (m, 2H), 4.15-4.04 (m, 1H), 3.87 (dd, *J* = 4.8, 17.2 Hz, 1H), 3.68-3.57 (m, 2H), 3.46 (dd, *J* = 6.4, 12.8 Hz, 1H), 1.66-1.59 (m, 1H), 1.49 (s, 9H), 1.45-1.35 (m, 1H).

[0201] *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorovinyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate:

To a solution of *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(2-bromo-1-fluoroethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (1.07 g, 2.49 mmol) in DMSO (20 mL) was added DBU (568 mg, 3.73 mmol). The mixture was stirred at 60 °C for 1 h. The reaction mixture was poured into H₂O (100 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: *m/z* = 294.1 [M-*t*-Bu+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 5.23 (dd, *J*

= 3.6, 49.2 Hz, 1H), 5.07 (dd, J = 3.6, 17.6 Hz, 1H), 4.87-4.62 (m, 2H), 4.26-4.11 (m, 1H), 4.02-3.91 (m, 1H), 3.64-3.50 (m, 1H), 1.74-1.67 (m, 1H), 1.58 (s, 9H), 1.54-1.44 (m, 1H).

[0202] *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(2,2-dichloro-1-fluorocyclopropyl)-1'H-

spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate: To a solution of *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorovinyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (650 mg, 1.86 mmol) in CHCl_3 (15 mL) at 0 °C were added benzyltriethylammonium chloride (17 mg, 0.07 mmol) followed by aq. NaOH (4.47 g, 55.8 mmol, 50 wt%) dropwise. The mixture was stirred at 0 °C for 0.5 h. The mixture was then stirred at 20 °C for 3 h. The reaction mixture was poured into ice-cold H_2O (20 mL) and extracted with DCM (2×10 mL). The combined organic layers were washed with aq. HCl (20 mL, 0.1 M), aq. sat. NaHCO_3 (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 375.9, 377.0, 377.9 $[\text{M}-t\text{-Bu}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.22 (d, J = 8.0 Hz, 1H), 7.40-7.31 (m, 1H), 6.89-6.81 (m, 1H), 4.76-4.56 (m, 2H), 4.18-4.05 (m, 1H), 3.87 (dd, J = 3.2, 17.2 Hz, 1H), 3.52-3.42 (m, 1H), 2.36-2.19 (m, 2H), 1.70-1.62 (m, 1H), 1.49 (s, 9H), 1.46-1.36 (m, 1H).

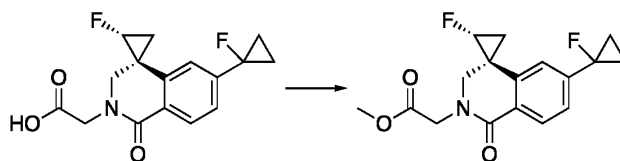
[0203] *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate: To a solution *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(2,2-dichloro-1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (100 mg, 0.23 mmol) in tri-*n*-butyl-tin hydride (660 mg, 2.27 mmol) was added AIBN (3.80 mg, 0.023 mmol). The mixture was stirred at 160 °C for 3 h. The reaction mixture was poured into aq. sat. KF (20 mL). The mixture was stirred 1 h at 20 °C and extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by preparative silica gel thin-layer chromatography. LCMS: m/z = 308.1 $[\text{M}-t\text{Bu}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.13 (dd, J = 0.8, 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 1.6 Hz, 1H), 4.77-4.53 (m, 2H), 4.08 (dd, J = 2.0, 12.8 Hz, 1H), 3.87 (d, J = 17.6 Hz, 1H), 3.45 (d, J = 12.6 Hz, 1H), 1.59-1.51 (m, 2H), 1.48 (s, 9H), 1.43-1.32 (m, 2H), 1.14-1.09 (m, 2H).

[0204] 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-

isoquinolin]-2'(3'H)-yl)acetic acid: To a solution of *tert*-butyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (190 mg, 0.52 mmol) in DCM (4.0 mL) was added formic acid (1.0 mL). The mixture was stirred at 40 °C for 12 h. The mixture was concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 306.2 $[\text{M}-\text{H}]^-$.

Intermediate 8

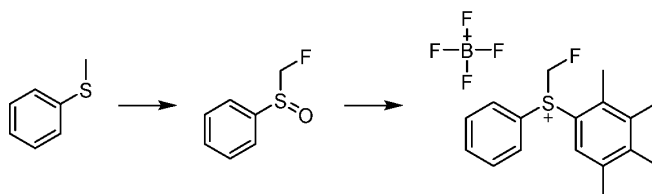
methyl 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate



[0205] To a solution of 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid (77 mg, 0.25 mmol, Int. 7) in DMF (2.0 mL) were added K_2CO_3 (52 mg, 0.38 mmol) and MeI (43 mg, 0.3 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by preparative silica gel thin-layer chromatography. LCMS: m/z = 322.1 $[M+H]^+$.

Intermediate 9

((fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate



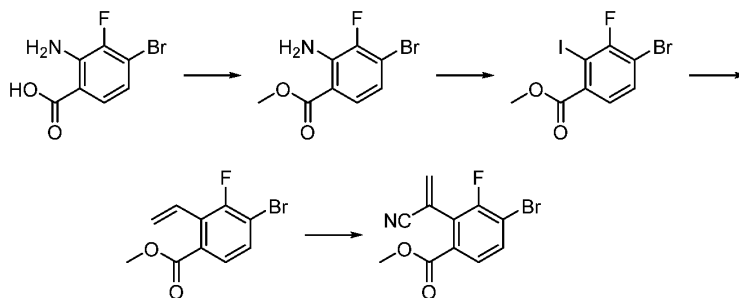
[0206] ((fluoromethyl)sulfinyl)benzene: To a suspension of SelectFluor (463.5 g, 1.31 mol) in MeCN (1500 mL) at 0 °C was added a solution of methyl(phenyl)sulfane (130.0 g, 1.05 mol) in MeCN (150 mL) over 10 min. Et_3N (132.4 g, 1.31 mol) was then added to the mixture at 0 °C. The reaction mixture was allowed to warm to 20 °C and stirred for 16 h. Two batches of the above were run in parallel and combined for workup. The combined batches were diluted with water (1000 mL) and extracted with DCM (3 × 500 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude residue was then dissolved in MeOH (2000 mL), diluted with water (200 mL), and cooled to 0 °C. NBS (372.6 g, 2.09 mol) was carefully added and the mixture was stirred for 16 h at 15 °C. The reaction mixture was diluted with 10% Na_2SO_3 solution (200 mL) followed by sat. aq. $NaHCO_3$ until pH = 7. Methanol was removed under reduced pressure and the remaining aqueous phase was extracted with DCM (3 × 500 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to provide a residue that was used directly.

[0207] ((fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate: To a solution of ((fluoromethyl)sulfinyl)benzene (10.0 g, 63.2 mmol) in diisopropyl ether (100 mL) at -10 °C were added 1,2,3,4-tetramethylbenzene (7.64 g, 56.9 mmol) and Tf_2O (17.8 g, 63.2 mmol). The reaction

mixture was allowed to warm to 20 °C and stirred for 1 h. The reaction mixture was filtered and the resulting solid was dissolved in DCM (200 mL) and washed with aq. NaBF₄ (1 M, 6 × 200 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was triturated with MTBE at 20 °C for 30 min and then filtered to provide the desired product. LCMS: m/z = 275.2 [M+H]⁺.

Intermediate 10

methyl 4-bromo-2-(1-cyanovinyl)-3-fluoro-benzoate



[0208] methyl 2-amino-4-bromo-3-fluorobenzoate: To a solution of 2-amino-4-bromo-3-fluorobenzoic acid (40.0 g, 170 mmol) in DCM (500 mL) and MeOH (500 mL) at 0 °C was added TMSCHN₂ (2 M in *n*-hexane, 427 mL, 854 mmol). The mixture was stirred for 16 h at 15 °C, cooled to 0 °C, and TMSCHN₂ (2 M in hexane, 171 mL) was added. The mixture was stirred for another 16 h at 15 °C. The mixture was quenched by addition of sat. aq. NH₄Cl (500 mL) and H₂O (500 mL). The mixture was concentrated under reduced pressure to remove organic solvent. The white precipitate was filtered and dried under reduced pressure. The filter cake was then suspended in *n*-hexane (300 mL), stirred for 10 min, filtered, and dried under reduced pressure to provide a residue that was used directly. LCMS: m/z = 247.9, 249.9 [M+H]⁺.

[0209] methyl 4-bromo-3-fluoro-2-iodobenzoate: To a solution of methyl 2-amino-4-bromo-3-fluorobenzoate (42.0 g, 170 mmol) in a mixture of conc. H₂SO₄ (420 mL) and MeCN (420 mL) at 0 °C was added a solution of NaNO₂ (14 g, 203 mmol) in H₂O (60 mL). The mixture was stirred for 1 h at 0 °C followed by the addition of a solution of KI (56 g, 338 mmol) in H₂O (60 mL). The mixture was stirred for 15 h at 15 °C. The mixture was cooled to 0 °C, diluted with sat. aq. Na₂S₂O₃ (1000 mL), and extracted with MTBE (4 × 500 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography.

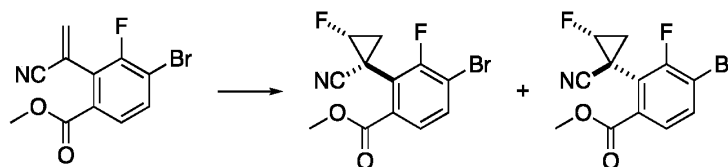
[0210] methyl 4-bromo-3-fluoro-2-vinylbenzoate: To a solution of methyl 4-bromo-3-fluoro-2-iodobenzoate (12.0 g, 33.0 mmol) and potassium hydride:trifluoro(vinyl)boron (5.6 g, 41.7 mmol) in 1,4-dioxane (300 mL) were added CsF (20.3 g, 133.7 mmol) and Pd(dppf)Cl₂ (4.89 g, 6.69 mmol). The mixture was stirred for 16 h at 100 °C. The mixture was filtered, the filtrate was diluted with water (1000 mL) and extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica

gel column chromatography. ^1H NMR (400 MHz, CDCl_3): δ 7.56-7.47 (m, 2H), 7.01 (dd, $J = 11.6$, 18 Hz, 1H), 5.81-5.72 (m, 1H), 5.66 (td, $J = 1.2$, 12.8 Hz, 1H), 3.90 (s, 3H).

[0211] methyl 4-bromo-2-(1-cyanovinyl)-3-fluoro-benzoate: To a solution of 6,6'-dimethyl-2,2'-bipyridine (711 mg, 3.86 mmol), Cu_2O (2.76 g, 19.3 mmol) and SelectFluor (10.3 g, 29.0 mmol) in acetone (60 mL) and water (30 mL) at 0 °C were added a solution of methyl 4-bromo-3-fluoro-2-vinylbenzoate (5.0 g, 19.3 mmol) in acetone (5 mL) and TMSCN (3.83 g, 38.6 mmol, 4.83 mL). The mixture was stirred for 16 h at 20 °C. The mixture was quenched with H_2O (100 mL) and extracted with EtOAc (5 $\times$ 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: $m/z = 283.9$, 285.9 $[\text{M}+\text{H}]^+$.

Intermediate 11 and 12

methyl 4-bromo-3-fluoro-2-[(1s,2r)-1-cyano-2-fluoro-cyclopropyl]benzoate and methyl 4-bromo-3-fluoro-2-[(1s,2s)-1-cyano-2-fluoro-cyclopropyl]benzoate



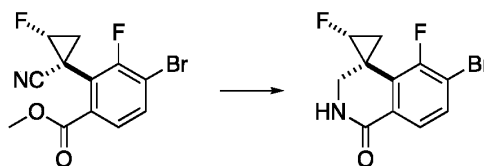
[0212] To a solution of methyl 4-bromo-2-(1-cyanovinyl)-3-fluoro-benzoate (6.0 g, 21.1 mmol, Int. 10) and (fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (11.5 g, 31.7 mmol) in THF (80 mL) at 0 °C was added NaH (3.38 g, 84.5 mmol, 60% purity). The mixture was stirred for 1 h at 20 °C. The mixture was cooled to 0 °C, diluted with sat. aq. NH_4Cl (150 mL), and extracted with EtOAc (3 $\times$ 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to provide:

[0213] methyl 4-bromo-3-fluoro-2-[(1s,2r)-1-cyano-2-fluoro-cyclopropyl]benzoate (Int. 11): ^1H NMR (400 MHz, CDCl_3): δ 7.73-7.66 (m, 2H), 4.83-4.63 (m, 1H), 4.03 (s, 3H), 2.39-2.28 (m, 1H), 1.67-1.57 (m, 1H).

[0214] methyl 4-bromo-3-fluoro-2-[(1s,2s)-1-cyano-2-fluoro-cyclopropyl]benzoate (Int. 12): ^1H NMR (400 MHz, CDCl_3): δ 7.74-7.67 (m, 2H), 5.29-5.06 (m, 1H), 3.99 (s, 3H), 2.37-2.29 (m, 1H), 1.78-1.67 (m, 1H).

Intermediate 13

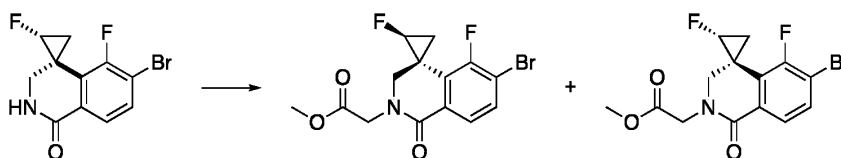
(2's,4r)-6-bromo-2',5-difluorospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one



[0215] To a solution of methyl 4-bromo-3-fluoro-2-[(1*s*,2*r*)-1-cyano-2-fluoro-cyclopropyl]benzoate (5.8 g, 18.3 mmol, Int. 11) and CoCl₂ (9.5 g, 73.4 mmol) in MeOH (180 mL) and H₂O (4.5 mL) at 0 °C was added NaBH₄ (2.78 g, 73.4 mmol). The mixture was stirred for 2 h at 20 °C. Additional NaBH₄ (694 mg, 18.3 mmol) was then added to the solution. The mixture was stirred for a further 1 h. The mixture was quenched by sat. aq. NH₄Cl (200 mL) at 0 °C and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure and purified by silica gel column chromatography. LCMS: *m/z* = 287.9, 289.9 [M+H]⁺.

Intermediate 14 and 15

methyl 2-[(2'*s*,4*r*)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate



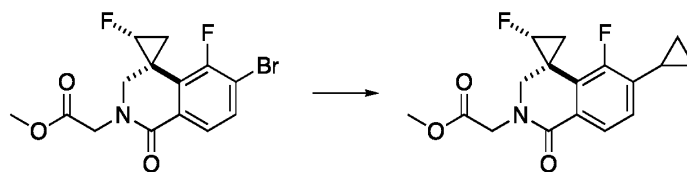
[0216] To a solution of (2'*s*,4*r*)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-1-one (31.0 g, 107 mmol, Int. 13) and NaI (1.61 g, 10.8 mmol) in DMF (350 mL) at 0 °C were added Cs₂CO₃ (70 g, 215 mmol) and methyl 2-bromoacetate (19.7 g, 129 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched by addition of aq. HCl (1 M, 700 mL) at 0 °C and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (3 × 350 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. The mixture was further purified by chiral SFC (Column: Daicel Chiralpak IG (250 mm × 50 mm, 10 μm particle size); Mobile phase: A: CO₂ and B: MeOH; Gradient: 35% B isocratic; Flow rate: 200 g/min; Detection wavelength: 220nm; Column temperature: 40 °C; System back pressure: 100 bar) to provide:

[0217] methyl 2-[(2'*s*,4*r*)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (first eluting isomer, Int. 14): LCMS: *m/z* = 359.9, 361.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.87 (dd, *J* = 1.0, 8.4 Hz, 1H), 7.54 (dd, *J* = 6.4, 8.4 Hz, 1H), 5.44-5.23 (m, 1H), 4.60 (d, *J* = 17.6 Hz, 1H), 4.12-4.00 (m, 1H), 3.81-3.77 (m, 4H), 3.62 (d, *J* = 12.8 Hz, 1H), 1.93-1.87 (m, 1H), 1.54-1.41 (m, 1H).

[0218] methyl 2-[(2'*s*,4*r*)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (second eluting isomer, Int. 15): LCMS: *m/z* = 359.9, 361.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.87 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.54 (dd, *J* = 6.4, 8.4 Hz, 1H), 5.46-5.23 (m, 1H), 4.60 (d, *J* = 17.6 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.81 (d, *J* = 2.6 Hz, 1H), 3.78 (s, 3H), 3.63 (d, *J* = 12.9 Hz, 1H), 1.93-1.87 (m, 1H), 1.55-1.40 (m, 1H).

Intermediate 16

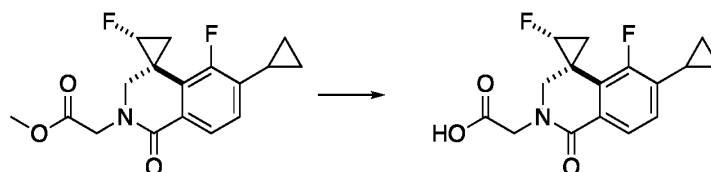
methyl 2-[(2's,4r)-6-cyclopropyl-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate



[0219] To a solution of methyl 2-[(2's,4r)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (50 mg, 0.14 mmol, Int. 15) and potassium cyclopropyltrifluoroborate (62 mg, 0.42 mmol) in 1,4-dioxane (1.0 mL) and H₂O (0.1 mL) were added CsF (63 mg, 0.42 mmol) and Pd(dppf)Cl₂ (10 mg, 0.014 mmol). The mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched with H₂O (6 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: m/z = 322.0 [M+H]⁺.

Intermediate 17

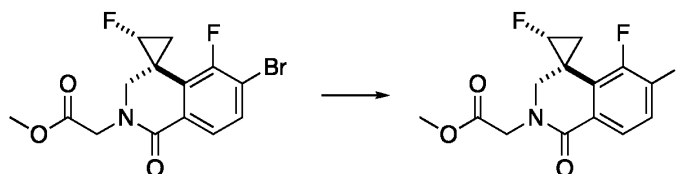
2-[(2's,4r)-6-cyclopropyl-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetic acid



[0220] To a solution of methyl 2-[(2's,4r)-6-cyclopropyl-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (260 mg, 0.81 mmol, Int. 16) in THF (3.0 mL) and H₂O (3.0 mL) was added LiOH•H₂O (85 mg, 2.02 mmol). The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with H₂O (10 mL) and washed with MTBE (4 mL). The aqueous phase was then adjusted pH = 3 by the addition of aq. HCl (3 M). The aqueous was then extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 308.1 [M+H]⁺.

Intermediate 18

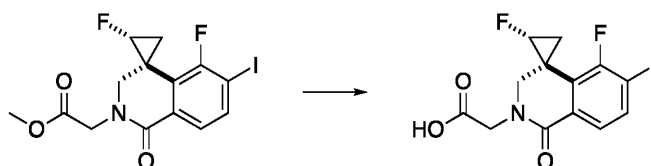
methyl 2-[(2's,4r)-2',5-difluoro-6-iodo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate



[0221] To a solution of methyl 2-[(2's,4r)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (300 mg, 0.83 mmol, Int. 15) in toluene (5.0 mL) were added CuI (32 mg, 0.17 mmol), N1,N2-dimethylcyclohexane-1,2-diamine (47 mg, 0.33 mmol), and NaI (499 mg, 3.33 mmol). The reaction mixture was stirred at 130 °C for 32 h. The reaction mixture was then cooled to ambient temperature, poured into H₂O (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: *m/z* = 407.9 [M+H]⁺.

Intermediate 19

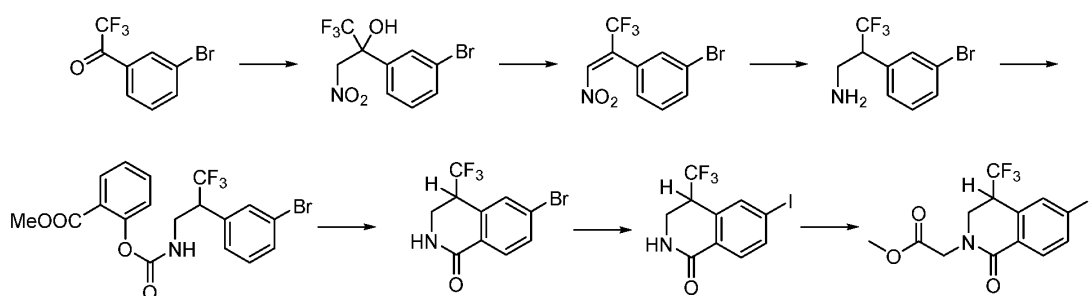
2-[(2's,4r)-2',5-difluoro-6-iodo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetic acid



[0222] To a solution of methyl 2-[(2's,4r)-2',5-difluoro-6-iodo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (145 mg, 0.35 mmol, Int. 18) in THF (2.0 mL) and water (0.5 mL) was added LiOH•H₂O (30 mg, 0.71 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into ice-cold water (10 mL) and the aqueous phase was adjusted pH = 3 by the addition of aq. HCl (4 M). The aqueous was then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and concentrated under reduced pressure to provide a residue that was used directly. LCMS: *m/z* = 394.0 [M+H]⁺.

Intermediate 20

methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate



[0223] 2-(3-bromophenyl)-1,1,1-trifluoro-3-nitropropan-2-ol: To a mixture of nitromethane (116 g, 1.90 mol) in THF (400 mL) at 0 °C were added 1-(3-bromophenyl)-2,2,2-trifluoro-ethanone (40 g, 158 mmol) and Et₃N (48 g, 474 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H₂O (100 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 residue was purified by silica gel column chromatography.

[0224] 1-bromo-3-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)benzene: To a mixture of 2-(3-bromophenyl)-1,1,1-trifluoro-3-nitro-propan-2-ol (108 g, 343 mmol) in toluene (1000 mL) at 0 °C were

added SOCl₂ (61.0 g, 516 mmol) and pyridine (54.0 g, 687 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

[0225] 2-(3-bromophenyl)-3,3,3-trifluoropropan-1-amine: To a mixture of 1-bromo-3-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)benzene (26.0 g, 88.0 mmol) in MeOH (300 mL) at 0 °C were added conc. HCl (84 mL, 878 mmol) and zinc metal (29.0 g, 439 mmol). The mixture was stirred at 0 °C for 1 h. The mixture was filtered and concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 268.0, 270.0 [M+H]⁺.

[0226] methyl 2-(((2-(3-bromophenyl)-3,3,3-trifluoropropyl)carbamoyl)oxy)benzoate: A mixture of 2-(3-bromophenyl)-3,3,3-trifluoro-propan-1-amine (41.5 g, 155 mmol) and methyl 2-(2-methoxycarbonylphenoxy)carbonyloxybenzoate (76.7 g, 232 mmol) in THF (430 mL) was stirred for 12 h at 25 °C. The mixture was concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC.

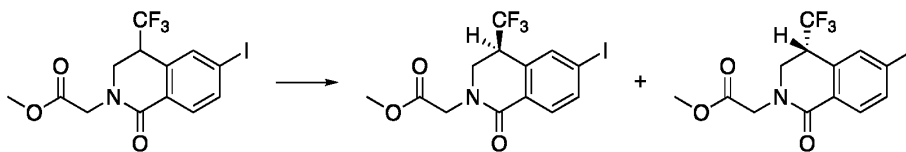
[0227] 6-bromo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-1(2H)-one: To a mixture of methyl 2-[[2-(3-bromophenyl)-3,3,3-trifluoro-propyl]carbamoyloxy]benzoate (30 g, 67 mmol) in DCM (300 mL) at 0 °C was added TfOH (150 mL, 1.70 mol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H₂O (200 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 residue was purified by silica gel column chromatography. LCMS: m/z = 293.9, 295.9 [M+H]⁺.

[0228] 6-iodo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-1(2H)-one: To a solution of 6-bromo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-1(2H)-one (2.00 g, 6.80 mmol) in 1,4-dioxane (50 mL) were added NaI (10.2 g, 68.0 mmol) and *N*1,*N*2-dimethylcyclohexane-1,2-diamine (484 mg, 3.40 mmol) and CuI (1.30 g, 6.80 mmol). The mixture was stirred at 140 °C for 5 h. The reaction mixture was filtered, washed with EtOAc (3 × 20 mL), and concentrated under reduced pressure. The residue was poured into H₂O (100 mL) and then extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 341.9 [M+H]⁺.

[0229] methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate (Int. 20): 6-iodo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-1(2H)-one (2.0 g, 5.86 mmol) and methyl 2-iodoacetate (1.29 g, 6.45 mmol) in DMF (20 mL) at 20 °C was added Cs₂CO₃ (4.01 g, 12.3 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (700 mL) and then extracted with EtOAc (3 × 300 mL). The combined organic layers were wash with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 414.0 [M+H]⁺.

Intermediate 20a and 20b

methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate



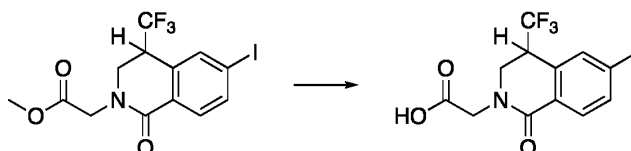
[0230] methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate (Int. 20) was further separated by chiral SFC (Column: Daicel Chiralpak IG (250mm x 50mm, 10 μ m particle size); Mobile phase: A: CO₂, B: 0.1% NH₄OH in *i*-PrOH; Gradient: 55% B isocratic; Flow Rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column Temperature: 35 °C; System Back Pressure: 2000 psi) to provide:

[0231] methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate (first eluting isomer, Int. 20a): ¹H NMR (400 MHz, CDCl₃): δ 7.89 (s, 2H), 7.75 (s, 1H), 4.80 (d, J = 17.2 Hz, 1H), 4.18 (br dd, J = 4.4, 13.6 Hz, 1H), 3.91 (d, J = 17.2 Hz, 1H), 3.77 (s, 3H), 3.74 (dd, J = 2.4, 13.6 Hz, 1H), 3.62-3.50 (m, 1H).

[0232] methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate (second eluting isomer, Int. 20b): ¹H NMR (400 MHz, CDCl₃): δ 7.89 (s, 2H), 7.75 (s, 1H), 4.80 (d, J = 17.6 Hz, 1H), 4.18 (br dd, J = 4.4, 13.6 Hz, 1H), 3.91 (d, J = 17.2 Hz, 1H), 3.77 (s, 3H), 3.74 (dd, J = 2.4, 13.6 Hz, 1H), 3.62-3.50 (m, 1H).

Intermediate 21

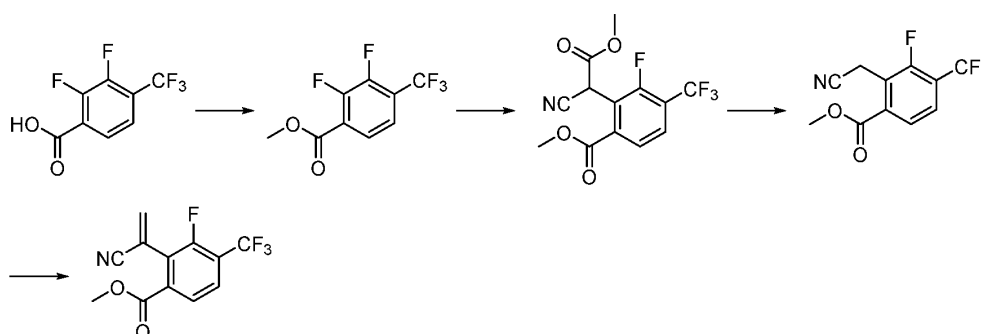
methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate



[0233] To a solution of methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1 g, 2.42 mmol, Int. 20) in THF (15 mL) and H₂O (5 mL) at was added LiOH·H₂O (406 mg, 9.68 mmol). The mixture was stirred for 20 min. The reaction mixture was diluted with water (5 mL) and washed with MTBE (10 mL). The aq. phase was adjusted to pH = 2 with aq. HCl (3M) and the mixture was 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 to provide a residue that was used directly. LCMS: m/z = 399.9.

Intermediate 22

methyl 2-(1-cyanovinyl)-3-fluoro-4-(trifluoromethyl)benzoate



[0234] methyl 2,3-difluoro-4-(trifluoromethyl)benzoate: To a solution of 2,3-difluoro-4-(trifluoromethyl)benzoic acid (50.0 g, 221 mmol) in DMF (700 mL) were added K_2CO_3 (61.1 g, 442 mmol) and MeI (34.5 g, 243 mmol). The reaction mixture was stirred for 4 h at 20 °C. The reaction mixture was diluted with water (300 mL), filtered, and the filtrate was extracted with EtOAc (3 × 200 mL). The combined organics were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to provide a residue that was used directly.

[0235] methyl 2-(1-cyano-2-methoxy-2-oxoethyl)-3-fluoro-4-(trifluoromethyl)benzoate: To a solution of methyl 2,3-difluoro-4-(trifluoromethyl)benzoate (36.5 g, 152 mmol) and methyl 2-cyanoacetate (18.1 g, 182.4 mmol) in DMF (370 mL) was added K_2CO_3 (42.0 g, 304 mmol). The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was poured into ice-cold water (300 mL), adjusted pH = 3 by the addition of aq. HCl (3 M), and extracted with EtOAc (3 × 500 mL). The combined organics were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 320.0 $[M+H]^+$.

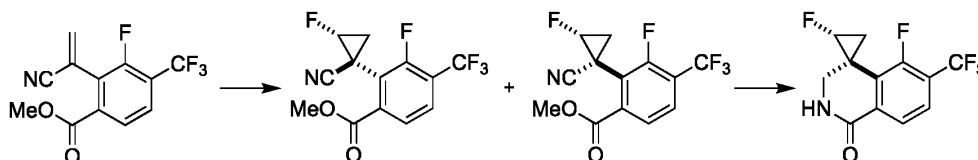
[0236] methyl 2-(cyanomethyl)-3-fluoro-4-(trifluoromethyl)benzoate: To a solution of methyl 2-(1-cyano-2-methoxy-2-oxoethyl)-3-fluoro-4-(trifluoromethyl)benzoate (48.0 g, 150 mmol) in DMSO (420 mL) was added a solution of NaCl (11.4 g, 195 mmol) in H_2O (60 mL). The reaction mixture was stirred at 120 °C for 12 h. The reaction mixture was diluted with water (1000 mL) and extracted with EtOAc (3 × 300 mL). The combined organics were washed with brine (3 × 100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 262.1 $[M+H]^+$.

[0237] methyl 2-(1-cyanovinyl)-3-fluoro-4-(trifluoromethyl)benzoate (Int. 22): To a solution of methyl 2-(cyanomethyl)-3-fluoro-4-(trifluoromethyl)benzoate (5.0 g, 19.1 mmol) and N,N,N',N' -tetramethylmethanedi-amine (2.9 g, 28.7 mmol) in DMSO (50 mL) was added Ac_2O (6.5 g, 63.2 mmol). The reaction mixture was stirred at 20 °C for 4 h. The reaction mixture was diluted with H_2O (200 mL), filtered, and the filtrate was extracted with EtOAc (3 × 50 mL). The combined organics were washed with aq. sat. $NaHCO_3$ (3 × 100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography. ^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, J = 8.4 Hz, 1H), 7.81-7.72 (m, 1H), 6.48 (s, 1H), 6.07 (d, J = 0.8 Hz, 1H), 3.98 (s, 3H).

Intermediate 23

(2's,4r)-2',5-difluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one

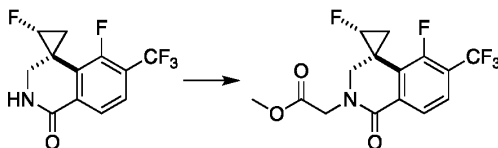


[0238] Methyl 2-((1r,2s)-1-cyano-2-fluorocyclopropyl)-3-fluoro-4-(trifluoromethyl)benzoate and methyl 2-((1r,2r)-1-cyano-2-fluorocyclopropyl)-3-fluoro-4-(trifluoromethyl)benzoate: To a solution of methyl 2-(1-cyanovinyl)-3-fluoro-4-(trifluoromethyl)benzoate (678 mg, 2.48 mmol) and (4-chlorophenyl)(fluoromethyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (1.08 g, 2.73 mmol) in MeCN (5.0 mL) at 0 °C was added NaH (129 mg, 3.23 mmol, 60% purity). The reaction mixture was stirred at 10 °C for 2 h. The reaction mixture was diluted with H_2O (15 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 residue was purified by silica gel column chromatography to provide the title products as a 2:5 mixture. LCMS: m/z = 306.0 $[\text{M}+\text{H}]^+$.

[0239] (2's,4r)-2',5-difluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (Int. 23): To a mixture of methyl 2-((1r,2s)-1-cyano-2-fluorocyclopropyl)-3-fluoro-4-(trifluoromethyl)benzoate and methyl 2-((1r,2r)-1-cyano-2-fluorocyclopropyl)-3-fluoro-4-(trifluoromethyl)benzoate (340 mg, 1.11 mmol, 2:5 mixture) and CoCl_2 (145 mg, 1.11 mmol) in MeOH (3.0 mL) at 0 °C was added NaBH_4 (211 mg, 5.57 mmol). The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture cooled to 0 °C, diluted with sat. aq. NH_4Cl (20 mL), and extracted with EtOAc (4×15 mL). The combined organic layers were washed with brine (3×10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 278.1 $[\text{M}+\text{H}]^+$.

Intermediate 24

methyl 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate

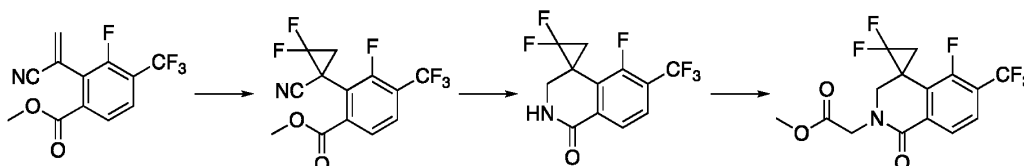


[0240] To a solution of (2's,4r)-2',5-difluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (70 mg, 0.25 mmol) in DMF (2.0 mL) were added NaI (25 mg, 0.17 mmol), Cs_2CO_3 (165 mg, 0.50 mmol), and methyl 2-bromoacetate (58 mg, 0.37 mmol). The reaction mixture was stirred

at 20 °C for 2 h. The reaction mixture was cooled to 0 °C, diluted with H₂O (10 mL), and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 350.1 [M+H]⁺.

Intermediate 25

methyl 2-(2,2,5'-trifluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate



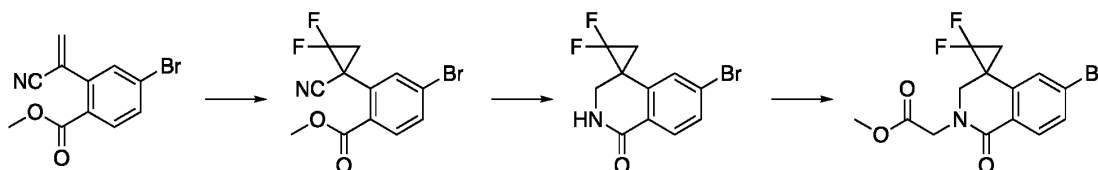
[0241] methyl 2-(1-cyano-2,2-difluorocyclopropyl)-3-fluoro-4-(trifluoromethyl)benzoate: To a solution of methyl 2-(1-cyanovinyl)-3-fluoro-4-(trifluoromethyl)benzoate (1.00 g, 3.66 mmol) in 1,4-dioxane (7.0 mL) was added (2-bromo-2,2-difluoroacetyl)oxysodium (2.16 g, 10.98 mmol). The reaction mixture was stirred at 150 °C for 20 min under microwave irradiation. The reaction mixture was cooled to 0 °C, diluted with H₂O (10 mL), and extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (25 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC.

[0242] 2,2,5'-trifluoro-6'-(trifluoromethyl)-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one: To a solution of methyl 2-(1-cyano-2,2-difluoro-cyclopropyl)-3-fluoro-4-(trifluoromethyl)benzoate (200 mg, 0.62 mmol) in MeOH (4.0 mL) at 0 °C were added dichlorocobalt (80 mg, 0.62 mmol) and NaBH₄ (70 mg, 1.86 mmol). The reaction mixture was stirred at 0 °C for 1 h and then 20 °C for a further 12 h. The reaction mixture was quenched by addition of sat. aq. 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 residue was purified by silica gel column chromatography.

[0243] methyl 2-(2,2,5'-trifluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (Int 25): To a solution of 2,2,5'-trifluoro-6'-(trifluoromethyl)-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one (320 mg, 1.08 mmol) in DMF (7.0 mL) were added NaI (106 mg, 0.70 mmol), Cs₂CO₃ (706 mg, 2.17 mmol), and methyl 2-bromoacetate (249 mg, 1.63 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was cooled to 0 °C, diluted with H₂O (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 368.1 [M+H]⁺.

Intermediate 26

methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate



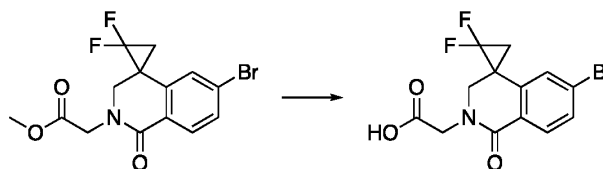
[0244] methyl 4-bromo-2-(1-cyano-2,2-difluorocyclopropyl)benzoate: A solution of methyl 4-bromo-2-(1-cyanovinyl)benzoate (1.00 g, 3.76 mmol) and sodium 2-bromo-2,2-difluoroacetate (2.22 g, 11.27 mmol) in 1,4-dioxane (6.0 mL) was heated under microwave irradiation at 150 °C for 20 min. The reaction mixture was poured into H₂O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was triturated with MTBE to provide a residue that was used directly. LCMS: m/z = 316.0, 318.0 [M+H]⁺.

[0245] 6'-bromo-2,2-difluoro-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one: To a solution of methyl 4-bromo-2-(1-cyano-2,2-difluorocyclopropyl)benzoate (11.2 g, 35.4 mmol), ZnCl₂ (9.7 g, 70.9 mmol), and CoCl₂•6H₂O (11.0 g, 46.1 mmol) in MeOH (150 mL) at 0 °C was added NaBH₄ (6.7 g, 177.2 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was cooled to 0 °C, diluted with sat. aq. NH₄Cl (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 288.0, 290.0 [M+H]⁺.

[0246] methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (Int. 26): To a solution of 6'-bromo-2,2-difluoro-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one (380 mg, 1.32 mmol) in DMF (8.0 mL) were added NaI (129 mg, 0.86 mmol), Cs₂CO₃ (860 mg, 2.64 mmol), and methyl 2-bromoacetate (303 mg, 1.98 mmol). The reaction mixture was stirred for 2 h at 25 °C. 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 residue was purified by silica gel column chromatography. LCMS: m/z = 359.9, 361.9 [M+H]⁺.

Intermediate 27

2-(6'-bromo-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid:

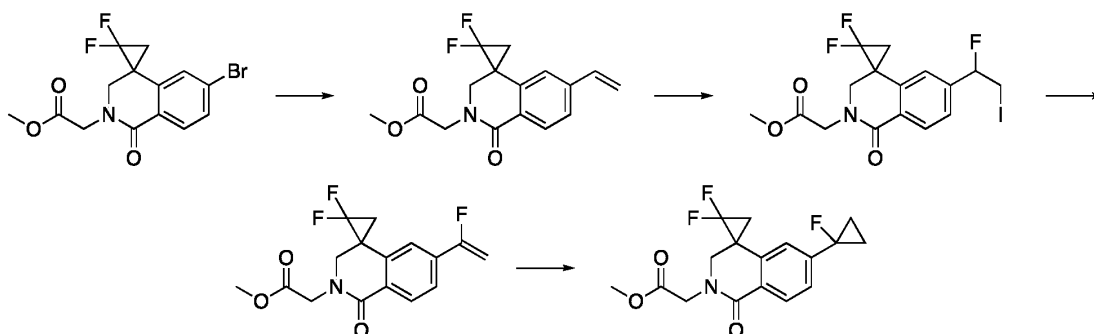


[0247] To a solution of methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (180 mg, 0.50 mmol) in THF (2.0 mL) and H₂O (0.4 mL) was added LiOH•H₂O (42 mg, 0.01 mmol). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture

was diluted with H₂O (5 mL) and washed with MTBE (2 × 10 mL). The aqueous was then acidified to pH = 4 by the addition of aq. HCl and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 346.0, 348.0 [M+H]⁺.

Intermediate 28

methyl 2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate:



[0248] methyl 2-(2,2-difluoro-1'-oxo-6'-vinyl-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate: To a solution of methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (6.00 g, 16.7 mmol) in 1,4-dioxane (200 mL) were added potassium vinyltrifluoroborate (6.69 g, 50.0 mmol), CsF (7.59 g, 50.0 mmol), and Pd(dppf)Cl₂ (1.22 g, 1.67 mmol). The reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 308.1 [M+H]⁺.

[0249] methyl 2-(2,2-difluoro-6'-(1-fluoro-2-iodoethyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate: To a solution of methyl 2-(2,2-difluoro-1'-oxo-6'-vinyl-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (4.8 g, 15.6 mmol) in DCM (100 mL) at 0 °C was added NIS (7.0 g, 31.2 mmol). The reaction mixture was stirred for 30 min prior to the addition of N,N-diethylethanamine; trihydrofluoride (12.6 g, 78.1 mmol). The reaction was then stirred at 20 °C for a further 16 h. The reaction mixture was poured into brine (30 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 454.0 [M+H]⁺.

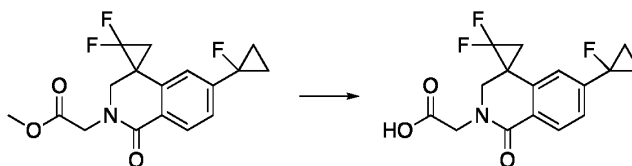
[0250] methyl 2-(2,2-difluoro-6'-(1-fluorovinyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate: To a solution of methyl 2-(2,2-difluoro-6'-(1-fluoro-2-iodoethyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (4.75 g, 10.5 mmol) in DMSO (50 mL) was added DBU (2.39 g, 15.72 mmol). The reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was poured into brine (10 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 residue was purified by reverse-phase preparative HPLC. LCMS: $m/z = 326.1$ $[\text{M}+\text{H}]^+$.

[0251] methyl 2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (Int. 28): To a solution of ZnEt_2 (2 M in *n*-hexane, 7.69 mL) at 0 °C was added a solution of TFA (1.75 g, 15.4 mmol) in DCM (1.0 mL). The reaction mixture was stirred at 0 °C for 10 min prior to the addition of CH_2I_2 (4.12 g, 15.4 mmol). The mixture was stirred at 0 °C for a further 20 min prior to the addition of a solution of methyl 2-(2,2-difluoro-6'-(1-fluorovinyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (500 mg, 1.54 mmol) in DCM (5.0 mL). The reaction mixture was then allowed to warm to 20 °C and stirred for a further 3 h. The reaction mixture was then warmed to 40 °C and stirred for a further 16 h. The reaction mixture was filtered and the filtrate was poured into sat. aq. NH_4Cl (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 residue was purified by silica gel chromatography. LCMS: $m/z = 340.1$ $[\text{M}+\text{H}]^+$.

Intermediate 29

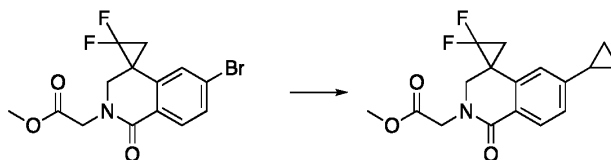
2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid



[0252] To a solution of methyl 2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (350 mg, 1.03 mmol) in THF (4.0 mL) and H_2O (4.0 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (87 mg, 2.06 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and washed with MTBE (10 mL). The aqueous was then acidified to pH = 3 by the addition of aq. HCl (3 M) and then extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: $m/z = 326.1$ $[\text{M}+\text{H}]^+$.

Intermediate 30

methyl 2-(6'-cyclopropyl-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate

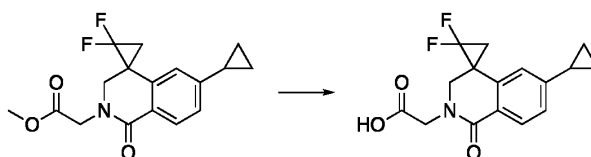


[0253] To a solution of potassium cyclopropyltrifluoroborate (1.03 g, 6.94 mmol) and methyl 2-(6-bromo-1',1'-difluoro-1-oxo-spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)acetate (500 mg, 1.39 mmol) in toluene (5.0 mL) and H_2O (0.5 mL) were added bis(1-adamantyl)-butyl-phosphane (100 mg, 0.28

mmol), Pd(OAc)₂ (31 mg, 0.14 mmol), and Cs₂CO₃ (905 mg, 2.78 mmol). The reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with MTBE (3 × 3 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 322.1 [M+H]⁺.

Intermediate 31

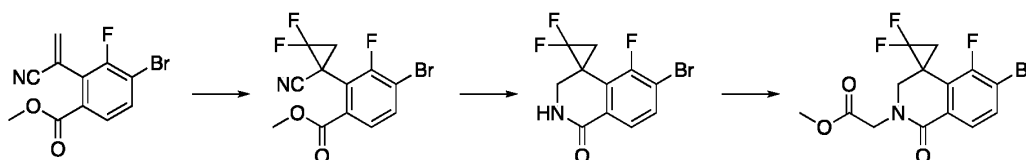
2-(6'-cyclopropyl-2,2-difluoro-1'-oxo-1'-H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid



[0254] To a solution of methyl 2-(6'-cyclopropyl-1',1'-difluoro-1-oxo-spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)acetate (275 mg, 0.86 mmol) in THF (4.0 mL) and H₂O (1.0 mL) was added LiOH·H₂O (72 mg, 1.71 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was diluted with ice-cold H₂O (10 mL), acidified to pH = 3 by the addition of aq. HCl (4 M), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 308.1 [M+H]⁺.

Intermediate 32

methyl 2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetate



[0255] **methyl 4-bromo-2-(1-cyano-2,2-difluorocyclopropyl)-3-fluorobenzoate:** To a solution of methyl 4-bromo-2-(1-cyanovinyl)-3-fluorobenzoate (450 mg, 1.58 mmol, Int. 10) in 1,4-dioxane (2.0 mL) was added sodium 2-chloro-2,2-difluoroacetate (725 mg, 4.75 mmol). The mixture was stirred at 150 °C for 20 min under microwave irradiation. The reaction mixture was poured into H₂O (20 mL) and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure and purified by reverse-phase preparative HPLC. LCMS: m/z = 333.9, 335.9 [M+H]⁺.

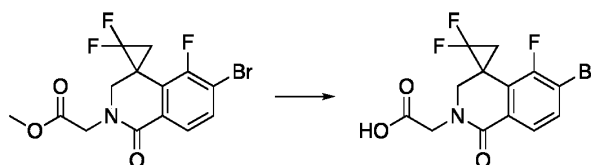
[0256] **6'-bromo-2,2,5'-trifluoro-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one:** To a mixture of methyl 4-bromo-2-(1-cyano-2,2-difluorocyclopropyl)-3-fluorobenzoate (600 mg, 1.80 mmol) and CoCl₂ (233 mg, 1.80 mmol) in MeOH (12 mL) and H₂O (1.2 mL) at -10 °C was added NaBH₄ (204 mg, 5.39 mmol). The mixture was stirred at 0 °C for 1 h and then -10 °C for a further 4 h. The reaction mixture was diluted with sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (4 × 15 mL).

The combined organic layers were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: $m/z = 306.0, 308.0$ $[\text{M}+\text{H}]^+$.

[0257] methyl 2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetate (Int. 32): To a solution of methyl 2-bromoacetate (82 mg, 0.54 mmol) in DMF (1.5 mL) were added 6'-bromo-2,2,5'-trifluoro-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one (110 mg, 0.36 mmol), Cs_2CO_3 (234 mg, 0.72 mmol), and NaI (27 mg, 0.18 mmol). The mixture was stirred at 20°C for 2 h. The reaction mixture was diluted with H_2O (10 mL) at 0°C and extracted with EtOAc (4×5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by silica gel column chromatography. LCMS: $m/z = 378.0, 380.0$ $[\text{M}+\text{H}]^+$.

Intermediate 33

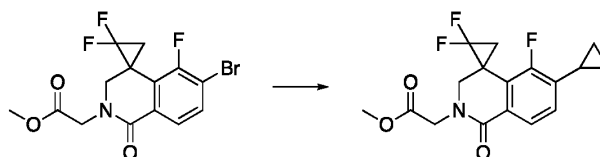
2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetic acid



[0258] To a solution of methyl 2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetate (115 mg, 0.30 mmol) in THF (3.0 mL) and H_2O (0.6 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (26 mg, 0.61 mmol). The mixture was stirred at 20°C for 1 h. The reaction mixture was poured into H_2O (10 mL) and washed with MTBE (3×5 mL). The aqueous layer was adjusted to $\text{pH} = 3$ with aq. HCl (3 M) at 0°C 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 to provide a residue that was used directly. LCMS: $m/z = 361.9, 363.9$ $[\text{M}-\text{H}]^-$.

Intermediate 34

methyl 2-(6'-cyclopropyl-2,2,5'-trifluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate

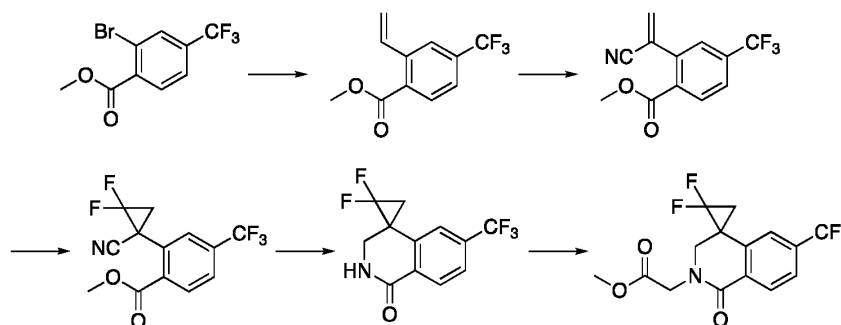


[0259] To a solution of methyl 2-(6'-bromo-2,2,5'-trifluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (2.7 g, 7.14 mmol) in toluene (40 mL) and H_2O (4 mL) were added potassium cyclopropyltrifluoroborate (3.17 g, 21.42 mmol), Cs_2CO_3 (4.65 g, 14.3 mmol), bis(1-adamantyl)-butyl-phosphane (512 mg, 1.43 mmol) and $\text{Pd}(\text{OAc})_2$ (160 mg, 0.71 mmol). The mixture was stirred at 100°C for 6 h. The mixture was diluted with water (40 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 ,

filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: $m/z = 340.1$ $[M+H]^+$. 1H NMR (400MHz, $CDCl_3$): δ 7.89 (d, $J = 8.0$ Hz, 1H), 6.90 (t, $J = 7.2$ Hz, 1H), 4.78-4.86 (m, 1H), 4.30-4.43 (m, 1H), 3.84 (d, $J = 17.6$ Hz, 1H), 3.75-3.78 (m, 3H), 2.88-3.07 (m, 2H), 2.07-2.17 (m, 1H), 1.45-1.56 (m, 1H), 1.01-1.13 (m, 2H), 0.70-0.86 (m, 2H).

Intermediate 35

methyl 2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate



[0260] methyl 4-(trifluoromethyl)-2-vinylbenzoate: To a solution of methyl 2-bromo-4-(trifluoromethyl)benzoate (100 g, 353 mmol) in 1,4-dioxane (2000 mL) was added potassium vinyltrifluoroborate (52 g, 388 mmol), CsF (161 g, 1.06 mol) and $Pd(dppf)Cl_2$ (12.9 g, 17.7 mmol). The mixture was stirred at 90 °C for 6 h. The mixture was diluted with H_2O (2000 mL) and extracted with EtOAc (3×700 mL). The combined organic layers were washed with brine (1500 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

[0261] methyl 2-(1-cyanovinyl)-4-(trifluoromethyl)benzoate: To a solution of Cu_2O (31.0 g, 217 mmol), 6,6'-dimethyl-2,2'-bipyridine (8.0 g, 43 mmol) and SelectFluor (115 g, 325 mmol) in acetone (1 L) and H_2O (500 mL) were added dropwise methyl 4-(trifluoromethyl)-2-vinylbenzoate (50 g, 217 mmol) and TMS-CN (64.6 g, 652 mmol). The mixture was stirred at 20 °C for 20 h. The mixture was poured into aq. sat. $NaHCO_3$ (200 mL) and H_2O (800 mL). The mixture was filtered and the filtrate was extracted with EtOAc (3×300 mL). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: $m/z = 256.0$ $[M+H]^+$.

[0262] methyl 2-(1-cyano-2,2-difluorocyclopropyl)-4-(trifluoromethyl)benzoate: A solution of methyl 2-(1-cyanovinyl)-4-(trifluoromethyl)benzoate (1.00 g, 3.92 mmol) and sodium 2-bromo-2,2-difluoroacetate (2.31 g, 11.8 mmol) in 1,4-dioxane (6.0 mL) was heated at 150 °C for 20 min under microwave irradiation. The reaction mixture was poured into H_2O (10 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 residue was purified by reverse-phase preparative HPLC.

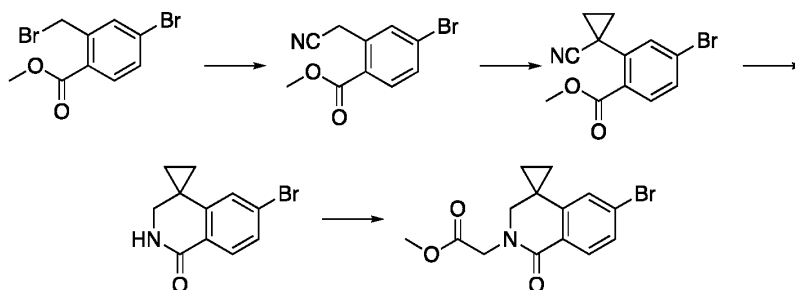
[0263] 2,2-difluoro-6'-(trifluoromethyl)-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one: To a solution of methyl 2-(1-cyano-2,2-difluorocyclopropyl)-4-(trifluoromethyl)benzoate (1.00 g,

3.28 mmol) in MeOH (10 mL) at 0 °C were added $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (1.01 g, 4.26 mmol) and NaBH_4 (620 mg, 16.4 mmol). The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was cooled to 0 °C, diluted with sat. aq. NH_4Cl (30 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. ^1H NMR (400 MHz, CDCl_3): δ 8.31 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.33 (s, 1H), 6.34 (br s, 1H), 3.92-3.87 (m, 1H), 3.50-3.46 (m, 1H), 2.17-2.14 (m, 1H), 1.75-1.71 (m, 1H).

[0264] methyl 2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (Int. 35): To a solution of 2,2-difluoro-6'-(trifluoromethyl)-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinolin]-1'-one (400 mg, 1.44 mmol) in DMF (10 mL) were added NaI (141 mg, 0.94 mmol), Cs_2CO_3 (941 mg, 2.89 mmol), and methyl 2-bromoacetate (331 mg, 2.16 mmol). The reaction mixture was stirred at 25 °C for 2 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 residue was purified by silica gel column chromatography. ^1H NMR (400 MHz, CDCl_3): δ 8.32 (d, $J = 8.0$ Hz, 1H), 7.71 (dd, $J = 0.8, 8.0$ Hz, 1H), 7.32 (s, 1H), 4.79 (d, $J = 17.2$ Hz, 1H), 4.18-4.10 (m, 1H), 3.98 (d, $J = 17.2$ Hz, 1H), 3.78 (s, 3H), 3.40 (dd, $J = 1.2, 12.8$ Hz, 1H), 2.17-2.12 (m, 1H), 1.80-1.75 (m, 1H).

Intermediate 36

methyl 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate



[0265] methyl 4-bromo-2-(cyanomethyl)benzoate: A solution of NaCN (8.4 g, 170 mmol) in H_2O (40 mL) was added dropwise to a solution of methyl 4-bromo-2-(bromomethyl)benzoate (35 g, 114 mmol) in DMSO (500 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H_2O (1.5 L) and extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine (3×200 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. ^1H NMR (400 MHz, CDCl_3): δ 7.93 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J = 2.0$ Hz, 1H), 7.57 (dd, $J = 2.0, 8.8$ Hz, 1H), 4.20 (s, 2H), 3.92 (s, 3H).

[0266] methyl 4-bromo-2-(1-cyanocyclopropyl)benzoate: Methyl 4-bromo-2-(cyanomethyl)benzoate (9.0 g, 35.4 mmol) was added to a solution of NaH (3.26 g, 81.5 mmol, 60% purity) in DMSO (90 mL).

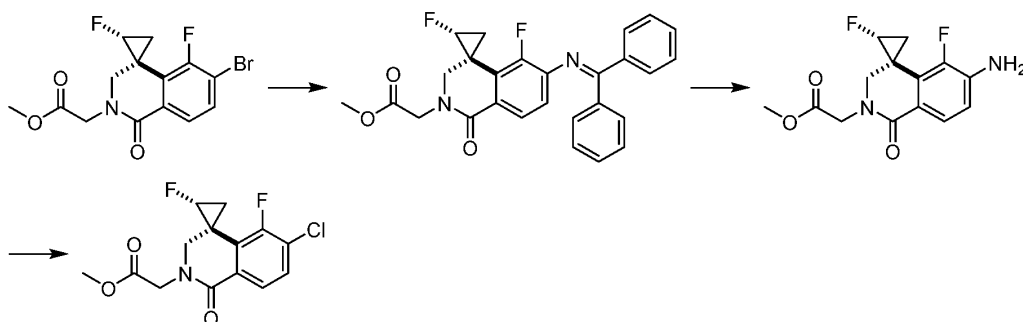
The reaction mixture was stirred at 20 °C for 1 h before the addition of 1-bromo-2-chloroethane (8.13 g, 56.7 mmol). The resultant mixture was stirred at 20 °C for a further 8 h. The reaction mixture was cooled to 0 °C, diluted with sat. aq. NH_4Cl (200 mL), and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 280.0, 282.0 $[\text{M}+\text{H}]^+$.

[0267] 6-bromospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: To a mixture of methyl 4-bromo-2-(1-cyanocyclopropyl)benzoate (2.50 g, 8.92 mmol) and dichlorocobalt (2.32 g, 17.9 mmol) in MeOH (40 mL) was added NaBH_4 (1.70 g, 44.9 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was cooled to 0 °C, diluted with sat. aq. NH_4Cl (50 mL), and extracted with DCM (4 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 252.0, 254.0 $[\text{M}+\text{H}]^+$.

[0268] methyl 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (Int. 36): To a solution of 6-bromospiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (2.30 g, 9.12 mmol) in DMF (30 mL) was added NaH (401 mg, 10.0 mmol, 60% purity) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h before the addition of methyl 2-bromoacetate (2.09 g, 13.7 mmol). The reaction mixture was then stirred at 20 °C for a further 2 h. The reaction mixture was cooled to 0 °C, diluted with sat. aq. NH_4Cl (50 mL), and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 324.0, 326.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, J = 8.4 Hz, 1H), 7.44 (dd, J = 2.0, 8.4 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 4.33 (s, 2H), 3.76 (s, 3H), 3.45 (s, 2H), 1.14-1.09 (m, 2H), 1.08-1.03 (m, 2H).

Intermediate 37

methyl 2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate



[0269] methyl 2-[(2's,4r)-6-((diphenylmethylene)amino)-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate: To a solution of methyl 2-[(2's,4r)-6-bromo-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (650 mg, 1.80 mmol, Int. 15) and diphenylmethanimine (654 mg, 3.61 mmol) in 1,4-dioxane (10 mL) were added $\text{Pd}2(\text{dba})_3$ (165 mg, 0.18

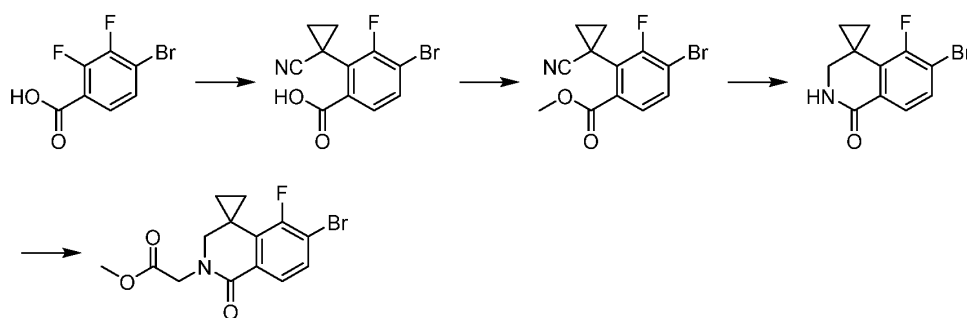
mmol), XPhos (172 mg, 0.36 mmol), and Cs₂CO₃ (1.18 g, 3.61 mmol). The mixture was stirred at 90 °C for 16 h. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

[0270] methyl 2-[(2's,4r)-6-amino-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate: A solution of methyl 2-[(2's,4r)-6-((diphenylmethylene)amino)-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (700 mg, 1.52 mmol), hydroxylamine hydrochloride (211 mg, 3.04 mmol), and NaOAc (374 mg, 4.56 mmol) in MeOH (10 mL) was stirred at 20 °C for 16 h. The mixture was quenched 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 residue was purified by silica gel column chromatography.

[0271] methyl 2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate: To a mixture of CuCl (100 mg, 1.01 mmol) in MeCN (5 mL) were added tert-butyl nitrite (94 mg, 0.91 mmol) and a solution of methyl 2-[(2's,4r)-6-amino-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (150 mg, 0.51 mmol) in MeCN (1.0 mL). The reaction was stirred at 60 °C for 5 h. The mixture was quenched 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 residue was purified by silica gel column chromatography. ¹H NMR (400 MHz, CDCl₃): δ 7.86 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.31 (dd, *J* = 7.2, 8.4 Hz, 1H), 5.38-5.13 (m, 1H), 4.53 (d, *J* = 17.2 Hz, 1H), 4.00 (d, *J* = 17.2 Hz, 1H), 3.75-3.68 (m, 4H), 3.55 (d, *J* = 12.8 Hz, 1H), 1.87-1.80 (m, 1H), 1.47-1.36 (m, 1H).

Intermediate 38

Methyl 2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate



[0272] 4-bromo-2-(1-cyanocyclopropyl)-3-fluorobenzoic acid: To a solution of 4-bromo-2,3-difluorobenzoic acid (40 g, 169 mmol) in THF (700 mL) was added cyclopropanecarbonitrile (34 g, 506 mmol). To the reaction mixture was cooled to -40 °C followed by the addition of KHMDS (438.8 mL, 1M in THF). The reaction mixture was stirred at 20 °C for 1 h, diluted with water (500 mL), and extracted with EtOAc (2 × 100 mL). The aqueous phase was adjusted to pH = 3 with aq. HCl (3 N) and extracted with EtOAc (3 × 200 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered,

and concentrated under reduced pressure to provide a solid that was used directly. LCMS: m/z = 284.0, 285.9 $[M+H]^+$.

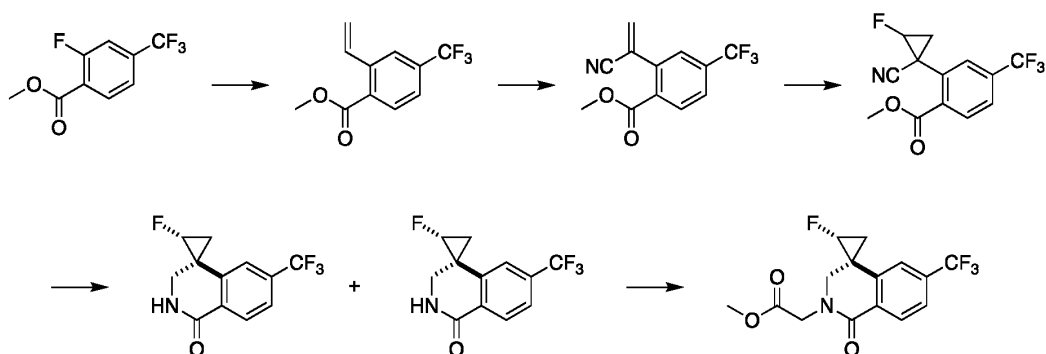
[0273] methyl 4-bromo-2-(1-cyanocyclopropyl)-3-fluorobenzoate: To a solution of 4-bromo-2-(1-cyanocyclopropyl)-3-fluorobenzoic acid (46 g, 162 mmol) in DMF (500 mL) at 0 °C was added K_2CO_3 (34 g, 243 mmol). To the mixture was added MeI (23 g, 162 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into ice cold water (500 mL), filtered, and the filter cake was washed with petroleum ether (2×100 mL). The filtrate was concentrated under reduced pressure to provide a solid that was used directly. LCMS: m/z = 298.1, 300.0 $[M+H]^+$.

[0274] 6-bromo-5-fluoro-spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: To a solution of methyl 4-bromo-2-(1-cyanocyclopropyl)-3-fluorobenzoate (42 g, 141 mmol) in MeOH (600 mL) and water (20 mL) at 0 °C was added dichlorocobalt (73 g, 563 mmol) and $NaBH_4$ (27.0 g, 704 mmol). The reaction mixture was stirred at 20 °C for 4 h. The reaction mixture was poured into sat. aq. NH_4Cl (600 mL), diluted with water (300 mL), and extracted with EtOAc (3×200 mL). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography. LCMS: m/z = 270.0, 272.0 $[M+H]^+$.

[0275] methyl 2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate: To a solution of 6-bromo-5-fluoro-spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (9.3 g, 34.4 mmol) in DMF (100 mL) at 0 °C was added NaH (2.1 g, 51.6 mmol, 60% purity). The reaction mixture was stirred at 0 °C for 0.5 h. To the reaction mixture was added methyl 2-bromoacetate (11 g, 68.9 mmol, 6.50 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched by the addition sat. aq. NH_4Cl (50 mL) and ice-cold water (300 mL) and extracted with EtOAc (3×80 mL). The combined organics were washed with brine (200 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, and the resulting product was slurried with MTBE:PE (2:1, 5 mL) at 25 °C to give a solid that was filtered and dried under reduced pressure. LCMS: m/z = 342.0, 344.0 $[M+H]^+$.

Intermediate 39

methyl 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate



[0276] methyl 4-(trifluoromethyl)-2-vinylbenzoate: To a solution of methyl 2-bromo-4-(trifluoromethyl)benzoate (100 g, 353 mmol) in 1,4-dioxane (2000 mL) was added potassium vinyltrifluoroborate (52 g, 388 mmol), CsF (161 g, 1.06 mol) and Pd(dppf)Cl₂ (12.9 g, 17.7 mmol). The mixture was stirred at 90 °C for 6 h. The mixture was diluted with H₂O (2000 mL) and extracted with EtOAc (3 × 700 mL). The combined organic layers were washed with brine (1500 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

[0277] methyl 2-(1-cyanovinyl)-4-(trifluoromethyl)benzoate: To a solution of Cu₂O (31.0 g, 217 mmol), 6,6'-dimethyl-2,2'-bipyridine (8.0 g, 43 mmol) and SelectFluor (115 g, 325 mmol) in acetone (1 L) and H₂O (500 mL) were added dropwise methyl 4-(trifluoromethyl)-2-vinylbenzoate (50 g, 217 mmol) and TMSCN (64.6 g, 652 mmol). The mixture was stirred at 20 °C for 20 h. The mixture was poured into aq. sat. NaHCO₃ (200 mL) and H₂O (800 mL). The mixture was filtered and the filtrate was extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 256.0 [M+H]⁺.

[0278] methyl 2-[(1*r*,2*s*)-1-cyano-2-fluoro-cyclopropyl]-4-(trifluoromethyl)benzoate and methyl 2-[(1*s*,2*s*)-1-cyano-2-fluoro-cyclopropyl]-4-(trifluoromethyl)benzoate: To a solution of methyl 2-(1-cyanovinyl)-4-(trifluoromethyl)benzoate (11.0 g, 43.1 mmol) in THF (200 mL) at 0 °C were added (fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (31.0 g, 86 mmol) and NaH (6.9 g, 172 mmol, 60% purity). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 288.0 [M+H]⁺.

[0279] (2'*s*,4*r*)-2'-fluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one and (2'*s*,4*s*)-2'-fluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: To a solution of methyl 2-[(1*r*,2*s*)-1-cyano-2-fluoro-cyclopropyl]-4-(trifluoromethyl)benzoate and methyl 2-[(1*s*,2*s*)-1-cyano-2-fluoro-cyclopropyl]-4-(trifluoromethyl)benzoate (12.0 g, 41.0 mmol) in MeOH (120 mL) was added Raney-Ni (5.0 g, 58.0 mmol). The mixture was stirred at 20 °C for 1 h under H₂ (30 psi). The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide:

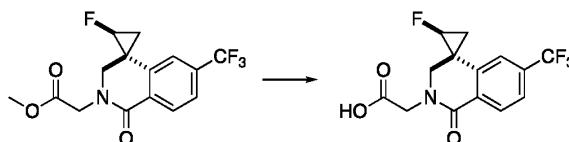
[0280] (2'*s*,4*r*)-2'-fluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: LCMS: m/z = 260.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.27 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.04 (br s, 1H), 6.95 (s, 1H), 4.75-4.52 (m, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.58 (dd, J = 4.4, 13.2 Hz, 1H), 1.61-1.72 (m, 1H), 1.47-1.36 (m, 1H);

[0281] (2'*s*,4*s*)-2'-fluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: LCMS: m/z = 260.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.27 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 0.8, 8.0 Hz, 1H), 7.48 (br s, 1H), 7.37 (s, 1H), 4.89-4.62 (m, 1H), 3.81 (dd, J = 7.6, 12.8 Hz, 1H), 2.81 (dd, J = 4.8, 13.2 Hz, 1H), 1.93-1.79 (m, 1H), 1.25-1.18 (m, 1H).

[0282] methyl 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate: To a solution of (2's,4r)-2'-fluoro-6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (2.4 g, 9.3 mmol) in DMF (30 mL) at 0 °C was added NaH (560 mg, 13.9 mmol, 60% purity). The mixture was stirred for 0.5 h at 0 °C. To the mixture was added methyl 2-bromoacetate (2.83 g, 18.5 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 h. The mixture was poured into sat. aq. NH₄Cl (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 332.2 [M+H]⁺.

Intermediate 40

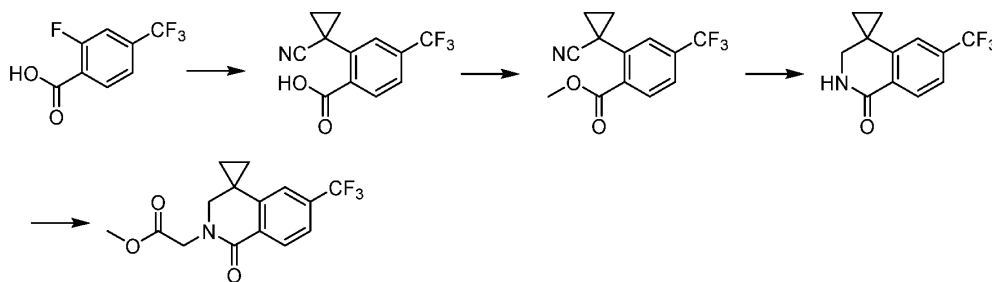
2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetic acid



[0283] To a solution of methyl 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (150 mg, 0.45 mmol) in THF (2.0 mL) and H₂O (2.0 mL) was added LiOH•H₂O (47 mg, 1.1 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was diluted with H₂O (3 mL) and extracted with MTBE (2 mL). The aqueous phase was adjusted to pH = 3 by addition of aq. HCl (3 M). The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude residue that was used directly. LCMS: m/z = 317.9 [M+H]⁺.

Intermediate 41

6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one



[0284] 2-(1-cyanocyclopropyl)-4-(trifluoromethyl)benzoic acid: To a solution of 2-fluoro-4-(trifluoromethyl)benzoic acid (2.00 g, 9.61 mmol) and cyclopropanecarbonitrile (1.93 g, 28.8 mmol) in THF (20 mL) at -40 °C was added dropwise KHMDS (25.0 mL, 1 M in THF). The reaction mixture was slowly warmed up to 20 °C then stirred at this temperature for 1 h. The reaction mixture was then heated to 70 °C and stirred for an additional 2 h. The reaction mixture was poured into H₂O (20 mL) and washed with EtOAc (50 mL). The aqueous layer was then adjusted to pH = 3~4 by the addition of aqueous HCl

(3 N). The aqueous was then extracted with EtOAc (3 × 20 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase HPLC.

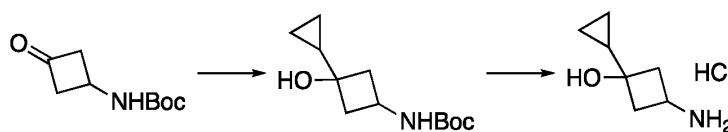
[0285] methyl 2-(1-cyanocyclopropyl)-4-(trifluoromethyl)benzoate: To a solution of 2-(1-cyanocyclopropyl)-4-(trifluoromethyl)benzoic acid (0.50 g, 1.96 mmol) in THF (10 mL) at 0 °C was added TMSCHN₂ (3.92 mmol, 2 M in *n*-hexane). The reaction mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched by the addition of AcOH (2 mL) and the resulting mixture was extracted with EtOAc (20 mL). The organic layer was washed with saturated aqueous NaHCO₃ (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

[0286] 6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one: To a mixture of methyl 2-(1-cyanocyclopropyl)-4-(trifluoromethyl)benzoate (0.30 g, 1.11 mmol) and dichlorocobalt (289 mg, 2.23 mmol) in MeOH (5 mL) and THF (2 mL) at 0 °C was added NaBH₄ (211 mg, 5.57 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture cooled to 0 °C, quenched by the addition of sat. aq. NH₄Cl (10 mL), and extracted with EtOAc (3 × 10 mL). The organics were combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to provide a residue that was used directly. LCMS: *m/z* = 242.1 [M+H]⁺

[0287] methyl 2-[1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate: To a solution of 6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (0.20 g, 0.83 mmol) in DMF (5.0 mL) at 0 °C was added NaH (36 mg, 0.91 mmol, 60% purity in mineral oil). The reaction mixture was stirred at 0 °C for 0.5 h followed by the addition of methyl 2-bromoacetate (190 mg, 1.24 mmol). The reaction mixture was stirred at 20 °C for a further 2 h. The reaction mixture was quenched by the addition of water (5 mL) and extracted with EtOAc (3 × 5 mL). These organics were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. ¹H NMR (400 MHz, CDCl₃): δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 4.35 (s, 2H), 3.76 (s, 3H), 3.48 (s, 2H), 1.21-1.06 (m, 4H).

Intermediate 42

3-amino-1-cyclopropylcyclobutanol



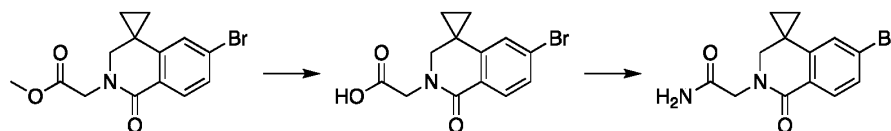
[0288] *tert*-butyl (3-cyclopropyl-3-hydroxycyclobutyl)carbamate: To a solution of bromo(cyclopropyl)magnesium (1 M in THF, 13.50 mL) in THF (15 mL) at -60 °C was added the solution of *tert*-butyl *N*-(3-oxocyclobutyl)carbamate (1.00 g, 5.40 mmol) in THF (15 mL). The mixture was stirred at -60 °C for 1 h. The mixture was quenched with aq. sat. NH₄Cl (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica

gel column chromatography. ^1H NMR (400 MHz, CDCl_3): δ 3.74-3.59 (m, 1H), 3.04-2.91 (m, 1H), 2.48-2.33 (m, 2H), 1.95-1.81 (m, 2H), 1.44 (s, 9H), 1.13-1.08 (m, 1H), 0.54-0.50 (m, 2H), 0.34-0.31 (m, 2H).

[0289] 3-amino-1-cyclopropylcyclobutanol HCl salt: A solution of tert-butyl (3-cyclopropyl-3-hydroxycyclobutyl)carbamate (1.00 g, 4.40 mmol) in HCl (4 M in MeOH, 10 mL) was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure to provide a residue that was used directly.

Intermediate 43

2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetamide

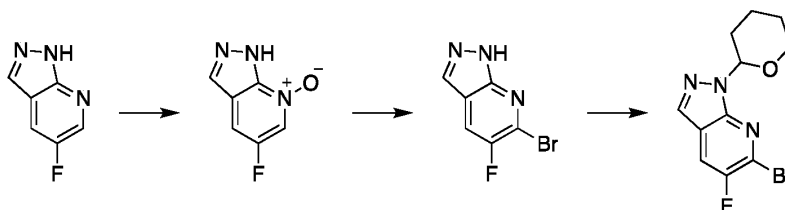


[0290] 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetic acid: To a solution of methyl 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (330 mg, 1.02 mmol) in THF (5 mL) was added a solution of LiOH (2.04 mL, 1 M in H₂O). The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was adjusted pH to 4 using aqueous 1 N HCl and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide a residue that was used directly. LCMS: m/z = 310.3, 312.3 [M+H]⁺.

[0291] 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetamide: To a solution of 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetic acid (2.0 g, 6.45 mmol), NH₄Cl (690 mg, 12.90 mmol), HOBT (1.05 g, 7.74 mmol) in DCM (20 mL) were added EDCI (1.48 g, 7.74 mmol) and DIPEA (1.67 g, 12.90 mmol). The mixture was stirred at 20 °C for 16 h. The mixture was added to H₂O (30 mL) and extracted with DCM (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product were triturated with MTBE at 25 °C for 30 min to provide a residue that was used directly. LCMS: m/z = 309.0, 311.0 [M+H]⁺.

Intermediate 44

6-bromo-5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine



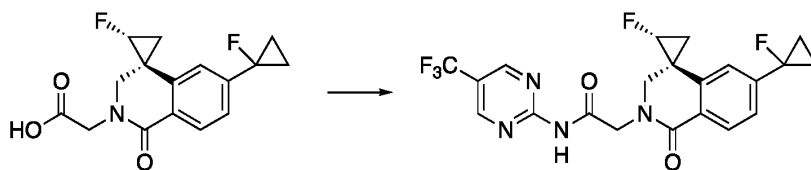
[0292] 5-fluoro-1H-pyrazolo[3,4-*b*]pyridine 7-oxide: To a solution of 5-fluoro-1H-pyrazolo[3,4-*b*]pyridine (3.0 g, 21.9 mmol) in EtOAc (30 mL) at 0 °C was added m-CPBA (5.55 g, 27.4 mmol, 85% purity). The mixture was stirred at 20 °C for 12 h. The mixture was filtered. The filter cake was washed with EtOAc (2 x 3 mL). The filter cake was dried under reduced pressure to provide a residue that was used directly. LCMS: m/z = 154.0 [M+H]⁺.

[0293] 6-bromo-5-fluoro-1H-pyrazolo[3,4-b]pyridine: To a solution of 5-fluoro-1H-pyrazolo[3,4-b]pyridine 7-oxide (2.70 g, 17.6 mmol) in CHCl_3 (100 mL) at 0 °C was added POBr_3 (7.58 g, 26.4 mmol). The mixture was stirred at 60 °C for 2 h. The mixture was diluted with H_2O (20 mL) and extracted with DCM (3×7 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: $m/z = 215.9, 217.9$ $[\text{M}+\text{H}]^+$.

[0294] 6-bromo-5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine: To a solution of 6-bromo-5-fluoro-1H-pyrazolo[3,4-b]pyridine (1.16 g, 5.37 mmol) in 1,4-dioxane (15 mL) at 20 °C was added 3,4-dihydro-2H-pyran (903 mg, 10.7 mmol) and *p*-TsOH (93 mg, 0.54 mmol). The mixture was stirred at 80 °C for 2 h. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: $m/z = 299.7, 301.6$ $[\text{M}+\text{H}]^+$.

Example 1

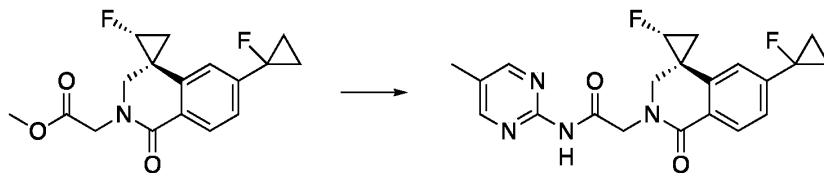
2-[(2'R,4S)-2'-fluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(5-(trifluoromethyl)pyrimidin-2-yl)acetamide (1)



[0295] To a solution of 5-(trifluoromethyl)pyrimidin-2-amine (40 mg, 0.24 mmol) in THF (2.0 mL) at 0 °C was added LiHMDS (1 M in THF, 0.24 mL). The reaction mixture was stirred at 0 °C for 3 h. Separately, to a solution of 2-((1S,2R)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid (50 mg, 0.16 mmol, Int. 7) in THF (2.0 mL) was added CDI (53 mg, 0.33 mmol). This mixture was stirred at 15 °C for 3 h and then added to the initial mixture at 0 °C. The combined reaction mixture was stirred at 0 °C for a further 1 h and then 15 °C for an additional 1 h. The reaction mixture was diluted with H_2O (10 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 residue was purified by reverse-phase preparative HPLC. LCMS: $m/z = 453.1$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.30 (s, 1H), 9.10 (d, $J = 0.4$ Hz, 2H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.31 (dd, $J = 1.6, 8.0$ Hz, 1H), 6.69 (d, $J = 1.2$ Hz, 1H), 5.17-4.94 (m, 1H), 4.84 (d, $J = 17.2$ Hz, 1H), 4.40 (d, $J = 17.2$ Hz, 1H), 3.93 (dd, $J = 2.0, 12.8$ Hz, 1H), 3.56 (d, $J = 13.2$ Hz, 1H), 1.78-1.67 (m, 1H), 1.59-1.40 (m, 3H), 1.33-1.21 (m, 2H).

Example 2

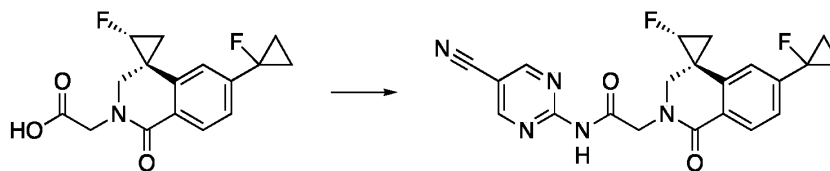
2-[(2'*R*,4*S*)-2'-fluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-
N-(5-methylpyrimidin-2-yl)acetamide (2)



[0296] To a mixture of methyl 2-((1*S*,2*R*)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (30 mg, 0.09 mmol, Int. 8), 5-methylpyrimidin-2-amine (20 mg, 0.19 mmol) in DCE (1.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.28 mL). The mixture was stirred for 6 h at 60 °C. The reaction mixture was poured into ice-cold H₂O (15 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 399.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.92 (br s, 1H), 8.44 (s, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 1.2 Hz, 1H), 5.03 (br s, 1H), 4.79-4.54 (m, 1H), 4.44 (br d, *J* = 17.2 Hz, 1H), 4.18 (dd, *J* = 1.6, 12.8 Hz, 1H), 3.55 (d, *J* = 12.8 Hz, 1H), 2.27 (s, 3H), 1.71-1.51 (m, 3H), 1.46-1.32 (m, 1H), 1.18-1.07 (m, 2H).

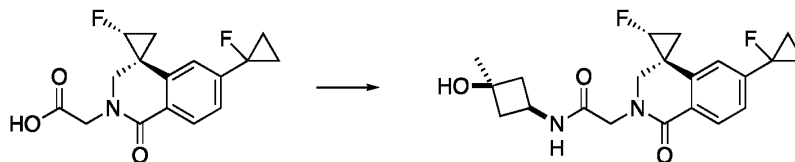
Example 3

2-[(2'*R*,4*S*)-2'-fluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-
N-(5-cyanopyrimidin-2-yl)acetamide (3)



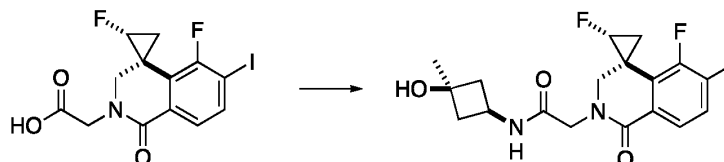
[0297] To a solution of 5-cyanopyrimidin-2-amine (18 mg, 0.15 mmol) in THF (2.0 mL) at 0 °C was added LiHMDS (1 M in THF, 0.15 mL). The reaction mixture was stirred at 0 °C for 3 h. Separately, to a solution of 2-((1*S*,2*R*)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid (30 mg, 0.10 mmol, Int. 7) in THF (1.0 mL) was added CDI (32 mg, 0.20 mmol). This mixture was stirred at 15 °C for 3 h and then added to the initial mixture at 0 °C. The combined reaction mixture was stirred at 0 °C for a further 1 h and then 15 °C for an additional 1 h. The reaction 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 residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 410.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.39 (s, 1H), 9.13 (s, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.69 (d, *J* = 1.2 Hz, 1H), 5.20-4.93 (m, 1H), 4.82 (d, *J* = 17.6 Hz, 1H), 4.39 (d, *J* = 17.6 Hz, 1H), 3.92 (dd, *J* = 1.6, 12.8 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 1.76-1.69 (m, 1H), 1.61-1.41 (m, 3H), 1.31-1.23 (m, 2H).

Example 4

N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[(2'*R*,4*S*)-2'-fluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetamide (4)

[0298] To a solution of 2-((1*S*,2*R*)-2-fluoro-1'-oxo-6'-(1-fluorocyclopropyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetic acid (30 mg, 0.10 mmol, Int. 7) in DMF (1.5 mL) were added 3-*cis*-amino-1-methylcyclobutanol HCl salt (27 mg, 0.19 mmol), DIPEA (63 mg, 0.49 mmol), HOBt (20 mg, 0.15 mmol), and EDCI (28 mg, 0.15 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (10 mL) and extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 391.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.54 (br d, J = 7.2 Hz, 1H), 4.71-4.48 (m, 1H), 4.39 (d, J = 16.0 Hz, 1H), 4.13-3.92 (m, 3H), 3.47 (d, J = 12.8 Hz, 1H), 2.57-2.45 (m, 2H), 2.11 (br s, 1H), 2.07-1.97 (m, 2H), 1.78-1.68 (m, 1H), 1.60-1.52 (m, 2H), 1.43-1.29 (m, 4H), 1.17-1.06 (m, 2H).

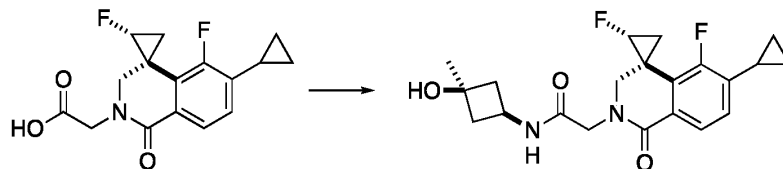
Example 5

N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[(2'*s*,4*r*)-2',5-difluoro-6-iodo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetamide (5)

[0299] To a solution of 2-[(2'*s*,4*r*)-2',5-difluoro-6-iodo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetic acid (140 mg, 0.36 mmol, Int. 18) in DMF (1.5 mL) were added 3-*cis*-amino-1-methylcyclobutanol HCl salt (98 mg, 0.71 mmol), DIPEA (230 mg, 1.78 mmol), HOBt (72 mg, 0.53 mmol), and EDCI (102 mg, 0.53 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 477.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.81-7.75 (m, 1H), 7.73-7.68 (m, 1H), 6.48 (br d, J = 7.2 Hz, 1H), 5.34-5.08 (m, 1H), 4.17 (s, 2H), 4.05-3.95 (m, 1H), 3.90 (dd, J = 2.4, 13.2 Hz, 1H), 3.55 (d, J = 13.2 Hz, 1H), 2.51 (ddd, J = 3.2, 8.0, 10.4 Hz, 2H), 2.18 (s, 1H), 2.07-1.97 (m, 3H), 1.51-1.39 (m, 1H), 1.37 (s, 3H).

Example 6

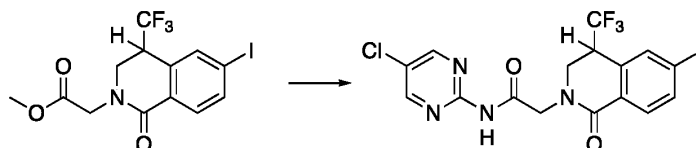
N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[(2'*s*,4*r*)-2',5-difluoro-6-cyclopropyl-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetamide (6)



[0300] To a solution of 2-[(2'*s*,4*r*)-6-cyclopropyl-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetic acid (50 mg, 0.16 mmol, Int. 17) in DMF (1.0 mL) were added 3-*cis*-amino-1-methylcyclobutanol HCl salt (45 mg, 0.33 mmol), DIPEA (110 mg, 0.82 mmol), HOBt (33 mg, 0.25 mmol), and EDCI (47 mg, 0.25 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (5 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 391.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.85 (d, *J* = 8.0 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.62 (br d, *J* = 7.2 Hz, 1H), 5.37-5.13 (m, 1H), 4.27-4.08 (m, 2H), 4.04-3.91 (m, 1H), 3.87 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.53 (d, *J* = 12.8 Hz, 1H), 2.56-2.44 (m, 2H), 2.32 (s, 1H), 2.12-1.95 (m, 4H), 1.41-1.36 (m, 4H), 1.10-1.02 (m, 2H), 0.80-0.72 (m, 2H).

Example 7

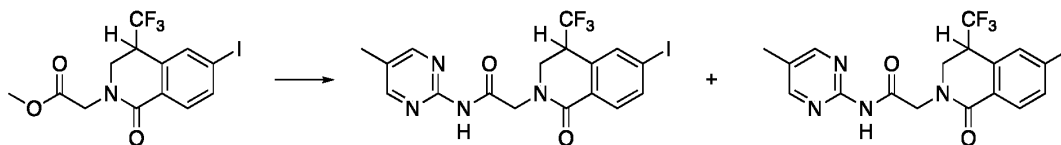
N-(5-chloropyrimidin-2-yl)-2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (7)



[0301] To a solution of a single isomer of methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (100 mg, 0.24 mmol, Int. 20b) in DCE (2.0 mL) were added 5-chloropyrimidin-2-amine (38 mg, 0.30 mmol) and AlMe₃ (1 M in *n*-heptane, 0.37 mL). The reaction mixture was stirred at 90 °C for 1.5 h. The reaction mixture was cooled to ambient temperature, diluted with water (6 mL), and extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with brine (6 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC to provide the title compound as a single unassigned enantiomer. LCMS: *m/z* = 510.9, 512.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.61 (br s, 1H), 8.55 (s, 2H), 7.93-7.90 (m, 2H), 7.76 (s, 1H), 5.20-5.14 (m, 1H), 4.33 (d, *J* = 16.8 Hz, 1H), 4.28 (br dd, *J* = 4.4, 13.6 Hz, 1H), 3.84 (dd, *J* = 4.0, 13.6 Hz, 1H), 3.62-3.56 (m, 1H).

Examples 8 and 9

2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(5-methylpyrimidin-2-yl)acetamide (8) and 2-(6-methyl-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(5-methylpyrimidin-2-yl)acetamide (9)



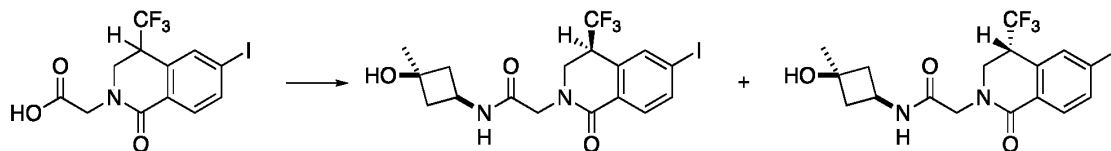
[0302] To a solution of a single isomer of methyl 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (100 mg, 0.24 mmol, Int. 20b) in DCE (1.0 mL) were added 5-methylpyrimidin-2-amine (32 mg, 0.30 mmol) and AlMe₃ (1 M in *n*-heptane, 0.37 mL). The reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was cooled to ambient temperature, diluted with water (6 mL), and extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with brine (6 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide the title compounds as a single unassigned enantiomers. The residue was purified by reverse-phase preparative HPLC to provide:

[0303] 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(5-methylpyrimidin-2-yl)acetamide (8): LCMS: m/z = 490.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.63 (br s, 1H), 8.45 (s, 2H), 7.94 (m, 2H), 7.77 (s, 1H), 5.32-5.26 (m, 1H), 4.38 (d, J = 17.2 Hz, 1H), 4.31 (br dd, J = 4.0, 13.6 Hz, 1H), 3.84 (dd, J = 2.0, 14.0 Hz, 1H), 3.64-3.56 (m, 1H), 2.23 (s, 3H).

[0304] 2-(6-methyl-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(5-methylpyrimidin-2-yl)acetamide (9): LCMS: m/z = 379.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.62 (br s, 1H), 8.43 (s, 2H), 8.11 (d, J = 8.0 Hz, 1H), 7.34 (br d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 5.22-5.09 (m, 1H), 4.36 (d, J = 16.8 Hz, 1H), 4.25 (br dd, J = 4.8, 13.6 Hz, 1H), 3.85 (br d, J = 12.8 Hz, 1H), 3.61-3.54 (m, 1H), 2.44 (s, 3H), 2.28 (s, 3H).

Examples 10 and 11

N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (10 and 11)



[0305] To a solution of 2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetic acid (150 mg, 0.38 mmol, Int. 21) in DMF (2.0 mL) were added 3-*cis*-amino-1-methylcyclobutanol HCl salt (103 mg, 0.76 mmol), DIPEA (242 mg, 1.88 mmol), HOBT (76 mg, 0.56 mmol), and EDCI (108 mg, 0.56 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was

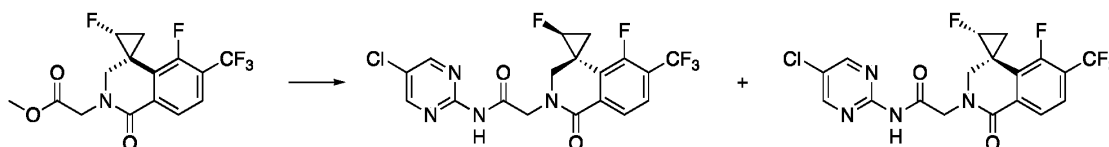
purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in EtOH; Gradient: B%: 40% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0306] N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (first eluting isomer, 10): LCMS: m/z = 483.0 [M+H]⁺.

[0307] N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-(6-iodo-1-oxo-4-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (second eluting isomer, 11): LCMS: m/z = 482.9 [M+H]⁺.

Examples 12 and 13

2-[(2'*s*,4*r*)-2',5-difluoro-1-oxo-6-(trifluoromethyl)spiro[3*H*-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(5-chloropyrimidin-2-yl)acetamide (12 and 13)



[0308] To a solution of methyl 2-[(2'*s*,4*r*)-2',5-difluoro-1-oxo-6-(trifluoromethyl)spiro[3*H*-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (70 mg, 0.20 mmol, Int. 24) in DCE (2.0 mL) were added 5-chloropyrimidin-2-amine (31 mg, 0.24 mmol) and AlMe₃ (1 M in *n*-heptane, 0.30 mL). The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was cooled to 0 °C, diluted with H₂O (10 mL), and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: Chiralpak IG-3 (50 mm × 4.6 mm × 3 μm particle size); Mobile phase: A: CO₂ B: 0.1% *i*-PrNH₂ in *i*-PrOH; Gradient: B%: 50% isocratic; Flow rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

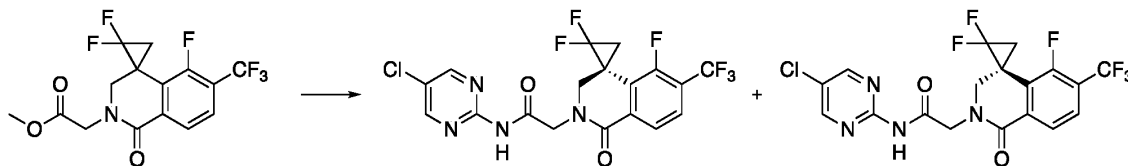
[0309] 2-[(2'*s*,4*r*)-2',5-difluoro-1-oxo-6-(trifluoromethyl)spiro[3*H*-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(5-chloropyrimidin-2-yl)acetamide (first eluting isomer, 12): LCMS: m/z = 447.0, 449.0

[M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.70 (br s, 1H), 8.56 (br s, 2H), 8.12 (d, J = 8.0 Hz, 1H), 7.62-7.57 (m, 1H), 5.45-5.26 (m, 1H), 5.07 (br d, J = 16.4 Hz, 1H), 4.54 (br d, J = 17.2 Hz, 1H), 3.96 (dd, J = 2.8, 13.2 Hz, 1H), 3.70 (d, J = 13.2 Hz, 1H), 2.03 (td, J = 7.6, 11.6 Hz, 1H), 1.61-1.50 (m, 1H).

[0310] 2-[(2'*s*,4*r*)-2',5-difluoro-1-oxo-6-(trifluoromethyl)spiro[3*H*-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(5-chloropyrimidin-2-yl)acetamide (second eluting isomer, 13): LCMS: m/z = 447.0, 449.0

[M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.74 (br s, 1H), 8.56 (br s, 2H), 8.11 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 5.45-5.27 (m, 1H), 5.07 (br d, J = 16.8 Hz, 1H), 4.54 (br d, J = 17.2 Hz, 1H), 3.94 (dd, J = 2.0, 13.2 Hz, 1H), 3.70 (d, J = 12.8 Hz, 1H), 2.03 (td, J = 6.8, 11.2 Hz, 1H), 1.59-1.51 (m, 1H).

Examples 14 and 15

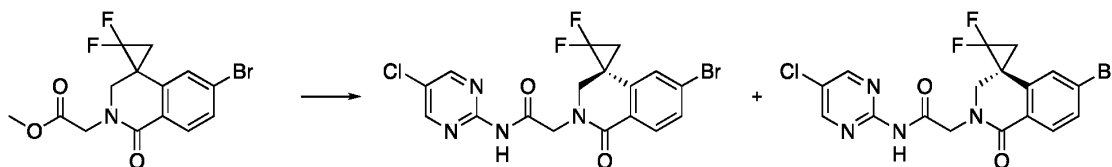
N-(5-chloropyrimidin-2-yl)-2-[1',1',5-trifluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (14 and 15)

[0311] To a solution of methyl 2-(2,2,5'-trifluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (120 mg, 0.33 mmol) in DCE (2.0 mL) were added 5-chloropyrimidin-2-amine (51 mg, 0.39 mmol) and AlMe_3 (1 M in *n*-heptane, 0.49 mL). The reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was diluted with H_2O (12 mL) and extracted with EtOAc (3 × 12 mL). The combined organic layers were washed with brine (12 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO_2 B: 0.1% NH_4OH in *i*-PrOH; Gradient: B%: 32% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0312] **N-(5-chloropyrimidin-2-yl)-2-[1',1',5-trifluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 14):** LCMS: m/z = 465.0, 467.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.55 (s, 2H), 8.54-8.47 (m, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.3 Hz, 1H), 5.41-5.26 (m, 1H), 4.50 (dd, J = 6.4, 12.8 Hz, 1H), 4.28 (d, J = 17.6 Hz, 1H), 3.12 (br d, J = 13.2 Hz, 1H), 3.04-2.92 (m, 1H), 1.72-1.61 (m, 1H).

[0313] **N-(5-chloropyrimidin-2-yl)-2-[1',1',5-trifluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 15):** LCMS: m/z = 465.0, 467.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.64 (br s, 1H), 8.56 (s, 2H), 8.13 (d, J = 8.4 Hz, 1H), 7.73-7.66 (m, 1H), 5.42-5.25 (m, 1H), 4.50 (dd, J = 6.8, 13.2 Hz, 1H), 4.28 (d, J = 17.2 Hz, 1H), 3.16-3.07 (m, 1H), 3.04-2.93 (m, 1H), 1.72-1.61 (m, 1H).

Examples 16 and 17

N-(5-chloropyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (16 and 17)

[0314] **N-(5-chloropyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide:** To a mixture of 5-chloropyrimidin-2-amine (72 mg, 0.56 mmol) in toluene (4.0 mL) was added AlMe_3 (1 M in *n*-heptane, 0.56 mL). The reaction mixture was allowed to stir

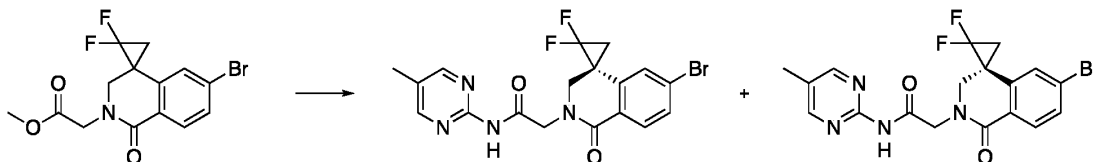
for 50 min at 25 °C before the addition of a solution of methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'-*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetate (100 mg, 0.28 mmol) in toluene (1.0 mL). The reaction mixture was then stirred at 90 °C for 2 h. The reaction mixture was diluted with water (4 mL) and extracted with EtOAc (3 × 2 mL). The combined organics were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: Chiralpak AD-3 (50 mm × 4.6 mm × 3 μm particle size); Mobile phase: A: CO₂ B: 0.1% *i*-PrNH₂ in EtOH; Gradient: B%: 50% isocratic; Flow rate: 4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0315] N-(5-chloropyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3*H*-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 16): LCMS: m/z = 456.9, 458.9, 460.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.89 (br s, 1H), 8.58 (s, 2H), 8.09 (d, J = 8.4 Hz, 1H), 7.63 (dd, J = 1.6, 8.4 Hz, 1H), 7.25 (s, 1H), 5.21-5.16 (m, 1H), 4.37 (br d, J = 16.8 Hz, 1H), 4.24 (dd, J = 5.6, 12.8 Hz, 1H), 3.46 (d, J = 12.4 Hz, 1H), 2.13-2.09 (m, 1H), 1.79-1.73 (m, 1H).

[0316] N-(5-chloropyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3*H*-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 17): LCMS: m/z = 456.9, 458.9, 460.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.02 (br s, 1H), 8.59 (s, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.62 (br d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 5.22-5.17 (m, 1H), 4.38 (br d, J = 17.2 Hz, 1H), 4.24 (br dd, J = 5.2, 12.8 Hz, 1H), 3.46 (br d, J = 12.8 Hz, 1H), 2.15-2.09 (m, 1H), 1.79-1.71 (m, 1H).

Examples 18 and 19

N-(5-methylpyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3*H*-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (18 and 19)



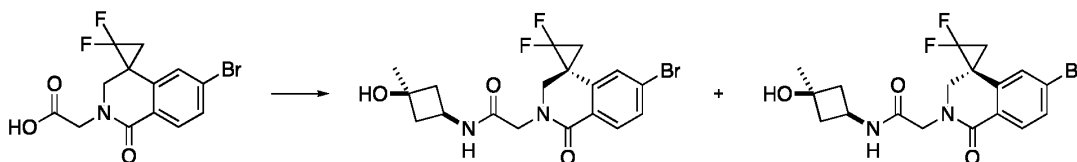
[0317] To a solution of methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'-*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetate (100 mg, 0.28 mmol) and 5-methylpyrimidin-2-amine (91 mg, 0.83 mmol) in DCE (2.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.80 mL). The reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to 0 °C, diluted with water (8 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in EtOH; Gradient: B%: 50% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0318] N-(5-methylpyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 18): LCMS: m/z = 436.9, 438.9 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 9.34 (br s, 1H), 8.46 (s, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.57 (dd, J = 1.8, 8.2 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 5.30 (br d, J = 14.8 Hz, 1H), 4.38 (br d, J = 17.2 Hz, 1H), 4.19 (dd, J = 5.2, 12.8 Hz, 1H), 3.42 (d, J = 12.8 Hz, 1H), 2.28 (s, 3H), 2.09-2.05 (m, 1H), 1.75-1.71 (m, 1H).

[0319] N-(5-methylpyrimidin-2-yl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 19): LCMS: m/z = 436.9, 438.9 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.45 (s, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 1.6, 8.4 Hz, 1H), 7.23 (d, J = 1.2 Hz, 1H), 5.29 (br d, J = 16.4 Hz, 1H), 4.38 (br d, J = 17.2 Hz, 1H), 4.19 (dd, J = 5.4, 12.8 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 2.28 (s, 3H), 2.09-2.04 (m, 1H), 1.75-1.71 (m, 1H).

Examples 20 and 21

N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (20 and 21)



[0320] To a solution of 2-(6-bromo-1',1'-difluoro-1-oxo-spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)acetic acid (100 mg, 0.29 mmol) in DMF (1.0 mL) at 0 °C were added 3-*cis*-amino-1-methylcyclobutanol HCl salt (101 mg, 0.58 mmol), HOBT (59 mg, 0.44 mmol), DIPEA (187 mg, 1.44 mmol), and EDCI (83 mg, 0.44 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into H_2O (3 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm $\times$ 30 mm $\times$ 10 μm particle size); Mobile phase: A: CO_2 B: *i*-PrOH (0.1% *i*-PrNH $_2$, v/v); Gradient: B%: 33% isocratic; Flow rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 2000 psi) to provide:

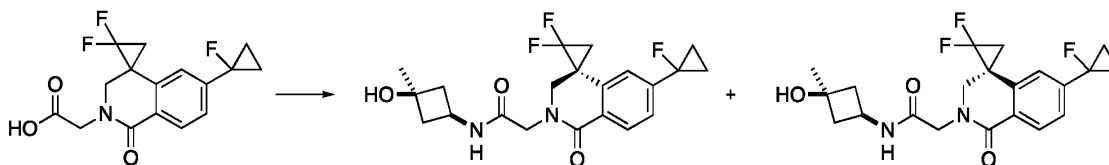
[0321] N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 20): LCMS: m/z = 429.0, 430.9 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 2.0, 8.4 Hz, 1H), 7.21 (d, J = 1.2 Hz, 1H), 6.49 (br d, J = 7.2 Hz, 1H), 4.18 (s, 2H), 4.07 (dd, J = 6.0, 13.2 Hz, 1H), 4.01-3.94 (m, 1H), 3.41 (dd, J = 1.2, 13.2 Hz, 1H), 2.56-2.48 (m, 2H), 2.18-2.09 (m, 2H), 2.07-1.99 (m, 2H), 1.72-1.70 (m, 1H), 1.37 (s, 3H).

[0322] N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 21): LCMS: m/z = 429.0, 430.9 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 2.0, 8.4 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 6.48 (br d, J = 7.2 Hz, 1H), 4.18 (s, 2H), 4.07 (dd, J = 6.0, 12.8 Hz, 1H), 4.01-

3.93 (m, 1H), 3.41 (dd, $J = 1.6, 13.2$ Hz, 1H), 2.57-2.48 (m, 2H), 2.16-2.08 (m, 2H), 2.07-1.99 (m, 2H), 1.72-1.70 (m, 1H), 1.37 (s, 3H).

Examples 22 and 23

N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (22 and 23)



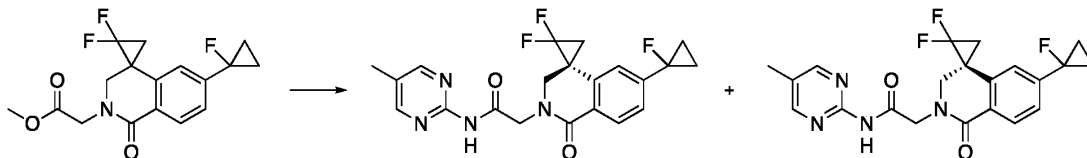
[0323] To a solution of 2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetic acid (100 mg, 0.30 mmol) and 3-*cis*-amino-1-methylcyclobutanol HCl salt (47 mg, 0.46 mmol) in DMF (1.0 mL) were added HOBt (62 mg, 0.46 mmol), DIPEA (119 mg, 0.90 mmol), and EDCI (88 mg, 0.46 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was cooled to 0 °C, poured into H₂O (5 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in EtOH; Gradient: B%: 30% isocratic; Flow rate: 65 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 100 bar) to provide:

[0324] N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, **22**): LCMS: $m/z = 409.1$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.14 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.04 (s, 1H), 6.54 (br d, $J = 7.2$ Hz, 1H), 4.29-4.12 (m, 2H), 4.08 (dd, $J = 6.0, 12.8$ Hz, 1H), 3.98 (d, $J = 8.0$ Hz, 1H), 3.46-3.34 (m, 1H), 2.57-2.45 (m, 2H), 2.25-2.11 (m, 2H), 2.04-2.02 (m, 2H), 1.74-1.53 (m, 3H), 1.37 (s, 3H), 1.20-1.10 (m, 2H).

[0325] N-(3-*cis*-hydroxy-3-methylcyclobutyl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, **23**): LCMS: $m/z = 409.1$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.14 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 1H), 7.04 (s, 1H), 6.54 (br d, $J = 7.2$ Hz, 1H), 4.29-4.12 (m, 2H), 4.08 (dd, $J = 6.0, 12.8$ Hz, 1H), 3.98 (d, $J = 8.0$ Hz, 1H), 3.40 (d, $J = 12.8$ Hz, 1H), 2.57-2.46 (m, 2H), 2.25-2.11 (m, 2H), 2.08-1.98 (m, 2H), 1.79-1.49 (m, 3H), 1.37 (s, 3H), 1.16-1.11 (m, 2H).

Examples 24 and 25

N-(5-methylpyrimidin-2-yl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (24 and 25)



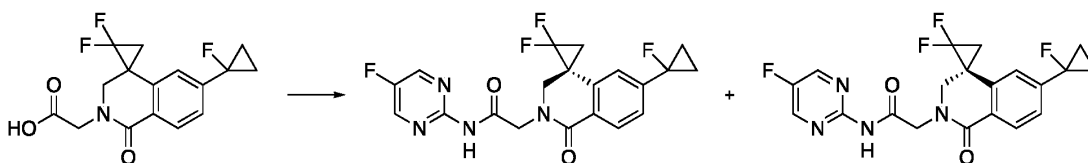
[0326] To a solution of 5-methylpyrimidin-2-amine (39 mg, 0.35 mmol) in DCE (0.5 mL) was added AlMe_3 (1 M in *n*-heptane, 0.44 mL). The reaction mixture was stirred at 20 °C for 0.5 h prior to the addition of a solution of methyl 2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetate (100 mg, 294.72 μmol) in DCE (1.0 mL). The reaction mixture was stirred at 70 °C for a further 4 h. The reaction mixture was diluted with H_2O (10 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm $\times$ 30 mm $\times$ 10 μm particle size); Mobile phase: A: CO_2 B: 0.1% NH_4OH in EtOH; Gradient: B%: 37% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0327] N-(5-methylpyrimidin-2-yl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 24): LCMS: m/z = 417.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.54 (br s, 1H), 8.43 (s, 2H), 8.18 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 5.29-5.10 (m, 1H), 4.34 (br d, J = 17.2 Hz, 1H), 4.21 (br dd, J = 5.6, 12.8 Hz, 1H), 3.42 (br d, J = 13.2 Hz, 1H), 2.28 (s, 3H), 2.17-2.14 (m, 1H), 1.77-1.65 (m, 1H), 1.64-1.59 (m, 1H), 1.58 (br s, 1H), 1.20-1.08 (m, 2H).

[0328] N-(5-methylpyrimidin-2-yl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 25): LCMS: m/z = 417.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.54 (br s, 1H), 8.43 (s, 2H), 8.19 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 5.31-5.08 (m, 1H), 4.34 (br d, J = 16.8 Hz, 1H), 4.21 (dd, J = 6.0, 12.8 Hz, 1H), 3.43 (d, J = 12.4 Hz, 1H), 2.28 (s, 3H), 2.21-2.10 (m, 1H), 1.72-1.56 (m, 3H), 1.19-1.11 (m, 2H).

Examples 26 and 27

N-(5-fluoropyrimidin-2-yl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (26 and 27)



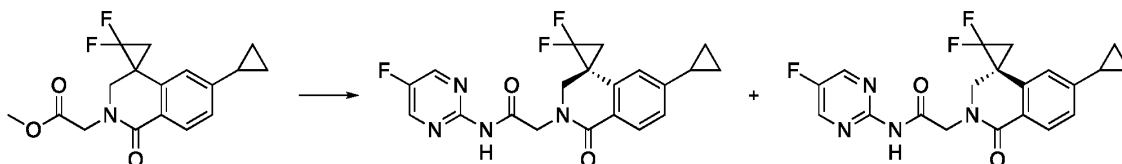
[0329] To a solution of 2-(2,2-difluoro-6'-(1-fluorocyclopropyl)-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetic acid (0.16 g, 0.49 mmol) in pyridine (4.0 mL) were added 5-fluoropyrimidin-2-amine (111 mg, 0.98 mmol) and EDCI (189 mg, 0.98 mmol). The reaction mixture was stirred at 25 °C for 2 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in EtOH; Gradient: B%: 33% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0330] N-(5-fluoropyrimidin-2-yl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 26): LCMS: m/z = 421.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.76 (br s, 1H), 8.48 (s, 2H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 5.14-4.98 (m, 1H), 4.31 (d, *J* = 16.4 Hz, 1H), 4.21 (dd, *J* = 6.0, 12.8 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 2.21-2.15 (m, 1H), 1.71-1.63 (m, 1H), 1.65-1.57 (m, 2H), 1.19-1.10 (m, 2H).

[0331] N-(5-fluoropyrimidin-2-yl)-2-[1',1'-difluoro-6-(1-fluorocyclopropyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 27): LCMS: m/z = 421.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.76 (br s, 1H), 8.48 (s, 2H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 5.14-4.98 (m, 1H), 4.31 (d, *J* = 16.4 Hz, 1H), 4.21 (dd, *J* = 6.0, 12.8 Hz, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 2.19-2.16 (m, 1H), 1.72-1.69 (m, 1H), 1.65-1.57 (m, 2H), 1.19-1.10 (m, 2H).

Examples 28 and 29

N-(5-fluoropyrimidin-2-yl)-2-[6-cyclopropyl-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (28 and 29)



[0332] To a solution of 2-(6'-cyclopropyl-2,2-difluoro-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetic (50 mg, 0.16 mmol) in pyridine (2.0 mL) were added 5-fluoropyrimidin-2-amine (37 mg, 0.32 mmol) and EDCI (94 mg, 0.48 mmol). The reaction mixture was stirred at 20 °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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in EtOH; Gradient: B%: 50% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

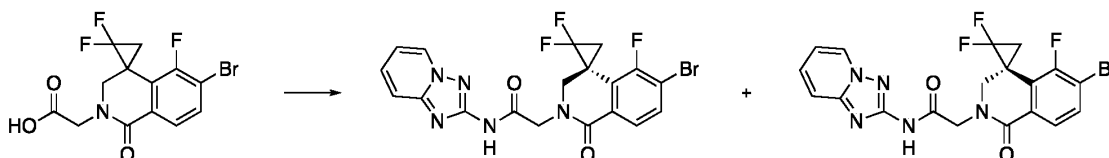
[0333] N-(5-fluoropyrimidin-2-yl)-2-[6-cyclopropyl-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 28): LCMS: m/z = 403.1 [M+H]⁺. ¹H NMR (400

MHz, DMSO-*d*₆): δ 10.95 (s, 1H), 8.76 (s, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 4.83 (br d, *J* = 17.2 Hz, 1H), 4.17 (br d, *J* = 17.2 Hz, 1H), 4.10 (br dd, *J* = 6.8, 12.8 Hz, 1H), 3.34 (br d, *J* = 13.2 Hz, 1H), 2.73-2.62 (m, 1H), 2.05-1.95 (m, 1H), 1.94-1.84 (m, 1H), 1.09-0.98 (m, 2H), 0.87-0.72 (m, 2H).

[0334] N-(5-fluoropyrimidin-2-yl)-2-[6-cyclopropyl-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 29): LCMS: *m/z* = 403.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.95 (br s, 1H), 8.76 (s, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.01 (s, 1H), 4.83 (br d, *J* = 17.2 Hz, 1H), 4.17 (br d, *J* = 17.2 Hz, 1H), 4.10 (br dd, *J* = 6.8, 13.2 Hz, 1H), 3.36 (s, 1H), 2.73-2.63 (m, 1H), 2.04-1.95 (m, 1H), 1.94-1.84 (m, 1H), 1.08-0.98 (m, 2H), 0.87-0.73 (m, 2H).

Examples 30 and 31

N-([1,2,4]triazolo[1,5-a]pyridin-2-yl)-2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (30 and 31)



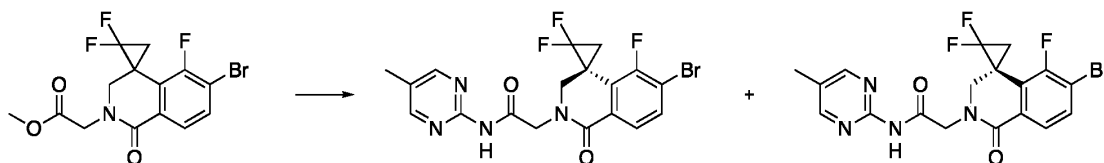
[0335] To a solution of 2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetic acid (300 mg, 0.82 mmol) and [1,2,4]triazolo[1,5-a]pyridin-2-amine (221 mg, 1.65 mmol) in pyridine (6.0 mL) was added EDCI (315 mg, 1.65 mmol). The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was diluted with water (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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: Chiralcel OD-3 (50 mm × 4.6 mm × 3 μm particle size); Mobile phase: A: CO₂ B: 0.1% *i*-PrNH₂ in MeOH; Gradient: B%: 40% isocratic; Flow rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0336] N-([1,2,4]triazolo[1,5-a]pyridin-2-yl)-2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 30): LCMS: *m/z* = 480.0, 482.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.75 (br s, 1H), 8.57 (br d, *J* = 6.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.74-7.60 (m, 2H), 7.57-7.52 (m, 1H), 7.04-7.00 (m, 1H), 5.12-3.84 (m, 3H), 3.36-3.09 (m, 1H), 3.04-2.84 (m, 1H), 1.71-1.54 (m, 1H).

[0337] N-([1,2,4]triazolo[1,5-a]pyridin-2-yl)-2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 31): LCMS: *m/z* = 480.0, 482.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.70 (br s, 1H), 8.57 (br d, *J* = 6.8 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.73-7.61 (m, 2H), 7.56-7.53 (m, 1H), 7.03-7.00 (m, 1H), 5.24-3.71 (m, 3H), 3.28-3.08 (m, 1H), 2.96-2.91 (m, 1H), 1.67-1.57 (m, 1H).

Examples 32 and 33

N-(5-methylpyrimidin-2-yl)-2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (32 and 33)



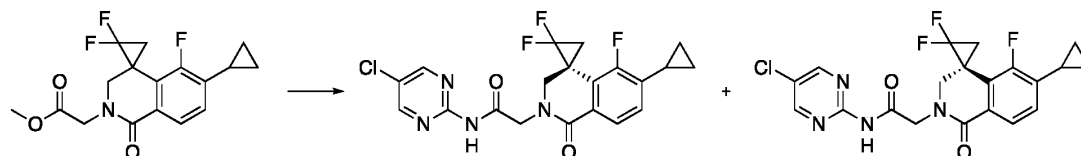
[0338] To a solution of methyl 2-(6'-bromo-2,2,5'-trifluoro-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetate (20 mg, 0.05 mmol) and 5-methylpyrimidin-2-amine (17 mg, 0.15 mmol) in DCE (1.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.15 mL). The reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to 0 °C, diluted with water (8 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in *i*-PrOH; Gradient: B%: 50% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0339] N-(5-methylpyrimidin-2-yl)-2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 32): LCMS: *m/z* = 455.0, 456.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.69 (br s, 1H), 8.43 (s, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.73-7.57 (m, 1H), 5.39 (br s, 1H), 4.48 (dd, *J* = 6.8, 19.6 Hz, 1H), 4.27 (br d, *J* = 17.2 Hz, 1H), 3.09 (br d, *J* = 12.8 Hz, 1H), 2.98-2.88 (m, 1H), 2.28 (s, 3H), 1.63 (br s, 1H).

[0340] N-(5-methylpyrimidin-2-yl)-2-[6-bromo-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 33): LCMS: *m/z* = 454.9, 456.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (br s, 1H), 8.43 (s, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.63 (dd, *J* = 6.4, 8.4 Hz, 1H), 5.48-5.24 (m, 1H), 4.48 (dd, *J* = 6.8, 13.2 Hz, 1H), 4.35-4.22 (m, 1H), 3.09 (br d, *J* = 12.8 Hz, 1H), 2.99-2.87 (m, 1H), 2.28 (s, 3H), 1.59-1.55 (m, 1H).

Examples 34 and 35

N-(5-chloropyrimidin-2-yl)-2-[6-cyclopropyl-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (34 and 35)



[0341] To a mixture of 5-chloropyrimidin-2-amine (229 mg, 1.77 mmol) in DCE (6.0 mL) was added AlMe₃ (1 M in *n*-heptane, 1.77 mL). The reaction mixture was stirred at 25 °C for 50 min prior to the addition of a solution of methyl 2-(6'-cyclopropyl-2,2,5'-trifluoro-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-

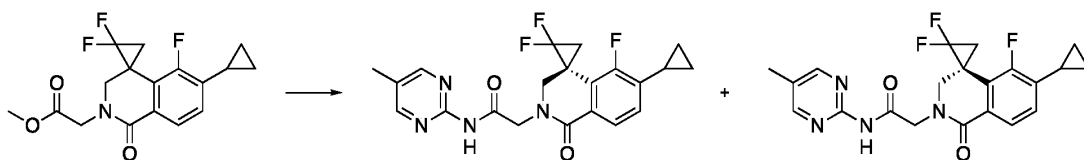
isoquinolin]-2'(3'H)-yl)acetate (300 mg, 0.88 mmol) in DCE (3.0 mL). The reaction mixture was stirred at 80 °C for 5 h and then heated to 100 °C and stirred for 5 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: Chiralpak AD (250 mm × 30 mm × 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in EtOH. Gradient: B%: 50% isocratic; Flow rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0342] N-(5-chloropyrimidin-2-yl)-2-[6-cyclopropyl-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 34): LCMS: m/z = 437.0, 439.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 11.04 (s, 1H), 8.78 (s, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.87 (br d, J = 17.2 Hz, 1H), 4.24 (br dd, J = 7.2, 13.6 Hz, 1H), 4.17 (br d, J = 17.2 Hz, 1H), 3.25 (br d, J = 13.6 Hz, 1H), 2.84 (br t, J = 10.4 Hz, 1H), 2.14-2.04 (m, 1H), 2.04-1.93 (m, 1H), 1.06-1.03 (m, 2H), 0.89-0.71 (m, 2H).

[0343] N-(5-chloropyrimidin-2-yl)-2-[6-cyclopropyl-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 35): LCMS: m/z = 437.0, 439.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 11.04 (s, 1H), 8.78 (s, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.87 (br d, J = 17.2 Hz, 1H), 4.24 (br dd, J = 7.2, 13.2 Hz, 1H), 4.17 (br d, J = 17.2 Hz, 1H), 3.25 (br d, J = 13.2 Hz, 1H), 2.84 (br t, J = 10.4 Hz, 1H), 2.14-2.04 (m, 1H), 2.04-1.93 (m, 1H), 1.06-1.03 (m, 2H), 0.89-0.71 (m, 2H).

Examples 36 and 37

N-(5-methylpyrimidin-2-yl)-2-[6-cyclopropyl-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (36 and 37)



[0344] To a mixture of 5-methylpyrimidin-2-amine (128 mg, 1.18 mmol) in DCE (5.0 mL) was added AlMe₃ (1 M in *n*-heptane, 1.18 mL). The reaction mixture was stirred at 25 °C for 60 min prior to the addition of a solution of methyl 2-(6'-cyclopropyl-2,2,5'-trifluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (200 mg, 0.59 mmol) in DCE (1.0 mL). The reaction mixture was stirred at 80 °C for a further 5 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (100 mm × 4.6 mm × 3 μm particle size); Mobile phase: A: CO₂ B: 0.1% *i*-PrNH₂ in EtOH; Gradient: B%: 40% isocratic; Flow rate:

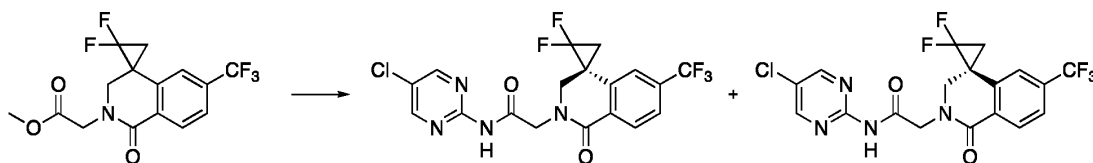
4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0345] N-(5-methylpyrimidin-2-yl)-2-[6-cyclopropyl-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 36): LCMS: $m/z = 417.1$ $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.62 (br s, 1H), 8.43 (s, 2H), 7.92 (d, $J = 8.0$ Hz, 1H), 6.91 (t, $J = 7.2$ Hz, 1H), 5.35-5.12 (m, 1H), 4.43 (br dd, $J = 7.2, 13.2$ Hz, 1H), 4.25 (br d, $J = 16.8$ Hz, 1H), 3.09 (br d, $J = 12.4$ Hz, 1H), 3.02-2.91 (m, 1H), 2.28 (s, 3H), 2.16-2.07 (m, 1H), 1.27 (br d, $J = 2.8$ Hz, 1H), 1.07 (br d, $J = 8.4$ Hz, 2H), 0.83-0.73 (m, 2H).

[0346] N-(5-methylpyrimidin-2-yl)-2-[6-cyclopropyl-1',1',5-trifluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 37): LCMS: $m/z = 417.1$ $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.69 (br s, 1H), 8.43 (s, 2H), 7.92 (d, $J = 8.0$ Hz, 1H), 6.90 (t, $J = 7.2$ Hz, 1H), 5.36-5.10 (m, 1H), 4.43 (br dd, $J = 7.2, 13.2$ Hz, 1H), 4.25 (br d, $J = 17.6$ Hz, 1H), 3.09 (br d, $J = 12.4$ Hz, 1H), 2.97 (br t, $J = 10.4$ Hz, 1H), 2.28 (s, 3H), 2.18-2.05 (m, 1H), 1.26 (br d, $J = 7.2$ Hz, 1H), 1.11-1.01 (m, 2H), 0.85-0.71 (m, 2H).

Examples 38 and 39

N-(5-chloropyrimidin-2-yl)-2-[1',1'-difluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (38 and 39)



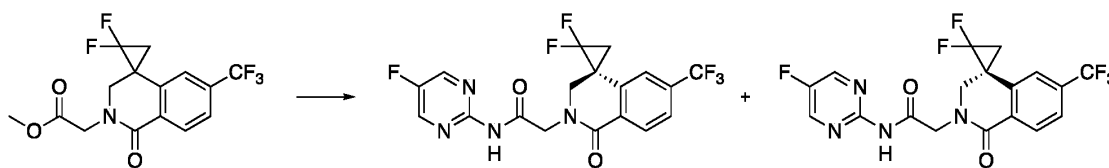
[0347] To a mixture of 5-chloropyrimidin-2-amine (223 mg, 1.72 mmol) in DCE (1.0 mL) was added $AlMe_3$ (1 M in *n*-heptane, 1.72 mL). The reaction mixture was stirred at 25 °C for 30 min prior to the addition of a solution of methyl 2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (200 mg, 0.57 mmol) in DCE (1.0 mL). The reaction mixture was stirred at 90 °C for a further 12 h. The mixture was diluted with water (10 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: Phenomenex Cellulose-2 (250 mm × 30 mm × 10 μ m particle size); Mobile phase: A: CO_2 B: 0.1% NH_4OH in EtOH; Gradient: B%: 35% isocratic; Flow rate: 65 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 120 bar) to provide:

[0348] N-(5-chloropyrimidin-2-yl)-2-[1',1'-difluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 38): LCMS: $m/z = 447.1, 449.0$ $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 2H), 8.52 (br s, 1H), 8.34 (d, $J = 8.0$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.33 (s, 1H), 5.31-5.16 (m, 1H), 4.37 (d, $J = 17.2$ Hz, 1H), 4.23 (dd, $J = 5.6, 12.8$ Hz, 1H), 3.46 (d, $J = 12.8$ Hz, 1H), 2.21-2.16 (m, 1H), 1.81-1.77 (m, 1H).

[0349] N-(5-chloropyrimidin-2-yl)-2-[1',1'-difluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 39): LCMS: m/z = 447.0, 449.0 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 2H), 8.54-8.48 (m, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 5.34-5.15 (m, 1H), 4.37 (d, J = 17.2 Hz, 1H), 4.23 (dd, J = 5.6, 12.8 Hz, 1H), 3.46 (d, J = 13.6 Hz, 1H), 2.19-2.15 (m, 1H), 1.81-1.77 (m, 1H).

Examples 40 and 41

N-(5-fluoropyrimidin-2-yl)-2-[1',1'-difluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (40 and 41)



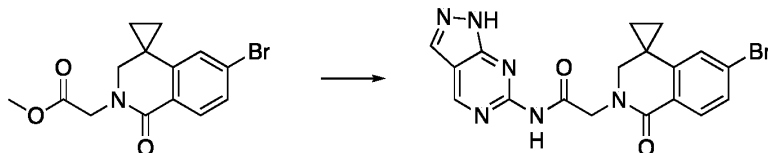
[0350] To a mixture of 5-fluoropyrimidin-2-amine (233 mg, 2.06 mmol) in DCE (3.0 mL) was added $AlMe_3$ (1 M in *n*-heptane, 2.29 mL). The reaction mixture was stirred at 25 °C for 30 min prior to the addition of a solution of methyl 2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (400 mg, 1.15 mmol) in DCE (5.0 mL). The reaction mixture was stirred at 85 °C for a further 3 h. The mixture was diluted with water (5 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm × 5 μ m particle size); Mobile phase: A: CO_2 B: 0.1% NH_4OH in *i*-PrOH; Gradient: B%: 30% to 50% over 15 min; Flow rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0351] N-(5-fluoropyrimidin-2-yl)-2-[1',1'-difluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (first eluting isomer, 40): LCMS: m/z = 431.0 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.59 (br s, 1H), 8.49 (s, 2H), 8.34 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 5.33-5.10 (m, 1H), 4.35 (br d, J = 17.2 Hz, 1H), 4.24 (dd, J = 5.2, 12.4 Hz, 1H), 3.47 (d, J = 13.2 Hz, 1H), 2.21-2.14 (m, 1H), 1.83-1.76 (m, 1H).

[0352] N-(5-fluoropyrimidin-2-yl)-2-[1',1'-difluoro-6-(trifluoromethyl)-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]acetamide (second eluting isomer, 41): LCMS: m/z = 431.0 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 8.57 (br s, 1H), 8.48 (s, 2H), 8.34 (d, J = 8.0 Hz, 1H), 7.71 (br d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 5.33-5.11 (m, 1H), 4.35 (br d, J = 17.2 Hz, 1H), 4.24 (br dd, J = 5.2, 12.8 Hz, 1H), 3.47 (br d, J = 12.8 Hz, 1H), 2.21-2.14 (m, 1H), 1.83-1.76 (m, 1H).

Example 42

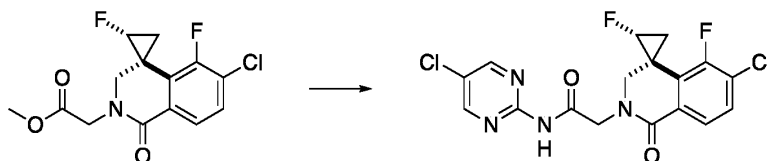
2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (42)



[0353] To a solution of methyl 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (100 mg, 0.31 mmol) and 1H-pyrazolo[3,4-d]pyrimidin-6-amine (63 mg, 0.46 mmol) in DCE (1.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.92 mmol). The reaction mixture was stirred at 90 °C for 3 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 427.1, 429.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.79 (br s, 1H), 10.91 (s, 1H), 9.18 (s, 1H), 8.24 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 4.61 (s, 2H), 3.51 (s, 2H), 1.19-1.14 (m, 2H), 1.09-1.03 (m, 2H).

Example 43

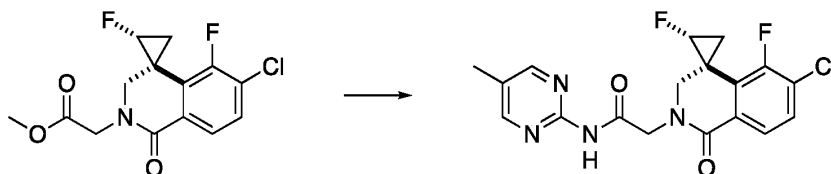
2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(5-chloropyrimidin-2-yl)acetamide (43)



[0354] To a solution of 5-chloropyrimidin-2-amine (62 mg, 0.45 mmol) in DCE (5.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.29 mL). The mixture was stirred for 0.5 h and then methyl 2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (30 mg, 0.09 mmol) was added. The mixture was stirred at 60 °C for a further 5 h. The mixture was quenched with H₂O (10 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 413.0, 415.0, 417.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 11.02 (br s, 1H), 8.78 (s, 2H), 7.85-7.73 (m, 1H), 7.61 (dd, *J* = 7.0, 8.4 Hz, 1H), 5.67-5.41 (m, 1H), 4.72 (d, *J* = 17.2 Hz, 1H), 4.40 (d, *J* = 17.2 Hz, 1H), 3.87-3.61 (m, 2H), 1.89-1.79 (m, 1H), 1.73-1.61 (m, 1H).

Example 44

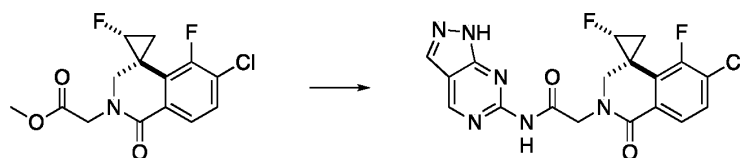
2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(5-methylpyrimidin-2-yl)acetamide (44)



[0355] To a solution of methyl 2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (40 mg, 0.13 mmol) in DCE (3.0 mL) were added 5-methylpyrimidin-2-amine (69 mg, 0.63 mmol) and AlMe_3 (1 M in *n*-heptane, 0.38 mL). The mixture was stirred at 60 °C for 4 h. The mixture was quenched with H_2O (5 mL) and extracted with DCM (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 residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 392.9, 395.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 10.72 (s, 1H), 8.51 (s, 2H), 7.80 (d, J = 8.6 Hz, 1H), 7.66-7.56 (m, 1H), 5.69-5.42 (m, 1H), 4.73 (br d, J = 17.2 Hz, 1H), 4.40 (br d, J = 17.2 Hz, 1H), 3.83-3.76 (m, 1H), 3.71-3.64 (m, 1H), 2.22 (s, 3H), 1.89-1.78 (m, 1H), 1.74-1.61 (m, 1H).

Example 45

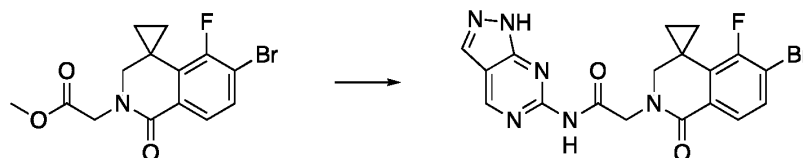
2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (45)



[0356] To a solution of 1H-pyrazolo[3,4-d]pyrimidin-6-amine (21 mg, 0.16 mmol) in toluene (1.0 mL) were added methyl 2-[(2's,4r)-6-chloro-2',5-difluoro-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (20 mg, 0.06 mmol) and AlMe_3 (1 M in *n*-heptane, 0.19 mL). The mixture was stirred at 90 °C for 4 h. The mixture was quenched with H_2O (10 mL) and extracted with DCM (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 residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 419.0, 421.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 9.07 (s, 1H), 8.14 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.48-7.35 (m, 1H), 5.51-5.14 (m, 2H), 4.83-4.69 (m, 1H), 4.02-3.66 (m, 2H), 2.04-1.94 (m, 1H), 0.93-0.78 (m, 1H).

Example 46

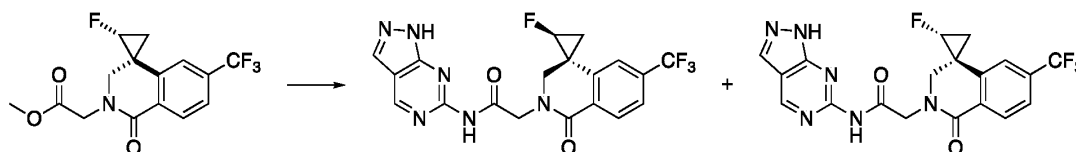
2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (46)



[0357] To a solution of methyl 2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (100 mg, 0.29 mmol) in DCE (1.5 mL) were added 1H-pyrazolo[3,4-d]pyrimidin-6-amine (59 mg, 0.44 mmol) and AlMe₃ (1 M in *n*-heptane, 0.88 mL). The mixture was stirred at 90 °C for 3 h. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 445.0, 447.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.73 (br s, 1H), 10.93 (br s, 1H), 9.18 (s, 1H), 8.24 (s, 1H), 7.59-7.81 (m, 2H), 4.61 (s, 2H), 3.48 (s, 2H), 1.44-1.52 (m, 2H), 1.04-1.15 (m, 2H).

Example 47 and 48

2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (47 and 48)



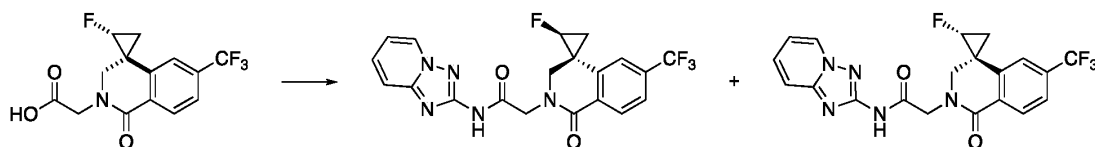
[0358] To a solution of methyl 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetate (200 mg, 0.61 mmol) and 1H-pyrazolo[3,4-d]pyrimidin-6-amine (122 mg, 0.91 mmol) in DCE (2.0 mL) was added AlMe₃ (1 M in *n*-heptane, 1.81 mL). The reaction mixture was stirred at 90 °C for 5 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm, 10 μm particle size); Mobile phase: A: CO₂ B: *i*-PrOH; Gradient: B%: 50% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0359] 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (first eluting isomer) (47): LCMS: *m/z* = 435.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 12.48 (br s, 1H), 11.35 (br s, 1H), 9.10 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 5.54 (br d, *J* = 18.0 Hz, 1H), 4.83 (br d, *J* = 18.0 Hz, 1H), 4.80-4.58 (m, 1H), 4.31 (dd, *J* = 1.6, 12.4 Hz, 1H), 3.60 (d, *J* = 12.8 Hz, 1H), 1.77-1.68 (m, 1H), 1.53-1.42 (m, 1H).

[0360] 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (second eluting isomer) (48): LCMS: m/z = 435.1 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 12.57 (br s, 1H), 11.43 (br s, 1H), 9.10 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 7.66 (br d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 5.55 (br d, J = 17.6 Hz, 1H), 4.83 (br d, J = 18.0 Hz, 1H), 4.79-4.58 (m, 1H), 4.31 (br d, J = 12.8 Hz, 1H), 3.60 (br d, J = 12.8 Hz, 1H), 1.79-1.67 (m, 1H), 1.54-1.41 (m, 1H).

Example 49 and 50

2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-([1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide (49 and 50)



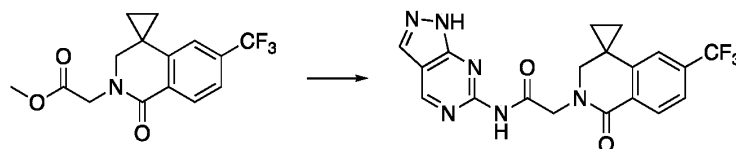
[0361] To a solution of 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]acetic acid (150 mg, 0.15 mmol) in pyridine (6.0 mL) were added [1,2,4]triazolo[1,5-a]pyridin-2-amine (127 mg, 0.31 mmol) and EDCI (181 mg, 0.32 mmol). The reaction mixture was stirred at 23 °C for 2 h. The reaction mixture was filtered and concentrated under reduce pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm $\times$ 30 mm, 5 μ m particle size); Mobile phase: A: CO_2 B: 0.1% *i*-PrNH₂ in EtOH; Gradient: B%: 47% isocratic; Flow rate: 3.4 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0362] 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-([1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide (first eluting isomer) (49): LCMS: m/z = 434.0 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$): δ 11.07 (br s, 1H), 8.85 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.67-7.62 (m, 1H), 7.38 (s, 1H), 7.13 (dt, J = 1.2, 6.8 Hz, 1H), 5.28-5.05 (m, 1H), 4.88-4.59 (m, 1H), 4.48-4.19 (m, 1H), 3.99 (dd, J = 1.2, 12.8 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 1.87-1.82 (m, 1H), 1.64-1.53 (m, 1H).

[0363] 2-[(2's,4r)-2'-fluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-([1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide (second eluting isomer) (50): LCMS: m/z = 434.0 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$): δ 11.07 (br s, 1H), 8.85 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.76 (br d, J = 8.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.67-7.61 (m, 1H), 7.38 (s, 1H), 7.14 (t, J = 6.8 Hz, 1H), 5.32-5.02 (m, 1H), 4.90-4.24 (m, 2H), 3.99 (br d, J = 12.8 Hz, 1H), 3.65 (br d, J = 12.8 Hz, 1H), 1.90-1.79 (m, 1H), 1.65-1.52 (m, 1H).

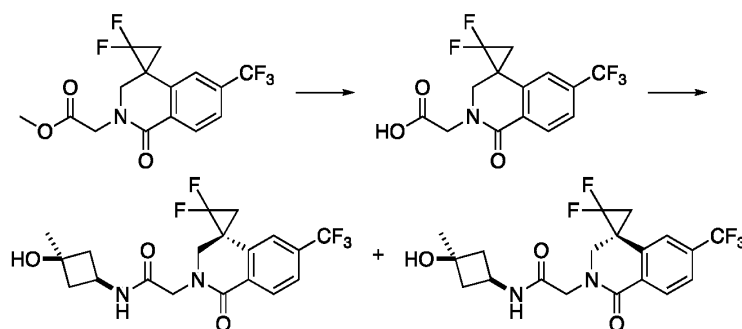
Example 51

2-[1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (51)



[0364] To a solution of 6-(trifluoromethyl)spiro[2,3-dihydroisoquinoline-4,1'-cyclopropane]-1-one (50 mg, 0.16 mmol) and 1H-pyrazolo[3,4-d]pyrimidin-6-amine (32 mg, 0.24 mmol) in DCE (2.0 mL) at 15 °C was added AlMe₃ (1 M in *n*-heptane, 0.24 mL). The reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to 0 °C, diluted with H₂O (8 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 417.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.56 (br s, 1H), 10.93 (br s, 1H), 9.18 (s, 1H), 8.24 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 4.65 (s, 2H), 3.56 (s, 2H), 1.26-1.22 (m, 2H), 1.13-1.09 (m, 2H).

Example 52 and 53

2-[1',1'-difluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]-N-(3-*cis*-hydroxy-3-methylcyclobutyl)acetamide (52 and 53)

[0365] **2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetic acid:** To a solution of methyl 2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetate (200 mg, 0.57 mmol) in THF (2.0 mL) and H₂O (2.0 mL) was added LiOH•H₂O (48 mg, 1.15 mmol). The reaction mixture was stirred for 2 h. The reaction mixture was diluted with H₂O (20 mL) and washed with MTBE (20 mL). The aqueous layer was adjusted pH = 3 with aq. HCl (3 M) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to provide a residue that was used directly.

[0366] **2-[1',1'-difluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]-N-(3-*cis*-hydroxy-3-methylcyclobutyl)acetamide:** To a solution of 2-(2,2-difluoro-1'-oxo-6'-(trifluoromethyl)-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)acetic acid (130 mg, 0.39 mmol)

and 3-*cis*-amino-1-methylcyclobutanol HCl salt (80 mg, 0.58 mmol) in DMF (5.0 mL) were added DIPEA (150 mg, 1.16 mmol), HOBT (78 mg, 0.58 mmol), and EDCI (112 mg, 0.58 mmol). The reaction mixture was stirred at 23 °C for 2 h. The reaction mixture was cooled to 0 °C, diluted with H₂O (5 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 residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column: REGIS(s,s) WHELK-O1 (250 mm × 30 mm, 5 μm particle size); Mobile phase: A: CO₂ B: 0.1% NH₄OH in *i*-PrOH; Gradient: B%: 25% isocratic; Flow rate: 70 g/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0367] 2-[1',1'-difluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]-N-(3-*cis*-hydroxy-3-methylcyclobutyl)acetamide (first eluting isomer) (52): LCMS: m/z = 419.1

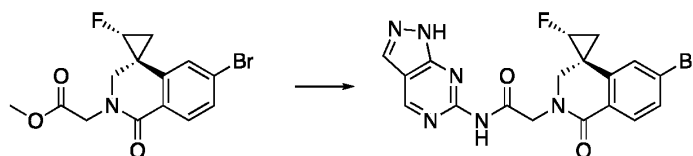
[M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.29 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 6.53 (br d, J = 7.2 Hz, 1H), 4.29-4.26 (m, 1H), 4.20-4.09 (m, 2H), 3.99-3.95 (m, 1H), 3.46 (dd, J = 0.8, 13.2 Hz, 1H), 2.53-2.51 (m, 2H), 2.23-2.18 (m, 2H), 2.04 (br t, J = 9.6 Hz, 2H), 1.78-1.77 (m, 1H), 1.37 (s, 3H).

[0368] 2-[1',1'-difluoro-1-oxo-6-(trifluoromethyl)spiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl]-N-(3-*cis*-hydroxy-3-methylcyclobutyl)acetamide (second eluting isomer) (53): LCMS: m/z = 419.1

[M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.29 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 6.53 (br d, J = 7.2 Hz, 1H), 4.33-4.25 (m, 1H), 4.16-4.12 (m, 2H), 4.03-3.95 (m, 1H), 3.46 (dd, J = 0.8, 13.2 Hz, 1H), 2.53-2.51 (m, 2H), 2.30 (br s, 1H), 2.21-2.18 (m, 1H), 2.06-2.01 (m, 2H), 1.80-1.77 (m, 1H), 1.37 (s, 3H).

Example 54

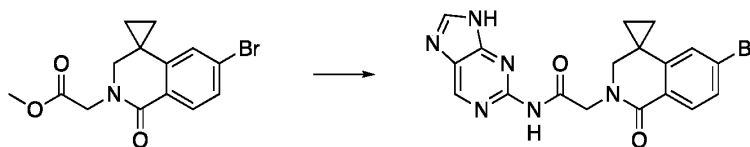
2-[(2'R,4S)-6-bromo-2'-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl]-N-(1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)acetamide (54)



[0369] To a solution of methyl 2-((1S,2R)-6'-bromo-2'-fluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (50 mg, 0.15 mmol, Int. 5) and 1H-pyrazolo[3,4-*d*]pyrimidin-6-amine (30 mg, 0.22 mmol) in DCE (1.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.46 mL). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was diluted with H₂O (3 mL) and extracted with EtOAc (3 × 1 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 445.0, 447.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 12.28 (br s, 1H), 11.04 (br s, 1H), 9.08 (s, 1H), 8.25-7.98 (m, 2H), 7.54 (dd, J = 1.8, 8.4 Hz, 1H), 6.88 (d, J = 1.6 Hz, 1H), 5.43 (d, J = 18.0 Hz, 1H), 4.93-4.47 (m, 2H), 4.26 (dd, J = 1.4, 12.6 Hz, 1H), 3.56 (d, J = 12.8 Hz, 1H), 1.68-1.61 (m, 1H), 1.49-1.36 (m, 1H).

Example 55

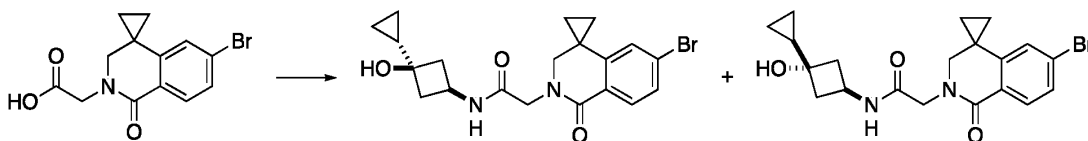
2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(9H-purin-2-yl)acetamide (55)



[0370] To a solution of methyl 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (100 mg, 0.31 mmol) and 9H-purin-2-amine (62 mg, 0.46 mmol) in DCE (2.0 mL) was added AlMe_3 (1 M in *n*-heptane, 0.6 mL). The reaction was sealed and heated at 120 °C for 3 h. The reaction mixture was cooled to 23 °C, diluted with H_2O (5 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 427.0, 429.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.62 (br s, 1H), 8.91 (s, 1H), 8.40 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 1.6, 8.3 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 4.58 (br s, 2H), 3.51 (s, 2H), 1.21-1.11 (m, 2H), 1.09-1.01 (m, 2H).

Example 56 and 57

2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(3-cyclopropyl-3-hydroxycyclobutyl)acetamide (56 and 57)



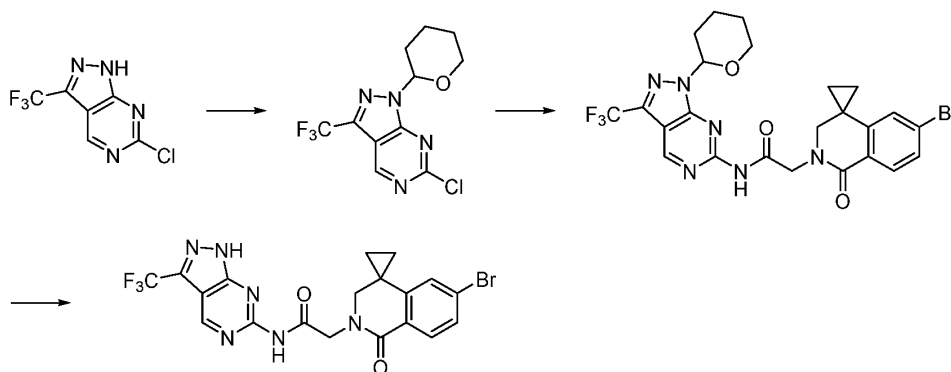
[0371] To a solution of 3-amino-1-cyclopropylcyclobutanol HCl salt (211 mg, 1.29 mmol) and 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetic acid (200 mg, 0.65 mmol) in DMF (2.0 mL) were added EDCI (186 mg, 0.97 mmol), HOBT (130 mg, 0.97 mmol), and DIPEA (416 mg, 3.22 mmol). The reaction mixture was stirred at 23 °C for 16 h. The reaction mixture was quenched with H_2O (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC and further purified by chiral SFC (Column Phenomenex-Cellulose-2 (250 mm × 30 mm, 5 μm particle size); Mobile phase: A: CO_2 B: 0.1% NH_4OH in MeOH; Gradient: B%: 50% isocratic; Flow rate: 70 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 1800 psi) to provide:

[0372] 2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(3-cyclopropyl-3-hydroxycyclobutyl)acetamide (first eluting isomer) (56): LCMS: m/z = 419.1, 421.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 1.8, 8.3 Hz, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.54 (br d, J = 6.8 Hz, 1H), 4.14 (s, 2H), 3.97-3.84 (m, 1H), 3.46 (s, 2H), 2.50-2.35 (m, 2H), 1.98-1.90 (m, 2H), 1.16-1.08 (m, 3H), 1.06-1.01 (m, 2H), 0.57-0.44 (m, 2H), 0.34-0.32 (m, 2H).

[0373] **2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(3-cyclopropyl-3-hydroxycyclobutyl)acetamide (second eluting isomer) (57):** LCMS: $m/z = 419.1, 421.1$ $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.47 (dd, $J = 1.8, 8.4$ Hz, 1H), 7.01 (d, $J = 1.8$ Hz, 1H), 6.53-6.38 (m, 1H), 4.58-4.44 (m, 1H), 4.13 (s, 2H), 3.47 (s, 2H), 2.38-2.27 (m, 2H), 1.89-1.77 (m, 2H), 1.18-0.97 (m, 5H), 0.53-0.40 (m, 2H), 0.27-0.24 (m, 2H).

Example 58

2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-[3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl]acetamide (58)



[0374] **6-chloro-1-(tetrahydro-2H-pyran-2-yl)-3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine:**

To a solution of 6-chloro-3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine (0.60 g, 2.70 mmol) and 3,4-dihydro-2H-pyran (453 mg, 5.39 mmol) in 1,4-dioxane (10 mL) was added *p*-TsOH·H₂O (512 mg, 2.70 mmol). The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to 0 °C, 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 residue was purified by silica gel chromatography.

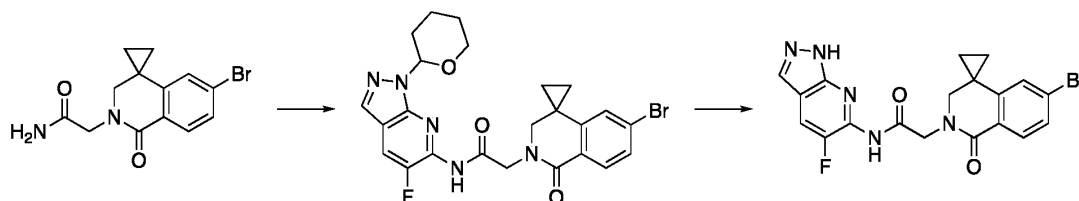
[0375] **2-(6'-bromo-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)-N-(1-(tetrahydro-2H-pyran-2-yl)-3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide:** To a solution of 6-chloro-1-(tetrahydro-2H-pyran-2-yl)-3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine (0.20 g, 0.65 mmol) in 1,4-dioxane (20 mL) were added 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetamide (201 mg, 0.65 mmol), Cs₂CO₃ (531 mg, 1.63 mmol), Xantphos (113 mg, 0.2 mmol), and Pd(OAc)₂ (30 mg, 0.13 mmol). The reaction mixture was stirred at 70 °C for 3 h. The reaction mixture was poured into H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

[0376] **2-(6'-bromo-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)-N-(3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide:** To a solution of 2-(6'-bromo-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)-N-(1-(tetrahydro-2H-pyran-2-yl)-3-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (100 mg, 0.17 mmol) in DCM (10 mL) was added TFA (5.0 mL). The reaction mixture was stirred at 23 °C for 4 h. The reaction mixture was

poured into aq. sat. NaHCO_3 (10 mL) and extracted with DCM (3×10 mL). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: $m/z = 495.0, 497.0$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 14.55 (br s, 1H), 11.11 (s, 1H), 9.29 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.53 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.27 (d, $J = 1.6$ Hz, 1H), 4.61 (s, 2H), 3.51 (s, 2H), 1.21-1.14 (m, 2H), 1.10-0.98 (m, 2H).

Example 59

2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-[5-fluoro-1H-pyrazolo[3,4-b]pyridin-6-yl]acetamide (59)

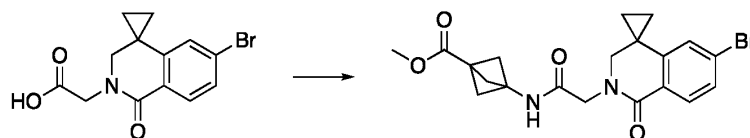


[0377] 2-(6'-bromo-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)-N-(5-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)acetamide: To a solution of 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetamide (100 mg, 0.32 mmol) in THF (4.0 mL) were added 6-bromo-5-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (146 mg, 0.49 mmol), Cs_2CO_3 (211 mg, 0.65 mmol), XPhos (15 mg, 0.03 mmol), and $\text{Pd}_2(\text{dba})_3$ (30 mg, 0.03 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: $m/z = 528.0, 529.8$ $[\text{M}+\text{H}]^+$.

[0378] 2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-[5-fluoro-1H-pyrazolo[3,4-*b*]pyridin-6-yl]acetamide: To a solution of 2-(6'-bromo-1'-oxo-1'*H*-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'*H*)-yl)-N-(5-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)acetamide (50 mg, 0.09 mmol) in DCM (1.0 mL) was added TFA (770 mg, 6.75 mmol). The mixture was stirred at 23 °C for 1 h. The mixture was diluted with aq. sat. NaHCO_3 (10 mL) and extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: $m/z = 444.0, 446.0$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 9.03 (br s, 1H), 8.10-7.94 (m, 2H), 7.77 (d, $J = 9.6$ Hz, 1H), 7.48 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.04-6.99 (m, 1H), 4.62 (s, 2H), 3.58 (s, 2H), 1.17-1.12 (m, 2H), 1.12-1.06 (m, 2H).

Example 60

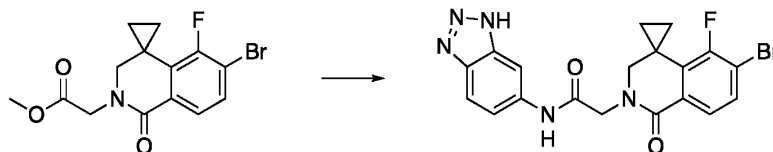
methyl 3-[[2-(6-bromo-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetyl]amino]bicyclo[1.1.1]pentane-1-carboxylate (60)



[0379] To a solution of 2-(6-bromo-1-oxo-spiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetic acid (70 mg, 0.23 mmol) in DMF (2.0 mL) were added methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate hydrochloride (100 mg, 0.56 mmol), DIPEA (145 mg, 1.13 mmol), HOBT (49 mg, 0.36 mmol), and EDCI (69 mg, 0.36 mmol). The mixture was stirred at 23 °C for 2 h. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. LCMS: m/z = 433.0, 435.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 1.6, 8.4 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 6.73 (s, 1H), 4.11 (s, 2H), 3.69 (s, 3H), 3.46 (s, 2H), 2.36 (s, 6H), 1.16-1.09 (m, 2H), 1.06-0.99 (m, 2H).

Example 61

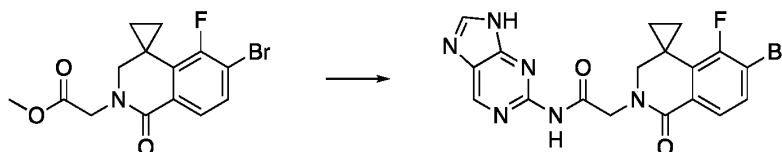
N-(3H-benzotriazol-5-yl)-2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetamide (61)



[0380] To a solution of methyl 2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (50 mg, 0.15 mmol) in DCE (1.0 mL) were added 1H-benzo[d][1,2,3]triazol-6-amine (29 mg, 0.22 mmol) and AlMe₃ (1 M in *n*-heptane, 0.24 mL). The mixture was stirred at 90 °C for 2 h. The mixture was quenched with H₂O (10 mL) and extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC. LCMS: m/z = 444.0, 446.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.44 (s, 1H), 8.31 (s, 1H), 7.91 (br d, J = 7.8 Hz, 1H), 7.80-7.63 (m, 2H), 7.39 (br d, J = 9.4 Hz, 1H), 4.38 (s, 2H), 3.52 (s, 2H), 1.61-1.45 (m, 2H), 1.15-1.11 (m, 2H).

Example 62

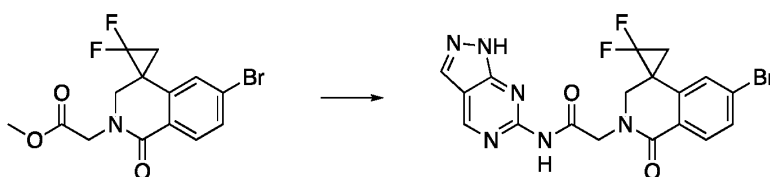
2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)-N-(9H-purin-2-yl)acetamide (62)



[0381] To a solution of methyl 2-(6-bromo-5-fluoro-1-oxospiro[3H-isoquinoline-4,1'-cyclopropane]-2-yl)acetate (50 mg, 0.15 mmol) and 9H-purin-2-amine (30 mg, 0.22 mmol) in DCE (2.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.3 mL). The reaction was sealed and heated to 120 °C for 3 h. The reaction mixture was cooled to 0 °C, diluted with H₂O (5 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 residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 445.0, 447.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.72 (s, 1H), 8.95 (s, 1H), 8.45 (s, 1H), 7.74-7.63 (m, 2H), 4.58 (br s, 2H), 3.47 (s, 2H), 1.50-1.44 (m, 2H), 1.12-1.09 (m, 2H).

Example 63

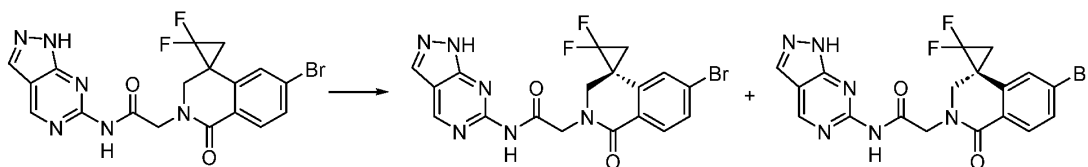
2-(6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (63)



[0382] To a solution of methyl 2-(6'-bromo-2,2-difluoro-1'-oxo-1'H-spiro[cyclopropane-1,4'-isoquinolin]-2'(3'H)-yl)acetate (70 mg, 0.19 mmol) and 1H-pyrazolo[3,4-d]pyrimidin-6-amine (52 mg, 0.38 mmol) in DCE (2.0 mL) was added AlMe₃ (1 M in *n*-heptane, 0.58 mL). The reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was quenched with H₂O (5 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 residue was purified by reverse-phase preparative HPLC. LCMS: *m/z* = 463.0, 465.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.77 (br s, 1H), 10.94 (s, 1H), 9.18 (s, 1H), 8.24 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.70 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.63 (s, 1H), 5.00-4.30 (m, 2H), 4.16 (dd, *J* = 6.8, 13.2 Hz, 1H), 3.41 (d, *J* = 13.2 Hz, 1H), 2.86-2.76 (m, 1H), 2.02-1.92 (m, 1H).

Examples 64 and 65

2-(6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (64 and 65)



[0383] 2-(6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (Example 62) could be further separated by chiral SFC (Column: DAICEL ChiralPak IG (250 mm × 30 mm, 10 μm particle size); Mobile phase: A: CO₂ B: 0.1% *i*-PrNH₂ in *i*-PrOH; Gradient: B%: 55% isocratic; Flow rate: 80 mL/min; Detection Wavelength: 220 nm; Column temperature: 35 °C; System back pressure: 100 bar) to provide:

[0384] 2-(6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (first eluting isomer) (64): LCMS: m/z = 463.0, 465.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.80 (br s, 1H), 10.94 (s, 1H), 9.18 (s, 1H), 8.23 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 1.6, 8.4 Hz, 1H), 7.63 (s, 1H), 5.03-4.24 (m, 2H), 4.16 (dd, J = 6.8, 13.2 Hz, 1H), 3.41 (br d, J = 13.2 Hz, 1H), 2.87-2.75 (m, 1H), 2.04-1.90 (m, 1H).

[0385] 2-(6-bromo-1',1'-difluoro-1-oxospiro[3H-isoquinoline-4,2'-cyclopropane]-2-yl)-N-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)acetamide (second eluting isomer) (65): LCMS: m/z = 463.0, 465.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.77 (br s, 1H), 10.93 (s, 1H), 9.18 (s, 1H), 8.24 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 1.6, 8.4 Hz, 1H), 7.63 (s, 1H), 5.01-4.28 (m, 2H), 4.16 (dd, J = 6.8, 13.2 Hz, 1H), 3.41 (br d, J = 13.2 Hz, 1H), 2.88-2.75 (m, 1H), 2.05-1.90 (m, 1H).

BIOLOGICAL EXAMPLE 1

Biochemical Assay of the Compounds

Procedure for culturing THP-1 cells

[0386] Compounds as provided herein were tested in the following assay. Cell culture medium employed contained RPMI 1640 medium (89%), FBS (10%), Pen/Strep (1%), and 2-mercaptoethanol (0.05 mM). Freezing medium was made up of 90% FBS and 10% DMSO. THP-1 cells were removed from the liquid nitrogen and placed into a 37 °C water bath to thaw, until signs of ice dissipated. The cells were then added to 9 mL of warm cell culture medium and centrifuged for 5 minutes at 1000 rpm. The supernatant was discarded, and the cells were resuspended in new cell culture medium. THP-1 cells were then split and cultured in the cell culture medium, being passaged every 2-3 days with the cell density will be maintained between 5x10⁵ and 1.5x10⁶ viable cells/mL.

[0387] To freeze, cells were resuspended with fresh freezing medium, adjusting the cell density to 5x10⁶ cells/mL. The cell suspension was partitioned into 1 mL aliquots per vial, and the vials were transferred to a -80 °C freezer. After one day at -80 °C, the cell vials were transferred to liquid nitrogen freezer for storage.

Procedure for IL-1 β secretion assay in 384-well plates

[0388] PMA was dissolved in DMSO to make a stock solution at 5 mg/ml and stored in 10 μ L aliquots at -20°C for single use. PMA is added to normal growth medium. LPS was diluted with 1 mL of water solution to provide a 1 mg/mL stock solution and stored in 15 μ L aliquots at -20 °C for single use. Nigericin is diluted in ice cold 100% ethanol to 5 mg/ml (6.7 mM) and stored in 75 μ L aliquots at -20 °C for single use. Serum-free media contains RPMI 1640 medium (99%), Pen/Strep (1%), and 2-mercaptoethanol (0.05 mM). The two control conditions used to qualify and normalize test compound dose-response curves were as follows: High Control = 25 ng/mL LPS, 5 μ M Nigericin, 0.5% DMSO, Low Control = 25 ng/mL, LPS, 0.5% DMSO.

Day 1: Differentiation with PMA

[0389] THP-1 cells were diluted to provide a suspension at a concentration of 1.0x10⁶ cells/mL with the total volume of suspension required to enable the desired number of assay plates. The growth media was

supplemented with PMA (5 ng/mL final concentration) and the cells were incubated at 37 °C under a humidified atmosphere of 5% CO₂ for 40 h.

Day 3: Plating with sequential LPS and nigericin stimulation

[0390] All media was carefully aspirated from each culture flask. The cells were washed carefully with 1x DPBS. The cells were then briefly digested with trypsin LE for 5 minutes at 23 °C and immediately resuspended in cell growth media. After resuspension, the cells were centrifuged at 1000 rpm for 3 minutes and the supernatant was discarded. The cells were resuspended in DPBS and once again centrifuged at 1000 rpm for 5 minutes. The supernatant was discarded and the cell pellet was resuspended in serum-free media supplemented with LPS (25 ng/mL final concentration) to enable the distribution of 30K THP-1 cells within 45 µL of media into each well of 384-well PDL-coated plates. The 384-well plates were then incubated at 37 °C under a humidified atmosphere of 5% CO₂ for 2 h. Following this period, test compounds were dispensed by Tecan across the desired concentration range with all wells normalized to a final 0.5 % DMSO concentration. The plates were then then incubated at 37 °C under a humidified atmosphere of 5% CO₂ for 1 h. Following this period, 5 µL of the 5 mg/mL nigericin stock solution was added to each of the appropriate wells and plates were centrifuged at 1000 rpm for 30 seconds. The plates were the immediately reintroduced to the incubator at 37 °C under a humidified atmosphere of 5% CO₂ for 2 h. After this time, 35 µL/well of supernatant was collected and transferred into v-bottom plate and centrifuged at 1000 rpm for 1 minute. These supernatant aliquots were analyzed using an IL-1β detection kit as described below. If needed, the test samples could be snap frozen and stored at -80 °C until analyzed.

IL-1β detection

[0391] To prepare each ELISA plate, capture antibody (mAb Mt175) was diluted with PBS to a final concentration of 2 µg/mL and then 20 µL of this solution was added to each well of the ELISA plate. Each plate was allowed to incubate overnight at 4 °C. The next day, the capture antibody solution was removed and discarded. Each ELISA plate was washed 4 times with PBST followed by the addition of 25 µL/well of blocking buffer (Licor-927-40010) supplemented with 0.1% Tween 20. Each ELISA plate was then allowed to incubate for 1 hour at 23 °C. After this time, the blocking buffer was removed and discarded. Each ELISA plate was washed 4 times with PBST. During this time, the v-bottomed plates containing the supernatant aliquots from the assay run were centrifuged at 300 g for 5 minutes before transferring 15 µL/well of the supernatant sample to each ELISA plate. Each ELISA plate was then allowed to incubate for 2 h at 23 °C. After this time, the supernatant samples were removed and discarded. Each ELISA plate was washed 4 times with PBST. To each ELISA plate was added 15 µL/well of mAb7P10-biotin at 0.5 µg/mL (1:1000 diluted in blocking buffer). Each ELISA plate was then allowed to incubate for 1 h at 23 °C. After this time, the antibody solution was removed and discarded. Each ELISA plate was washed 4 times with PBST. To each ELISA plate was added 20 µL/well of streptavidin-HRP (1:2000 diluted in blocking buffer). Each ELISA plate was then allowed to incubate for 1 h at 23 °C. After this time, the buffer was removed and discarded. Each ELISA plate was washed 4 times with PBST. To each ELISA plate was added 20 µL/well of HRP substrate. Each ELISA

plate was then allowed to incubate for 2 minutes at 23 °C. After this time, to each ELISA plate was added 40 µL/well of stop solution. Each ELISA plate was centrifuged at 1200 rpm for 30 seconds.

[0392] The plate was then read at 450 nm in a microplate reader. Percent inhibition was calculated as follows:

$$\% \text{ inhibition rate} = (\text{treated samples-high control}) / (\text{low control-high control}) \times 100$$

[0393] Activity of the tested compounds is provided in Table 3 below as follows: +++ = $IC_{50} < 1 \mu M$; ++ = $IC_{50} 1-10 \mu M$; + = $IC_{50} > 10 \mu M$.

Table 3

Ex. No.	Activity	Activity (µM)	Ex. No.	Activity	Activity (µM)
1	+++	0.024	25	+++	0.061
2	+++	0.018	26	++	5.88
3	+++	0.017	27	+++	0.128
4	+++	0.016	28	++	5.73
5	+++	0.002	29	+++	0.086
6	+++	0.072	30	+	29.2
7	+++	0.017	31	+++	0.033
8	+++	0.044	32	+	28.6
9	++	1.54	33	+++	0.055
10	++	4.08	34	++	15.6
11	+++	0.057	35	+++	0.016
12	+++	0.054	36	+	22.4
13	+++	0.232	37	+++	0.078
14	+	50	38	+++	0.126
15	+++	0.063	39	++	6.96
16	++	1.59	40	++	9.37
17	+++	0.028	41	+++	0.067
18	++	3.48	42	+++	0.061
19	+++	0.065	43	+++	0.051
20	+	12.9	44	+++	0.113
21	+++	0.058	45	+++	0.048
22		8.342	46	+++	0.038
23	+++	0.032	47	+++	0.231
24	++	6.09	48	+++	0.024

Ex. No.	Activity	Activity (μ M)
49	++	1.96
50	+++	0.184
51	+++	0.181
52	+	22.4
53	+++	0.472
54	+++	0.005
55	+++	0.114
56	+++	0.363
57	+	11.1

Ex. No.	Activity	Activity (μ M)
58	+++	0.279
59	+++	0.322
60	+++	0.216
61	+++	0.162
62	+++	0.080
63	+++	0.034
64	+++	0.008
65	+++	0.504

[0394] 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.

[0395] The embodiments 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 embodiments claimed.

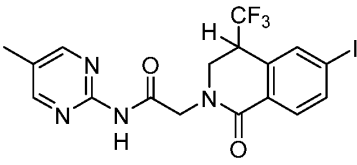
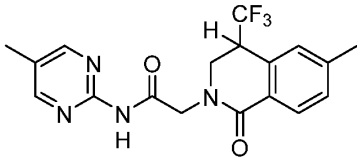
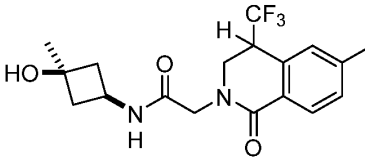
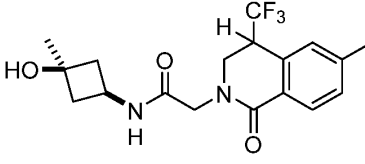
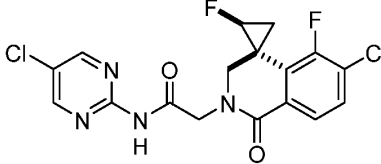
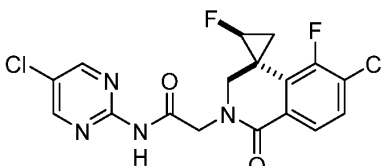
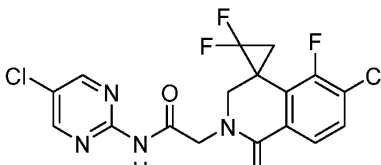
[0396] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

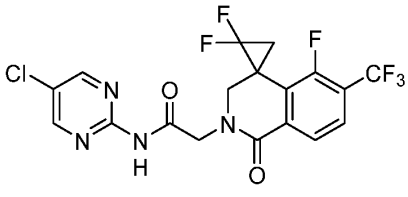
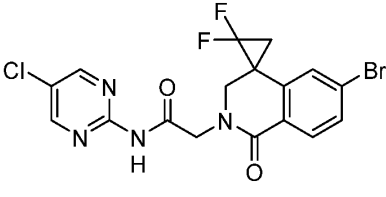
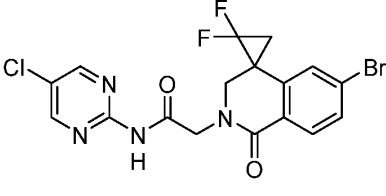
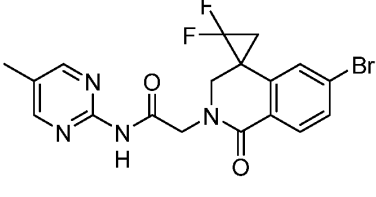
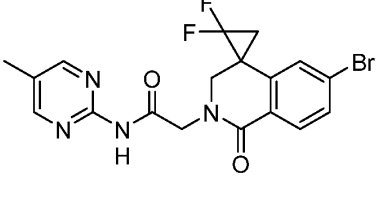
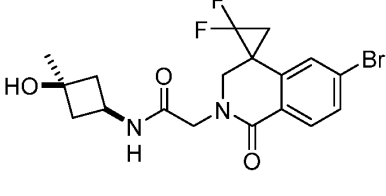
[0397] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

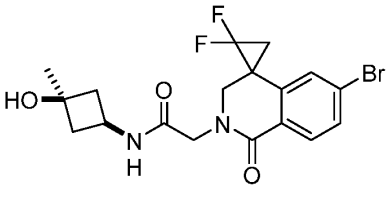
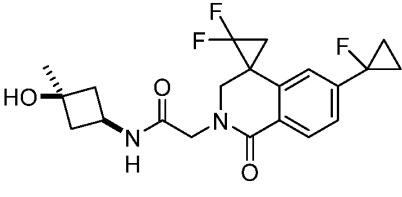
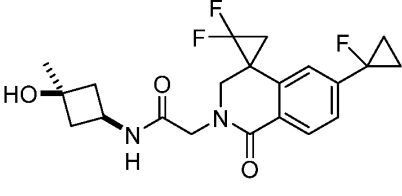
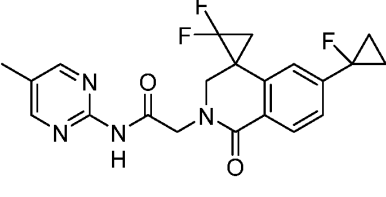
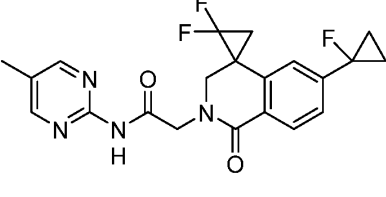
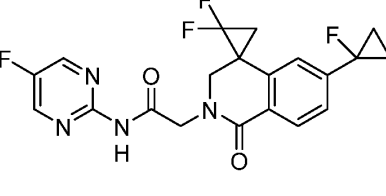
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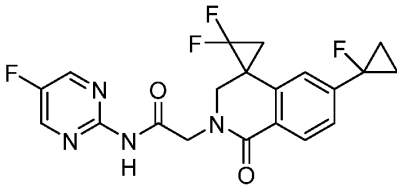
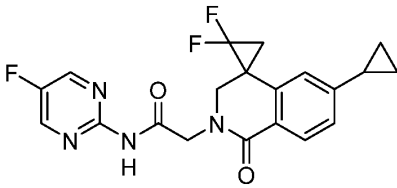
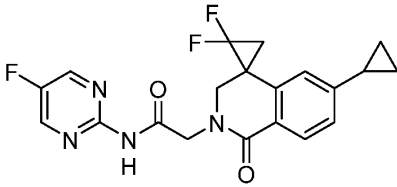
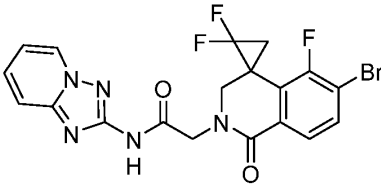
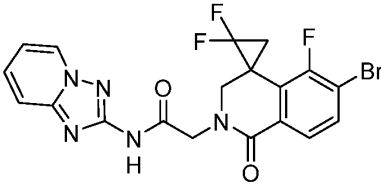
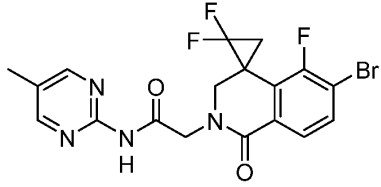
1. A compound or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, selected from:

Ex. No.	Structure
1	
2	
3	
4	
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7	

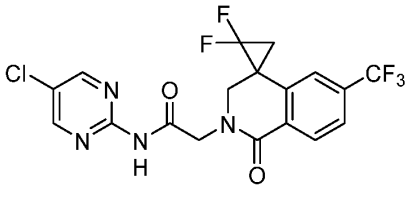
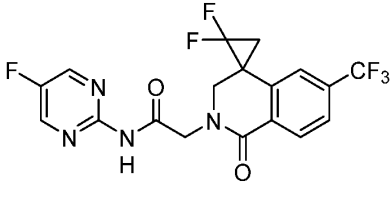
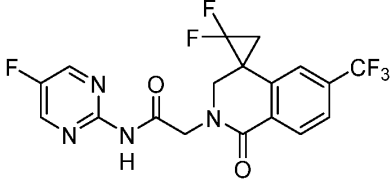
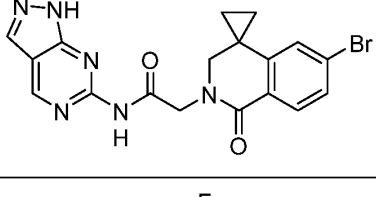
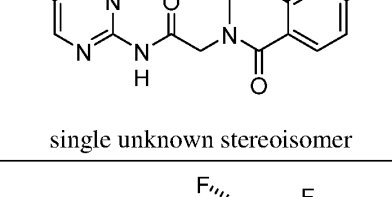
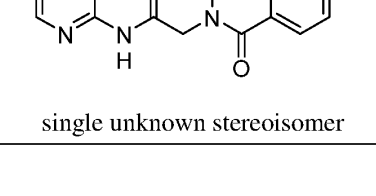
Ex. No.	Structure
8	
9	
10	 first eluting isomer
11	 second eluting isomer
12	 first eluting isomer
13	 second eluting isomer
14	 first eluting isomer

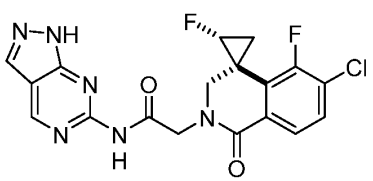
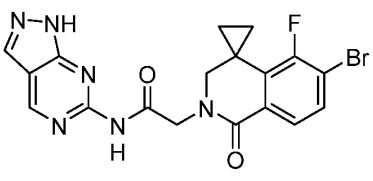
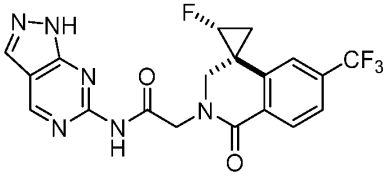
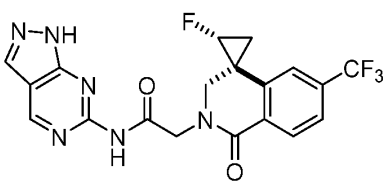
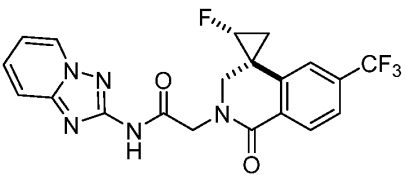
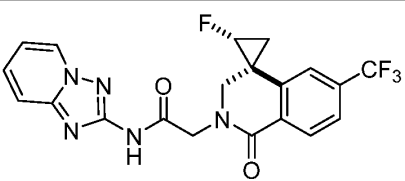
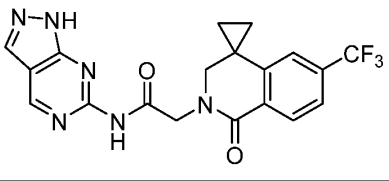
Ex. No.	Structure
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16	 first eluting isomer
17	 second eluting isomer
18	 first eluting isomer
19	 second eluting isomer
20	 first eluting isomer

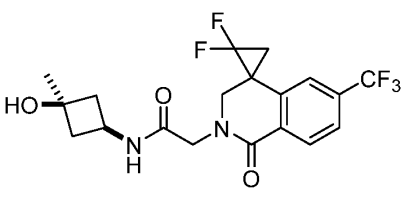
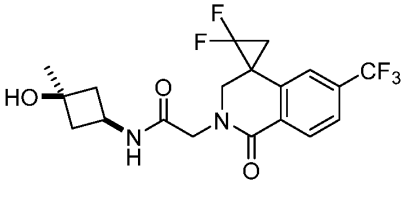
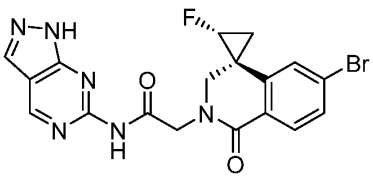
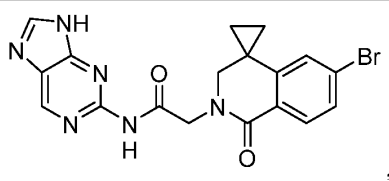
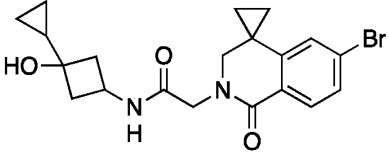
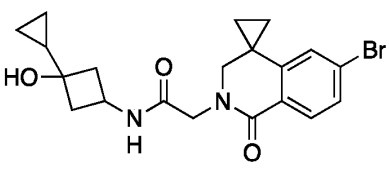
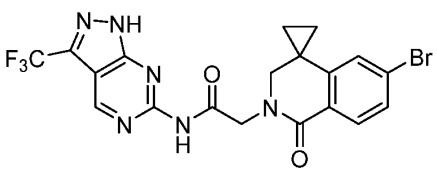
Ex. No.	Structure
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22	 first eluting isomer
23	 second eluting isomer
24	 first eluting isomer
25	 second eluting isomer
26	 first eluting isomer

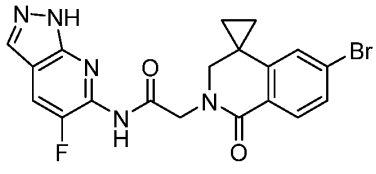
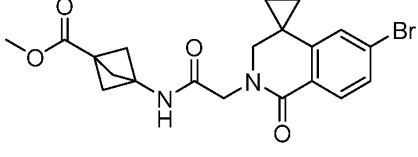
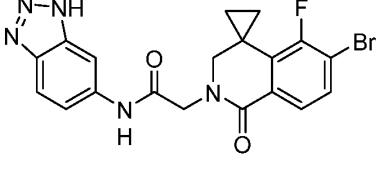
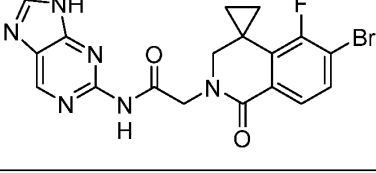
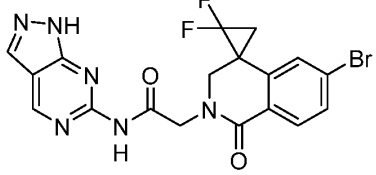
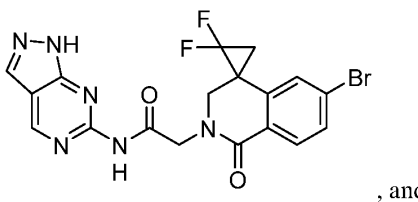
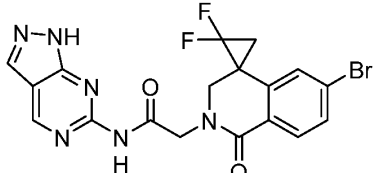
Ex. No.	Structure
27	 second eluting isomer
28	 first eluting isomer
29	 second eluting isomer
30	 first eluting isomer
31	 second eluting isomer
32	 first eluting isomer

Ex. No.	Structure
33	second eluting isomer
34	first eluting isomer
35	second eluting isomer
36	first eluting isomer
37	second eluting isomer
38	first eluting isomer

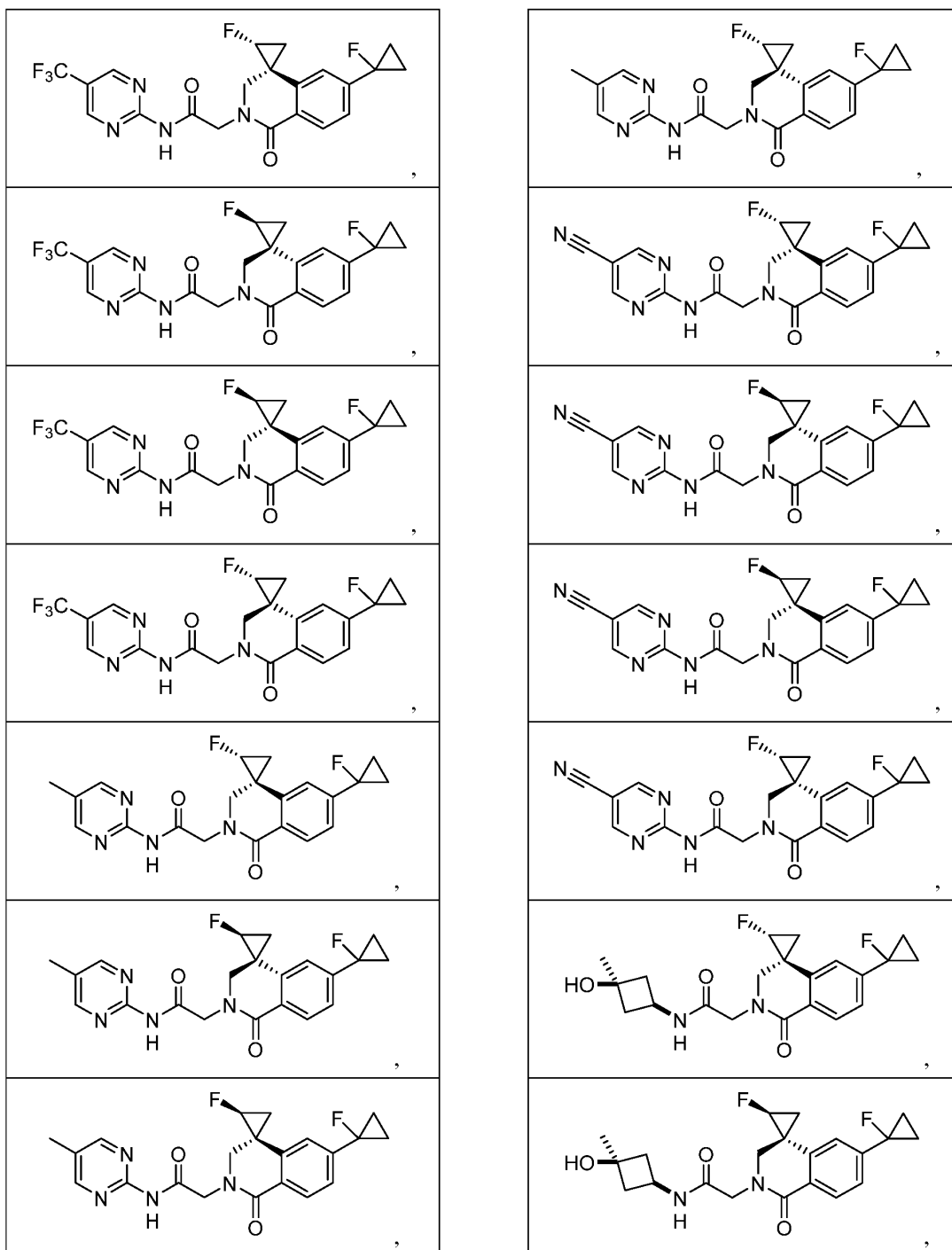
Ex. No.	Structure
39	 second eluting isomer
40	 first eluting isomer
41	 second eluting isomer
42	 single unknown stereoisomer
43	 single unknown stereoisomer
44	 single unknown stereoisomer

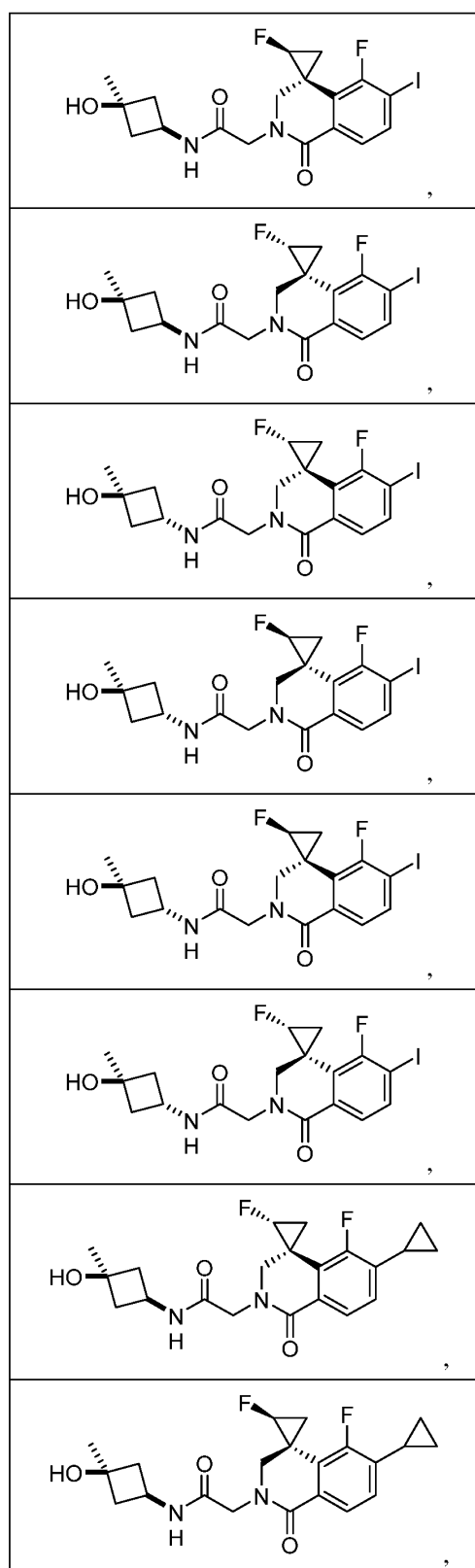
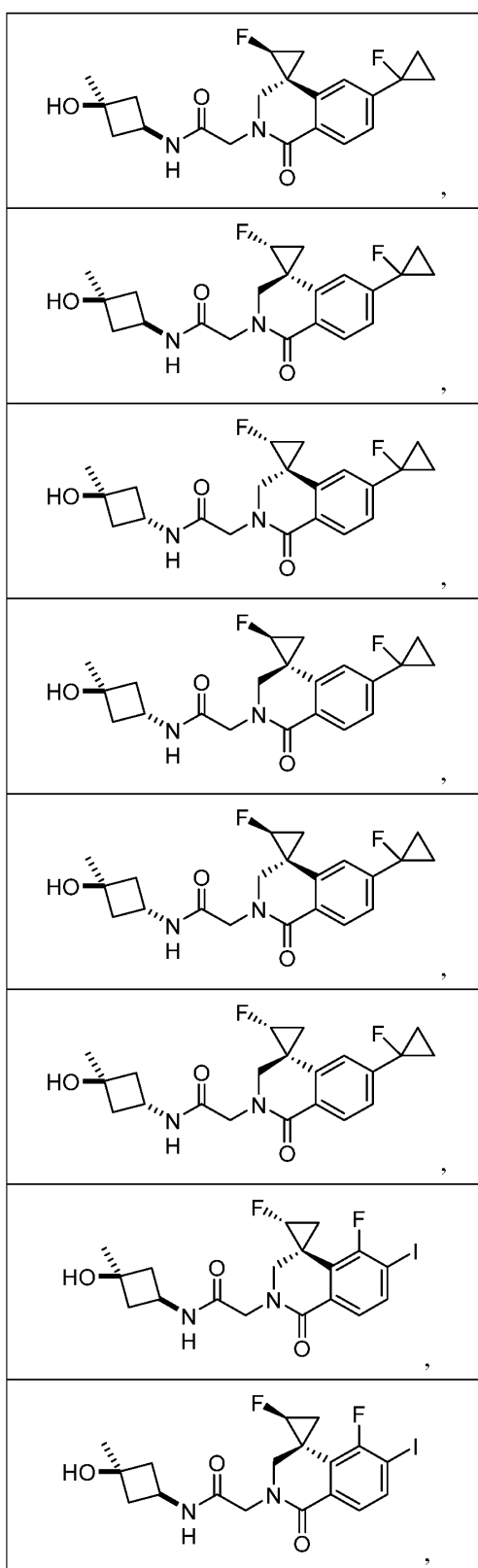
Ex. No.	Structure
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46	 ,
47	 first eluting isomer
48	 second eluting isomer
49	 first eluting isomer
50	 second eluting isomer
51	 ,

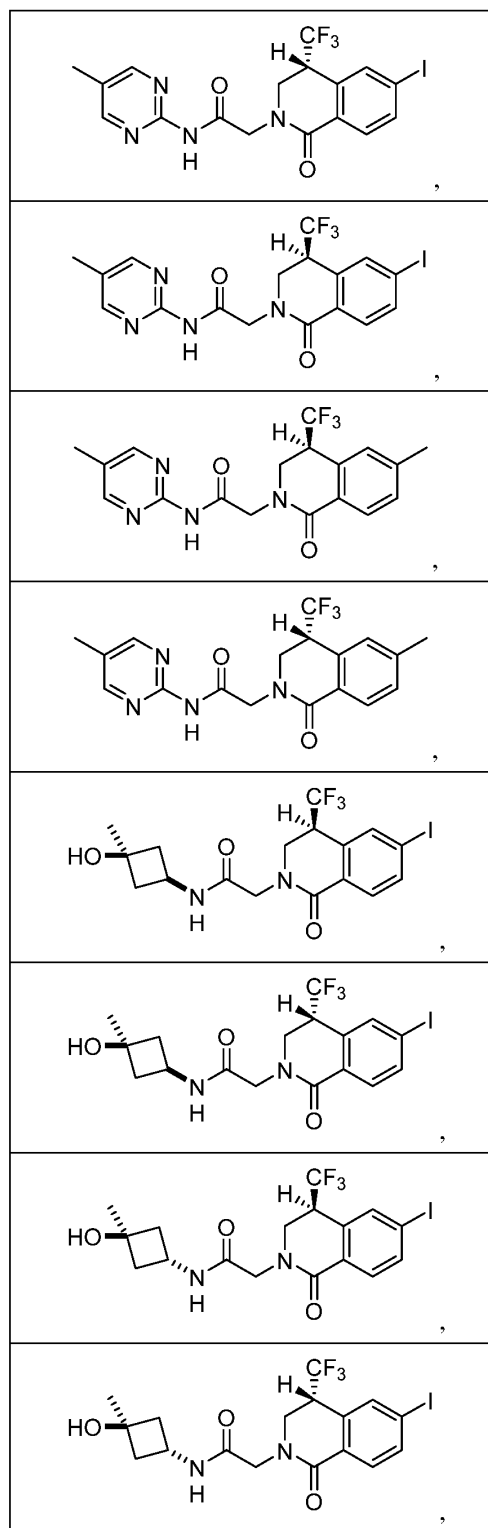
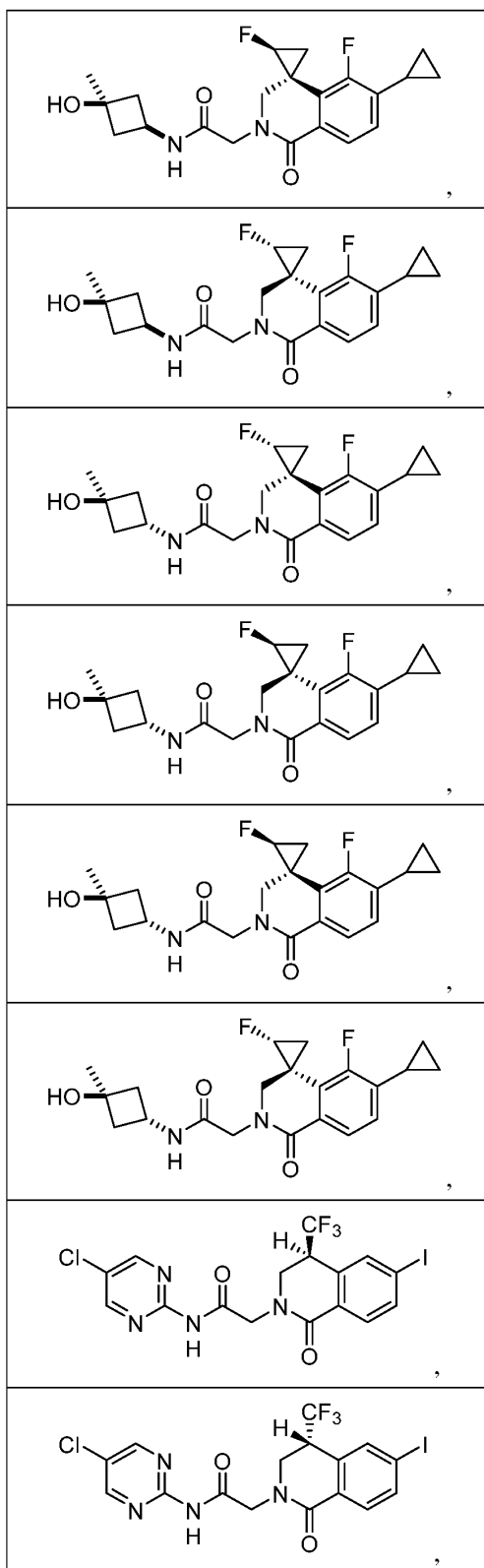
Ex. No.	Structure
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53	 second eluting isomer
54	 single known stereoisomer
55	 single known stereoisomer
56	 first eluting isomer
57	 second eluting isomer
58	 single known stereoisomer

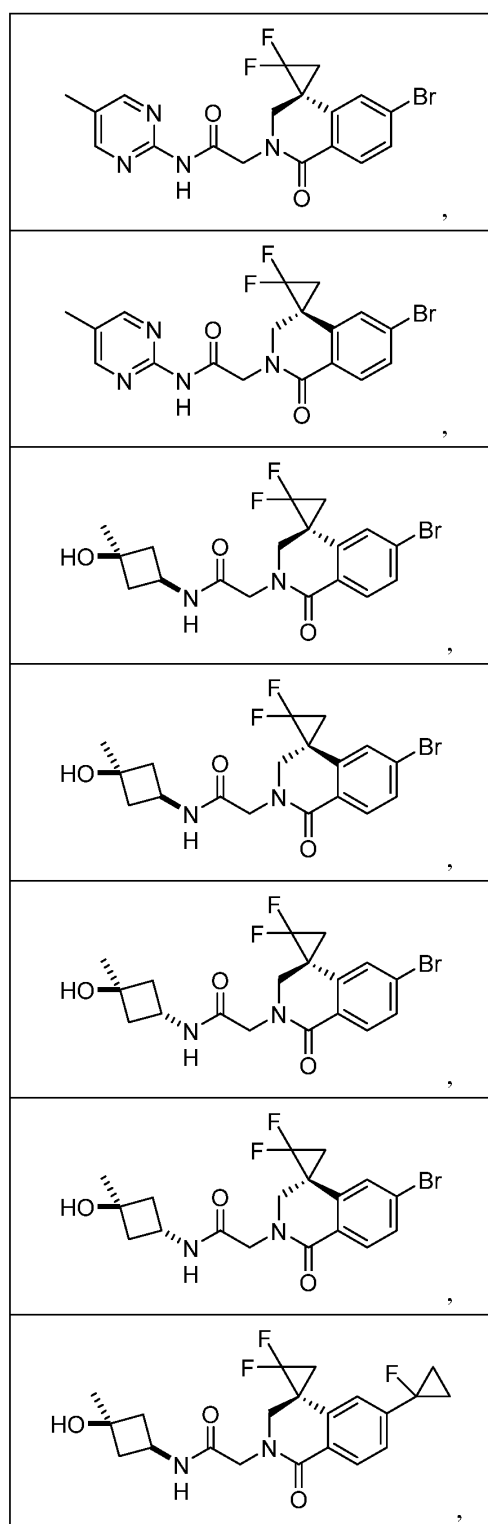
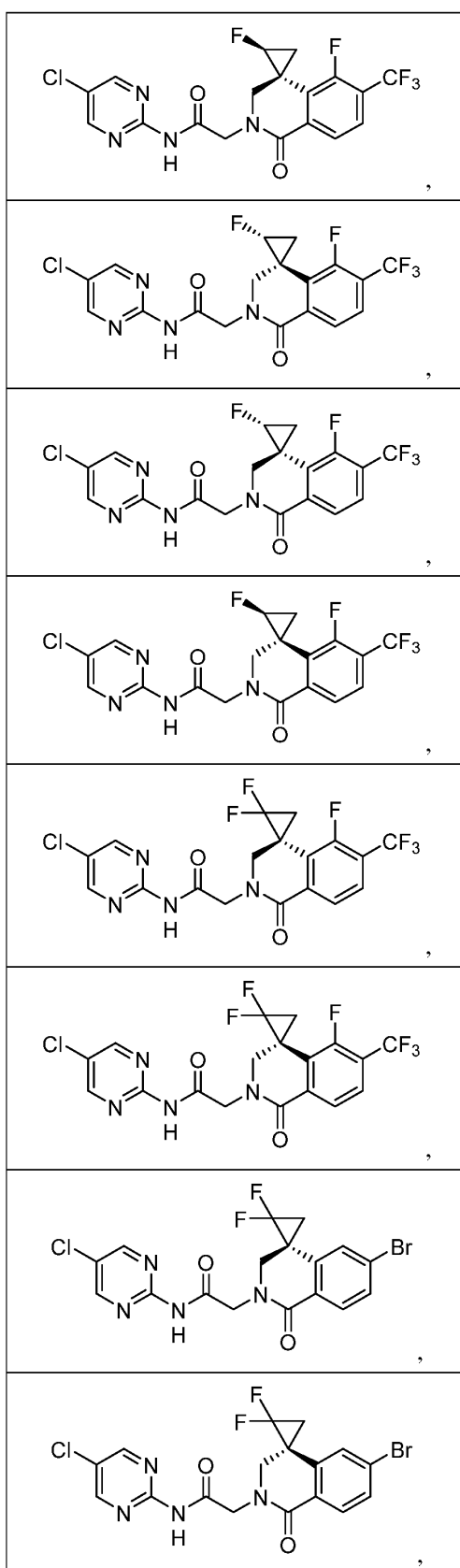
Ex. No.	Structure
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60	 ,
61	 ,
62	 ,
63	 , mixture of enantiomers
64	 , and first eluting isomer
65	 , second eluting isomer

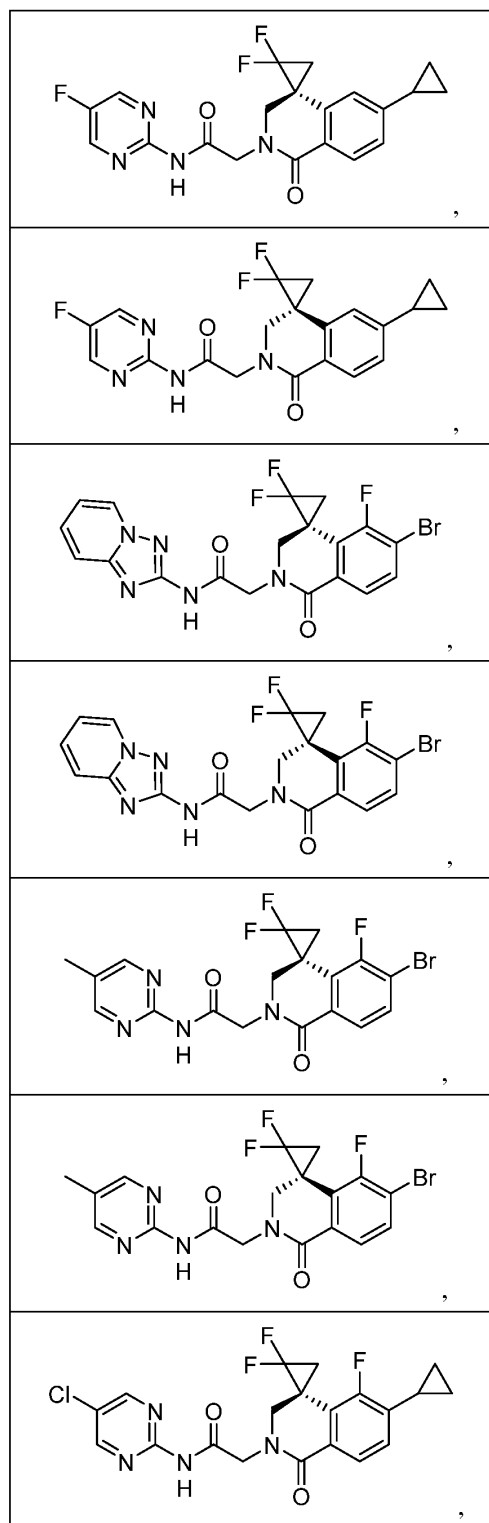
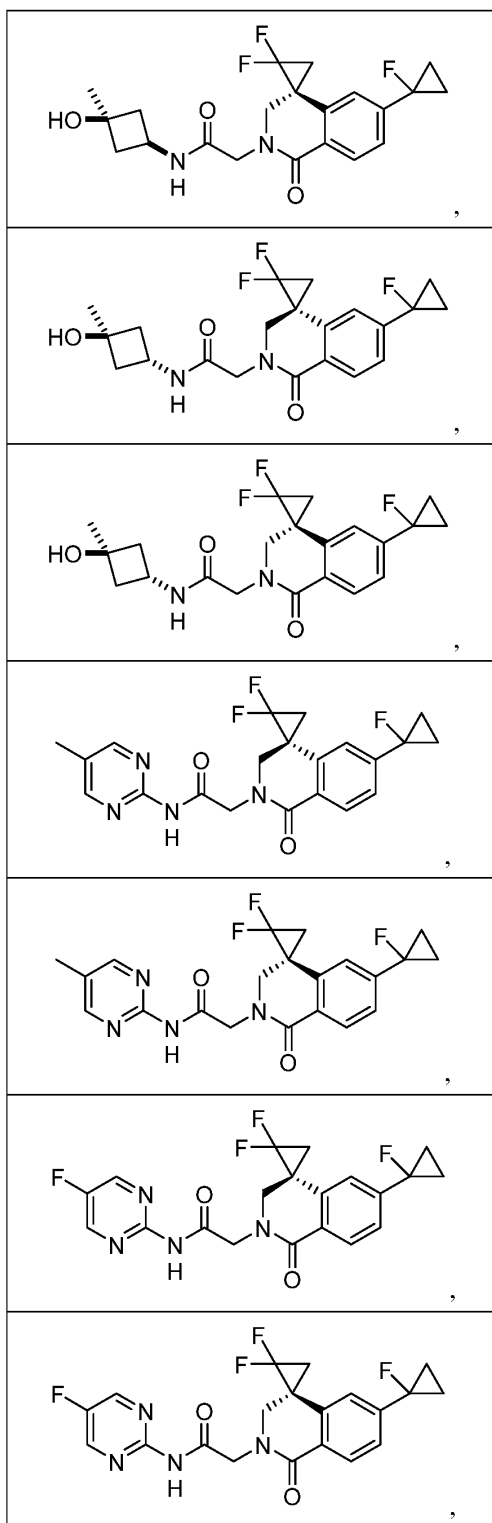
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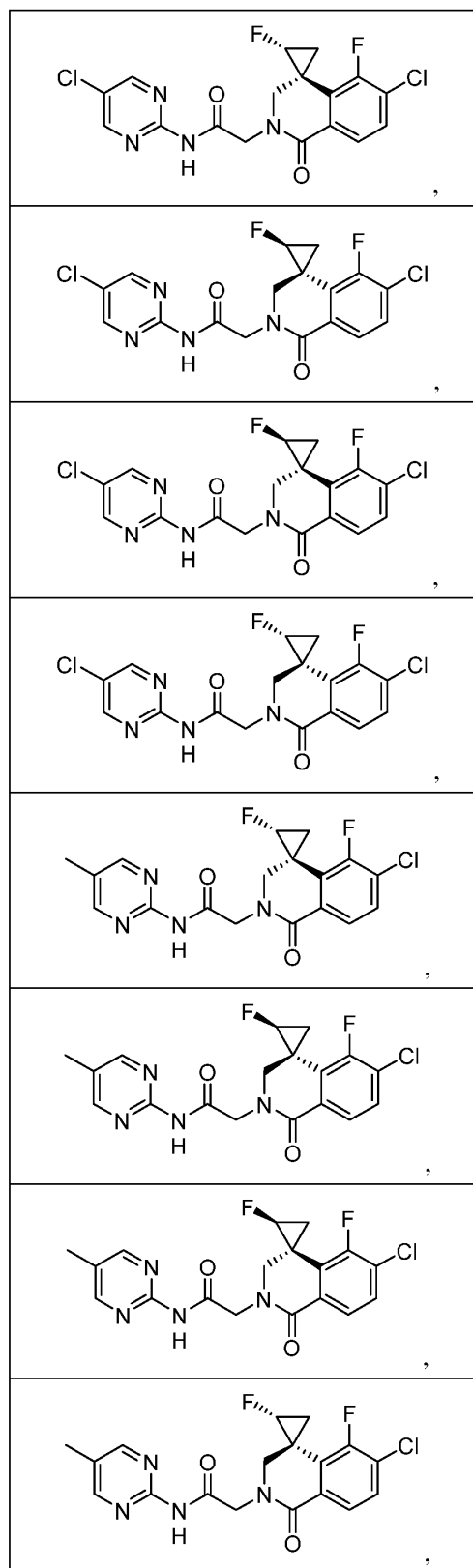
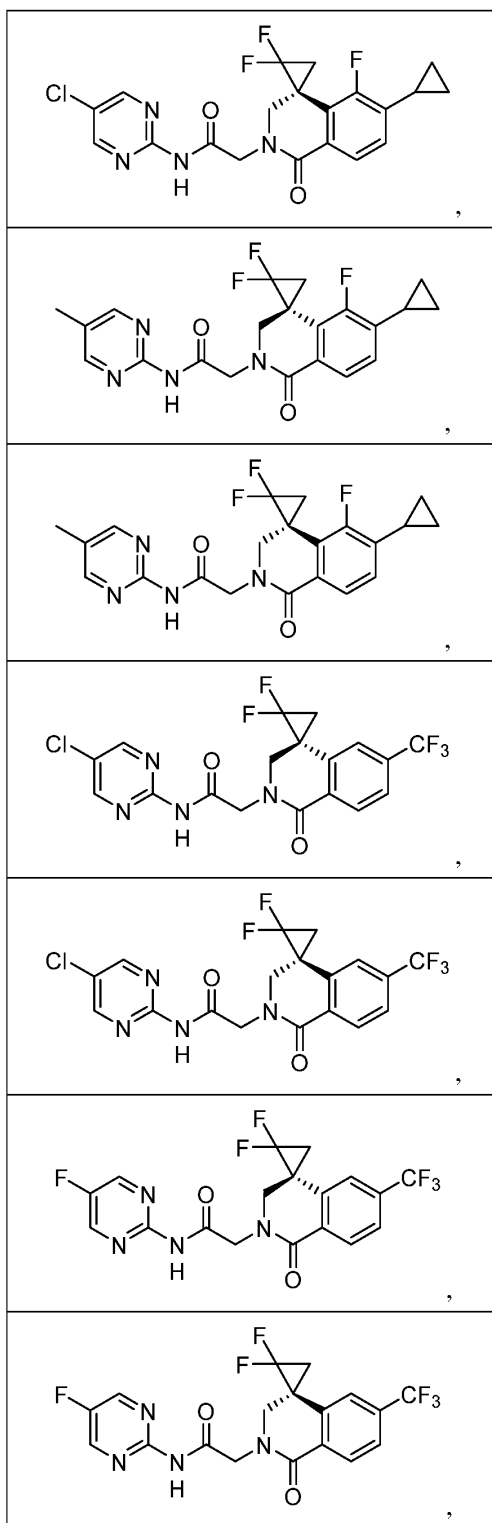


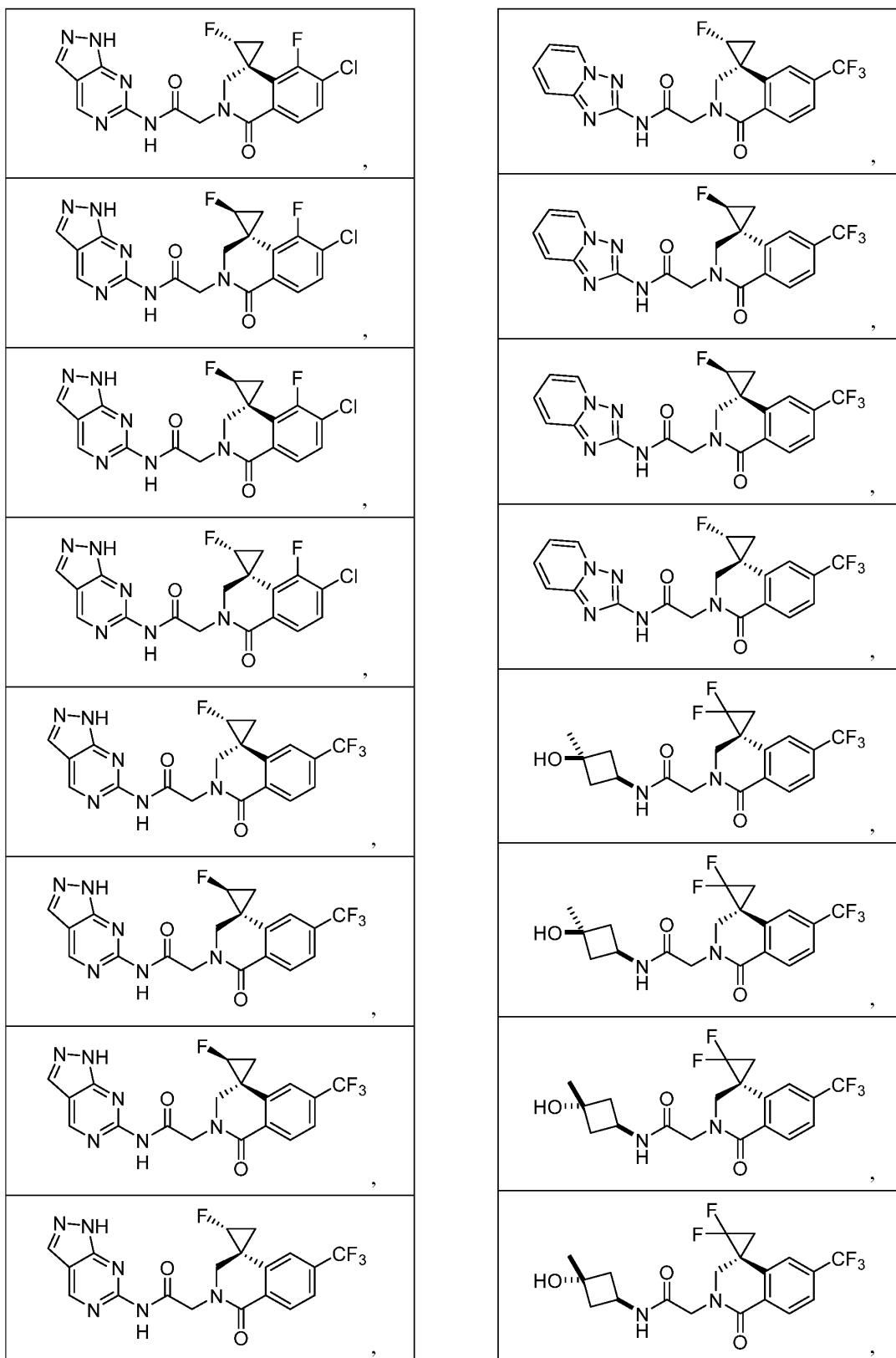


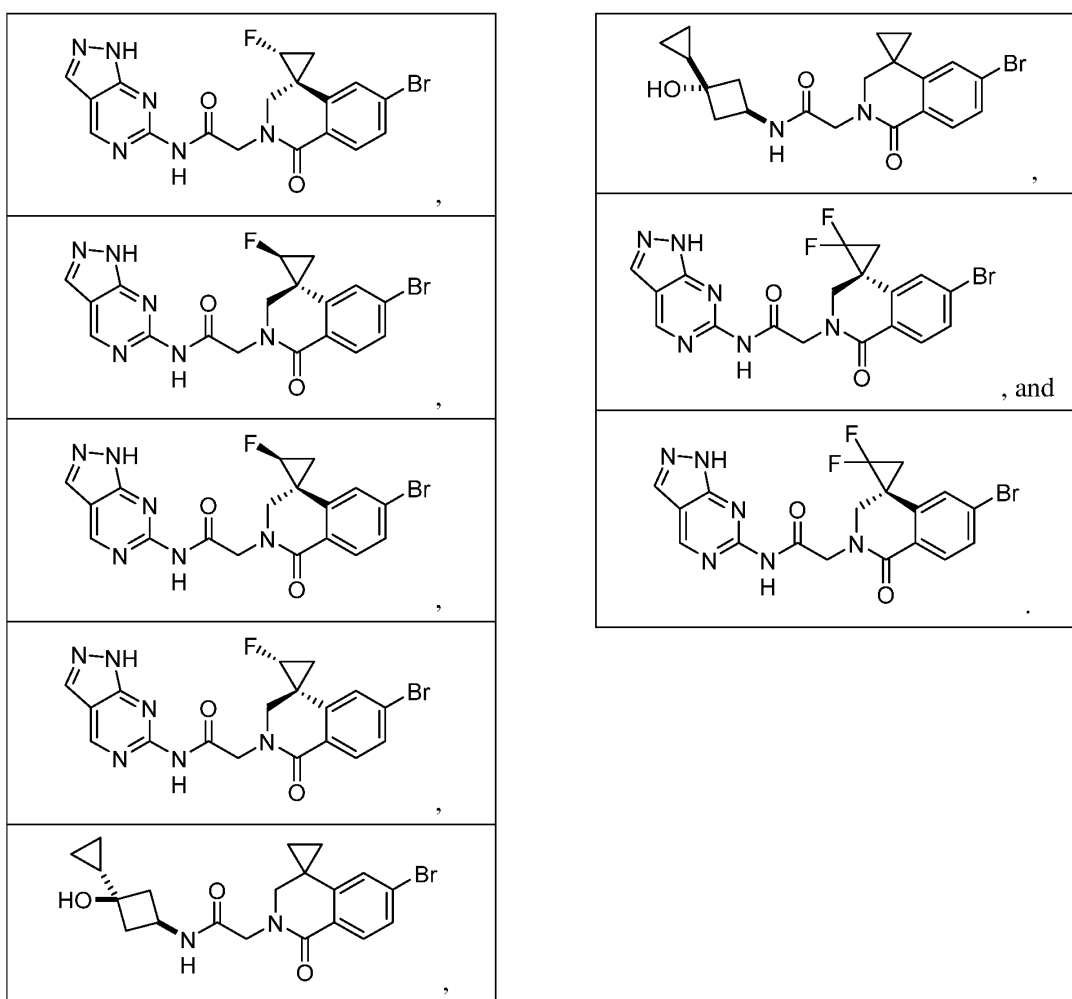




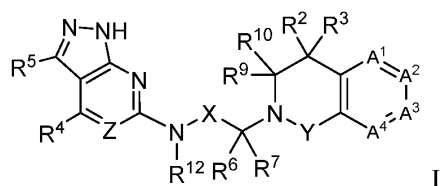








3. A compound of Formula I:



I

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

X is C(X¹), NR¹⁶, S(O)₂, or S(O)(NR¹⁸);

Y is C(Y¹), O, NR¹⁷, S(O)₂, or S(O)(NR¹⁹);

Z is CR⁸ or N;

X¹ is O, NR¹⁸, or S;

Y¹ is O, NR¹⁹, or S;

A¹, A², A³, and A⁴ are each independently N, CH, or CR¹; provided at least one of A¹, A², A³, and A⁴ is CR¹;

each R¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 eight Z¹; or any two adjacent R¹ together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z¹;

R² is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -NO₂, -SF₅, -OR¹¹, -N(R¹¹)₂, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -NR¹¹C(O)OR¹¹, -NR¹¹C(O)R¹¹, -OC(O)R¹¹, -OC(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, halo, or cyano; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z¹;

R³ is hydrogen, halo, cyano, 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 eight Z¹; or

R² and R³ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

R⁴ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁵ is hydrogen, halo, -NO₂, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, 5-6 membered heteroaryl, -OR¹⁴, -N(R¹⁴)₂, or -S(O)₀₋₂R¹⁴; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl; or

R⁴ and R⁵ together form a heterocyclyl or heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R⁶ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl may further be optionally substituted with one to five Z^{1b};

R⁷ is hydrogen, halo, cyano, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl; wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,

C₁₋₆ haloalkyl, C₂₋₆ heteroalkyl, C₃₋₁₀ cycloalkyl, or heterocyclyl, or may further be optionally substituted with one to five Z^{1b};

or R⁶ and R⁷ join to form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl ring may further be optionally substituted with one to five Z^{1b};

R⁸ is hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

R⁹ and R¹⁰ are each independently hydrogen, halo, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl, wherein each C₁₋₆ alkyl or C₁₋₆ haloalkyl is independently optionally substituted with one to five Z¹; or

R⁹ and R¹⁰ together form a C₃₋₁₀ cycloalkyl or heterocyclyl ring; wherein the C₃₋₁₀ cycloalkyl or heterocyclyl is optionally substituted with one to eight Z¹;

each Z¹ is independently halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹¹)₂, -OR¹¹, -C(O)R¹¹, -C(O)OR¹¹, -S(O)₀₋₂R¹¹, -NR¹¹S(O)₀₋₂R¹¹, -S(O)₀₋₂N(R¹¹)₂, -NR¹¹S(O)₀₋₂N(R¹¹)₂, -NR¹¹C(O)N(R¹¹)₂, -C(O)N(R¹¹)₂, -NR¹¹C(O)R¹¹, -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 Z^{1a};

each R¹¹ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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};

R¹² 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 optionally substituted with one to eight Z¹;

each Z^{1a} is independently hydroxy, halo, cyano, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, heteroaryl, -N(R¹³)₂, -OR¹³, -C(O)R¹³, -C(O)OR¹³, -S(O)₀₋₂R¹³, -NR¹³S(O)₀₋₂R¹³, -S(O)₀₋₂N(R¹³)₂, -NR¹³S(O)₀₋₂N(R¹³)₂, -NR¹³C(O)N(R¹³)₂, -C(O)N(R¹³)₂, -NR¹³C(O)R¹³, -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, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

each R¹⁴ is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one to five halo, hydroxy, -SH, -NH₂, -NO₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl;

R¹⁶ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

R¹⁷ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

R¹⁸ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; 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^{1b};

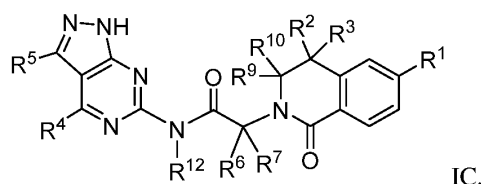
R¹⁹ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, hydroxy, -SH, -NH₂, -NO₂, -SF₅, 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-;

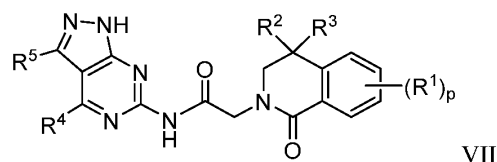
wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₁₀ cycloalkyl, heterocyclyl, aryl, and heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five hydroxy, halo, cyano, hydroxy, -SH, -NH₂, -NO₂, -SF₅, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆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

4. The compound of claim 3, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, represented by Formula IC:



IC.

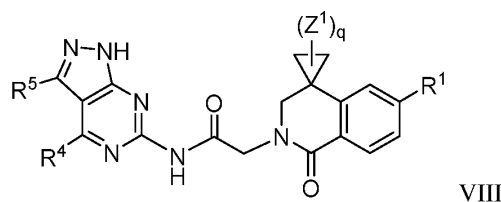
5. The compound of claim 3 or 4, wherein R⁹ and R¹⁰ are hydrogen.
6. The compound of any one of claims 3-5, wherein R¹² is hydrogen; R⁶ is hydrogen; and R⁷ is hydrogen.
7. The compound of claim 3, represented by Formula VII:



VII

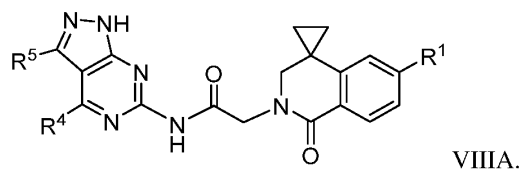
wherein p is 1, 2, 3, or 4.

8. The compound of claim 3, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, represented by Formula VIII:



wherein q is 0, 1, 2, 3, or 4.

9. The compound of claim 3, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, represented by Formula VIIIA:



10. The compound of any one of claims 3-9, wherein R¹ is halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkyl.
11. The compound of any one of claims 3-10, wherein R¹ is halo.
12. The compound of any one of claims 3-11, wherein R⁴ is hydrogen.
13. The compound of any one of claims 3-12, wherein R⁵ is hydrogen or C₁₋₆ haloalkyl.
14. The compound of any one of claims 3-13, wherein R⁵ is hydrogen or -CF₃.
15. A pharmaceutical composition comprising a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier.
16. A method for treating a disease or condition mediated, at least in part, by NLRP3, the method comprising administering an effective amount of the pharmaceutical composition of claim 15, to a subject in need thereof.
17. The method of claim 16, wherein the disease or condition is Alzheimer disease, atherosclerosis, asthma, allergic airway inflammation, cryopyrin-associated periodic syndromes, gout, inflammatory bowel disease and related disorders, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hypertension, myocardial infarction, multiple sclerosis, experimental autoimmune encephalitis, oxalate-induced nephropathy, hyperinflammation following influenza infection, graft-versus-host disease, stroke, silicosis, type 1 diabetes, obesity-induced inflammation or insulin resistance, rheumatoid arthritis, myelodysplastic syndrome, contact hypersensitivity, joint inflammation triggered by chikungunya virus, or traumatic brain injury.
18. The method of claim 16, wherein the disease is nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).
19. The method of claim 16, wherein the disease is Alzheimer's disease.

20. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for treating a disease or condition mediated, at least in part, by NLRP3.
21. The use of claim 20, wherein the disease or condition is Alzheimer disease, atherosclerosis, asthma, allergic airway inflammation, cryopyrin-associated periodic syndromes, gout, inflammatory bowel disease and related disorders, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hypertension, myocardial infarction, multiple sclerosis, experimental autoimmune encephalitis, oxalate-induced nephropathy, hyperinflammation following influenza infection, graft-versus-host disease, stroke, silicosis, type 1 diabetes, obesity-induced inflammation or insulin resistance, rheumatoid arthritis, myelodysplastic syndrome, contact hypersensitivity, joint inflammation triggered by chikungunya virus, or traumatic brain injury.
22. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in therapy.
23. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in treating Alzheimer's disease.
24. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in treating nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).
25. The use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for the manufacture of a medicament for treating a neurodegenerative disease, treating Alzheimer's disease, atherosclerosis, asthma, allergic airway inflammation, cryopyrin-associated periodic syndromes, gout, inflammatory bowel disease and related disorders, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hypertension, myocardial infarction, multiple sclerosis, experimental autoimmune encephalitis, oxalate-induced nephropathy, hyperinflammation following influenza infection, graft-versus-host disease, stroke, silicosis, type 1 diabetes, obesity-induced inflammation or insulin resistance, rheumatoid arthritis, myelodysplastic syndrome, contact hypersensitivity, joint inflammation triggered by chikungunya virus, or traumatic brain injury.