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(54) Title: KRAS INHIBITORS AND USES THEREOF

(57) Abstract: KRAS mutation inhibitors and pharmaceutical compositions comprising said inhibitors are useful for the treatment of a disease or disorder associated with KRAS mutation.

KRAS INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims the benefit of International Application No. PCT/CN2023/100280, filed June 14, 2023, and International Application No. PCT/CN2023/135668, filed November 30, 2023, each of which is incorporated herein by reference in its entirety.

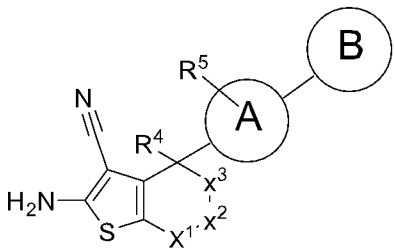
BACKGROUND

[0002] Cancer-associated mutations in RAS-family proteins suppress their intrinsic and GAP- induced GTPase activity leading to an increased population of GTP-bound/active RAS-family proteins. This in turn leads to persistent activation of effector pathways downstream of RAS-family proteins. KRAS mutations (e.g. amino acids G12, G13, Q61, A146) are found in a variety of human cancers including lung cancer, colorectal cancer and pancreatic.

[0003] KRAS mutations mediate immune escape by regulating the intrinsic characteristics of tumor cells. In KRAS-driven tumors, mutant KRAS mediates tumor immune escape by upregulating PD-L1 expression. KRAS (G12C), KRAS (G12V), KRAS (G12D), and KRAS (G13D) mutations are often associated with high PD-L1 expression.

SUMMARY

[0004] In one aspect, disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (I).

[0005] In one aspect, disclosed herein is a pharmaceutical composition comprising a compound of the disclosure and a pharmaceutically acceptable salt thereof. In one aspect, disclosed herein is a method of treating a cancer, the method comprising administering an effective amount of a compound of describe herein or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

INCORPORATION BY REFERENCE

[0006] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

Definitions

[0007] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the disclosed technology may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments.

Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0008] Reference throughout this specification to "some embodiments" or "an embodiment" means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0009] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0010] "oxo" refers to =O. In some embodiments, the oxo is illustrated as (O). For example, -C(O)N(R^{10})(R^{11}) and -C(O)OR^{10} represent -C(=O)N(R^{10})(R^{11}) and -C(=O)OR^{10}, respectively.

[0011] "Carboxyl" refers to -COOH.

[0012] "Cyano" refers to -CN.

[0013] "Alkyl" refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" or "C_{1-6}alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C_{1-10}alkyl. In some embodiments, the alkyl is a C_{1-6}alkyl. In some embodiments, the alkyl is a C_{1-5}alkyl. In some embodiments, the alkyl is a C_{1-4}alkyl. In some embodiments, the alkyl is a C_{1-3}alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0014] "Alkenyl" refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH_2), 1-propenyl (-CH_2CH=CH_2), isopropenyl [-C(CH_3)=CH_2], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" or "C_{2-6}alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro,

hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0015] "Alkynyl" refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkynyl" or "C_{2-6}alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0016] "Alkylene" refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0017] "Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0018] "Aryl" refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen. As used herein, "arylene" refers to a bivalent aryl radical as described herein. An arylene can be

bonded through the aryl at any suitable position. In some embodiments, when an arylene comprises an aryl fused with a cycloalkyl or heterocycloalkyl ring, the arylene is bonded at the aryl and the cycloalkyl, or the aryl and the heterocycloalkyl. In some embodiments, when an arylene comprises an aryl fused with a cycloalkyl or heterocycloalkyl ring, the arylene is bonded only at the aryl.

[0019] "Cycloalkyl" refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (e.g., C_3-C_{15} fully saturated cycloalkyl or C_3-C_{15} cycloalkenyl), from three to ten carbon atoms (e.g., C_3-C_{10} fully saturated cycloalkyl or C_3-C_{10} cycloalkenyl), from three to eight carbon atoms (e.g., C_3-C_8 fully saturated cycloalkyl or C_3-C_8 cycloalkenyl), from three to six carbon atoms (e.g., C_3-C_6 fully saturated cycloalkyl or C_3-C_6 cycloalkenyl), from three to five carbon atoms (e.g., C_3-C_5 fully saturated cycloalkyl or C_3-C_5 cycloalkenyl), or three to four carbon atoms (e.g., C_3-C_4 fully saturated cycloalkyl or C_3-C_4 cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen. As used herein, "cycloalkylene" refers to a bivalent cycloalkyl radical as described herein. In some embodiments, when a cycloalkylene comprises a cycloalkyl fused with an aryl or a heteroaryl ring, the cycloalkylene is bonded at the cycloalkyl and the aryl, or the cycloalkyl and the heteroaryl. In some embodiments, when a cycloalkylene comprises a cycloalkyl fused with an aryl or a heteroaryl ring, the cycloalkylene is bonded only at the cycloalkyl.

[0020] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0021] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0022] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0023] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is

substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0024] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH_2OCH_3, -$CH_2CH_2OCH_3$, -$CH_2CH_2OCH_2CH_2OCH_3$, -$CH(CH_3)OCH_3$, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -$CH_2CH_2NHCH_3$, or -$CH_2CH_2N(CH_3)_2$. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF_3, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0025] "Heterocyclyl" refers to a heterocycloalkyl or a heteroaryl, as described herein. Unless stated otherwise specifically in the specification, a heterocyclyl is optionally substituted. In some embodiments, the heterocyclyl is a heterocycloalkyl. In some embodiments, the heterocyclyl is a heteroaryl.

[0026] "Heterocycloalkyl" refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (e.g., C_2-C_{15} fully saturated heterocycloalkyl or C_2-C_{15} heterocycloalkenyl), from two to ten carbon atoms (e.g., C_2-C_{10} fully saturated heterocycloalkyl or C_2-C_{10} heterocycloalkenyl), from two to eight carbon atoms (e.g., C_2-C_8 fully saturated heterocycloalkyl or C_2-C_8 heterocycloalkenyl), from two to seven carbon atoms (e.g., C_2-C_7 fully saturated heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to six carbon atoms (e.g., C_2-C_6 fully saturated heterocycloalkyl or C_2-C_6 heterocycloalkenyl), from two to five carbon atoms (e.g., C_2-C_5 fully saturated heterocycloalkyl or C_2-C_5 heterocycloalkenyl), or two to four carbon atoms (e.g., C_2-C_4 fully saturated heterocycloalkyl or C_2-C_4 heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl,

thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

As used herein, "heterocycloalkylene" refers to a bivalent heterocycloalkyl radical as described herein. In some embodiments, when a heterocycloalkylene comprises a heterocycloalkyl fused with an aryl or a heteroaryl ring, the heterocycloalkylene is bonded at the heterocycloalkyl and the aryl, or the heterocycloalkyl and the heteroaryl. In some embodiments, when a heterocycloalkylene comprises a heterocycloalkyl fused with an aryl or a heteroaryl ring, the heterocycloalkylene is bonded only at the heterocycloalkyl.

[0027] "Heteroaryl" refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-

benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen. As used herein, "heteroarylene" refers to a bivalent heteroaryl radical as described herein. In some embodiments, when a heteroarylene comprises a heteroaryl fused with a cycloalkyl or heterocycloalkyl ring, the heteroarylene is bonded at the heteroaryl and the cycloalkyl, or the heteroaryl and the heterocycloalkyl. In some embodiments, when a heteroarylene comprises a heteroaryl fused with a cycloalkyl or heterocycloalkyl ring, the heteroarylene is bonded only at the heteroaryl.

[0028] The term "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. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0029] An "effective amount" or "therapeutically effective amount" refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

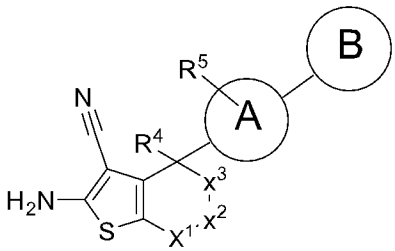
[0030] "Treatment" of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition.

Compounds

[0031] Described herein are compounds of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), or (Vg), or a pharmaceutically acceptable salt or stereoisomer thereof, useful in the treatment of a disease or disorder associated with KRAS inhibition. In some embodiments, the compounds, or a pharmaceutically

acceptable salt or stereoisomer thereof, are useful in the treatment of cancer. In some embodiments, the cancer is selected from intra-hepatic cholangiocarcinoma, urothelial cancer, gastric cancer, bladder cancer, breast cancer, endometrial cancer, kidney cancer, liver cancer, lung cancer, melanoma, pancreatic cancer, prostate cancer, or thyroid cancer.

[0032] In some embodiments disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (I);

wherein:

X^1 is $C(R^{1a})(R^{1b})$, O, S, or $N(R^{1c})$;

X^2 is $C(R^{2a})(R^{2b})$, O, S, or $N(R^{2c})$;

X^3 is $C(R^{3a})(R^{3b})$, O, S, or $N(R^{3c})$;

R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, R^{2c}, R^{3a}, R^{3b}, and R^{3c} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$; and optionally,

one of R^{1a}, R^{1b}, and R^{1c} and one of R^{2a}, R^{2b}, and R^{2c} together with the atom they are attached to form a 3-7 membered ring; or one of R^{2a}, R^{2b}, and R^{2c} and one of R^{3a}, R^{3b}, and R^{3c} together with the atom they are attached to form a 3-7 membered ring; or one of R^{1a}, R^{1b}, and R^{1c} and one of R^{3a}, R^{3b}, and R^{3c} form a bond, a C_{1-4}alkylene, or C_{1-3}heterolkylene; and optionally,

R^{1a} and R^{1b} together with the carbon atom they are attached to form a optionally substituted C3-6cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl; and/or R^{2a} and R^{2b} together with the carbon atom they are attached to form a optionally substituted C_{3-6}cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl; and/or R^{3a} and R^{3b} together with the carbon atom they are attached to form a optionally substituted C3-6cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl; wherein each of the C_{3-6}cycloalkyl is optionally

substituted with one, two or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$;

R^4 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$; or R^4 together with one of R^{1a}, R^{1b}, and R^{1c}, or R^4 together with one of R^{2a}, R^{2b}, and R^{2c}, or R^4 together with one of R^{3a}, R^{3b}, and R^{3c} form a group selected from -CH_2CH_2-, -$CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2$- optionally substituted by one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$;

R^5 is absent or is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -

$N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$; or R^4 and R^5 together with the atoms they are attached to form a C5-7cycloalkyl or a 5-7 membered heterocyclyl optionally substituted with 1-3 R^{4a}, wherein each R^{4a} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$; or

Ring A is a 5-8 membered ring optionally substituted with 1-3 R^A;

Ring B is a 5-8 membered ring optionally substituted with 1-4 R^B; or one of R^B and R^5 together with the atoms they are attached to form a 5-8 membered ring optionally substituted with 1-4 R^C;

each R^A is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^B is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C_{1-9}$heteroaryl-C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$,$-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, -

$N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^C is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy;

each R^{B10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-C_{1-3}$alkylene-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-C_{1-3}$alkylene-C_{1-9}heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-C_{1-3}$alkylene-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-C_{1-3}$alkylene-C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, $-C(O)R^{13}$, oxo, C_{1-6}alkyl, C_{1-6}heteroalkyl, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, -

$OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})-$, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, $-P(O)(R^{10})$, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein each of the C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, oxo, C_{1-6}alkyl, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy;

each R^{11} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

or R^{10} and R^{11}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy;

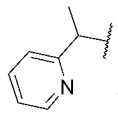
each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; and

each R^{13} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl.

[0033] In some embodiments disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein (1) Ring A is a 5-8 membered heteroaryl ring optionally substituted with 1, 2, or 3 R^A; (2) Ring A is a 5-8 membered heteroaryl ring substituted with 1, 2, or 3 R^A; and/or (3) Ring A is selected from furan, pyrrole, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrazole, imidazole, thiadiazole, triazole, pyridine, pyridazine, pyrimidine, pyrazine, azepine, diazepine, and triazepine. In some embodiments, ring A is optionally substituted 5-6 membered heteroaryl. In some embodiments, ring A is optionally substituted 6 membered heteroaryl. In some embodiments, ring A is optionally substituted 5 membered heteroaryl.

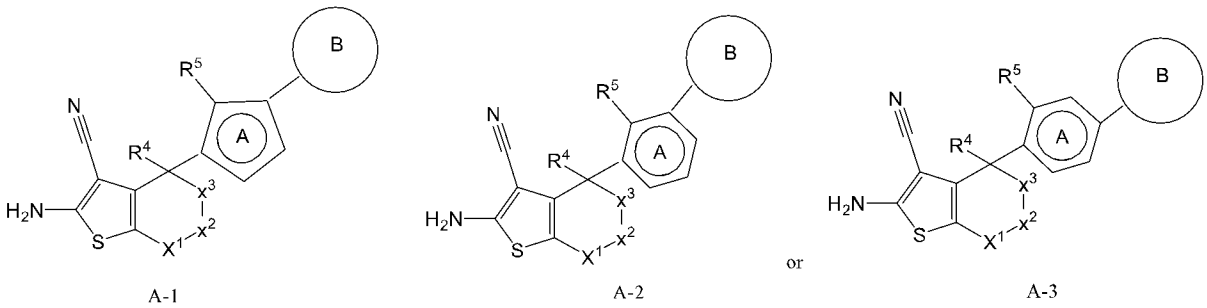
[0034] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), or (Vg), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from - halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy. In some embodiments, R^{10} is C_{1-6}alkyl. In some embodiments, R^{10} is methyl. In some embodiments, R^{10} is optionally substituted C_{2-9}heterocycloalkyl. In some embodiments, R^{10} is optionally substituted 4-6 membered heterocycloalkyl. In some embodiments, R^{10} is $-CH_2-C_{3-6}$cycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, or $-CH_2-C_{1-9}$heteroaryl, each of which is optionally substituted. In some embodiment, when R^{10} is $-CH_2-C_{3-}$

$_{6}$cycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -CH_2-C_{6-10}aryl, or -CH_2-C_{1-9}heteroaryl, R^{10} is optionally substituted at the -CH_2- position.

[0035] In some embodiments, R^{10} is -CH_2-C_{3-6}cycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -CH_2-C_{6-10}aryl, or -CH_2-C_{1-9}heteroaryl, each of which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl , wherein the C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy. In some embodiments, R^{10} is -CH_2-C_{2-9}heterocycloalkyl, optionally substituted with one, two, or three C_{1-6}alkyl (e.g., R^{10} is ).

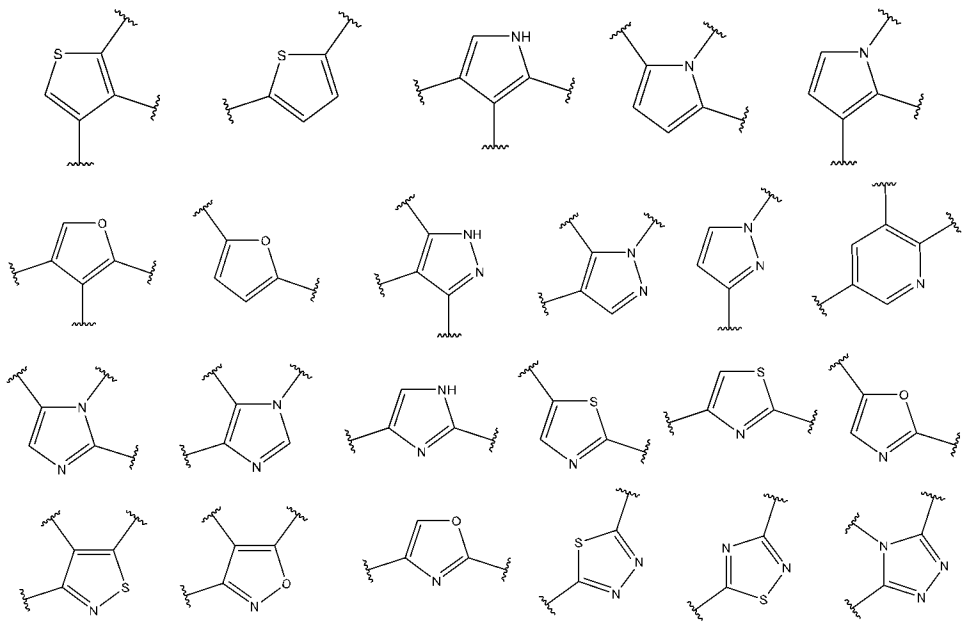
[0036] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), or a pharmaceutically acceptable salt or stereoisomer thereof, R^{11} is hydrogen, C_{1-6}alkyl, or C_{1-6}haloalkyl. In some embodiments, R^{11} is hydrogen. In some embodiments, R^{11} is methyl.

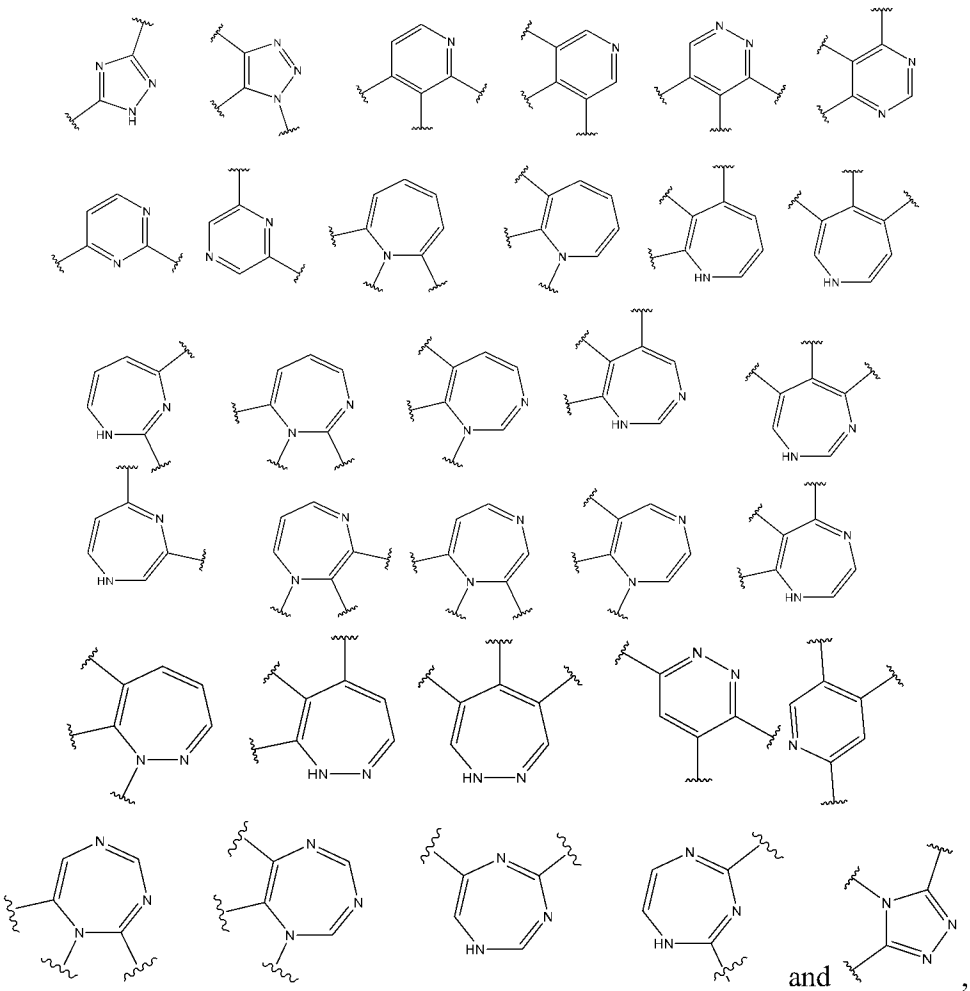
[0037] In some embodiments disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof, having the structure of:



A-1 A-2 A-3

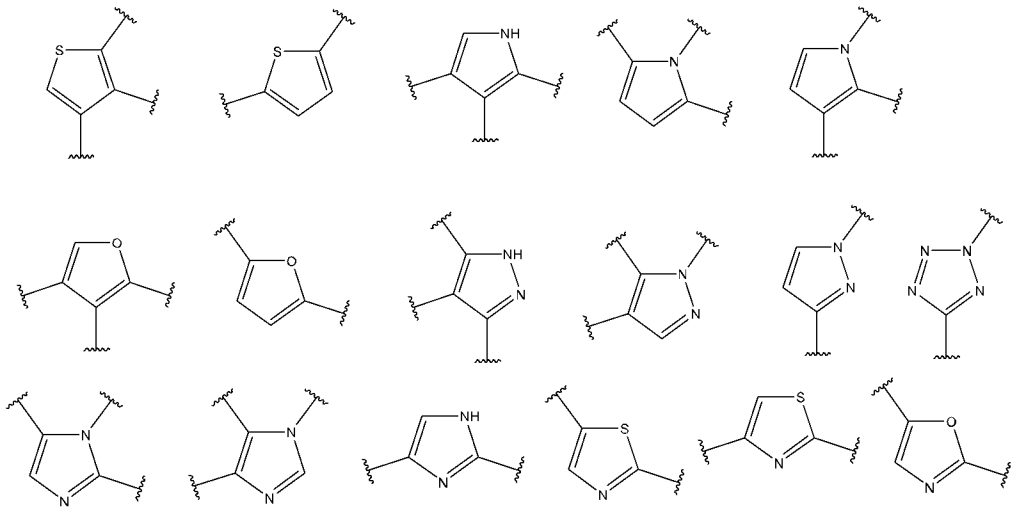
[0038] In some embodiments the compounds disclosed herein may have a Ring A selected from:

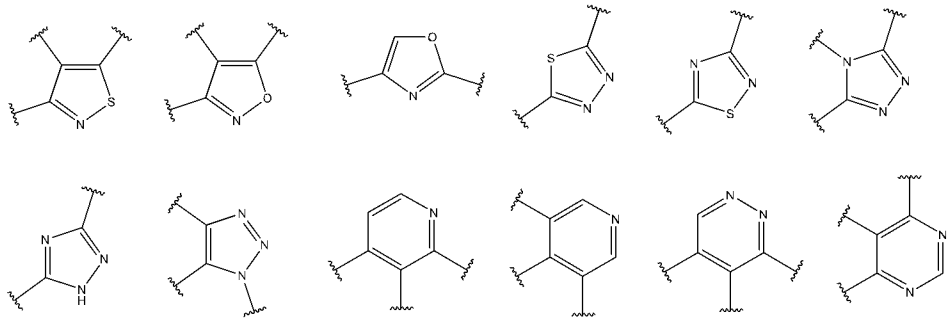




and wherein each hydrogen on a ring atom is independently and optionally replaced by a R^A group.

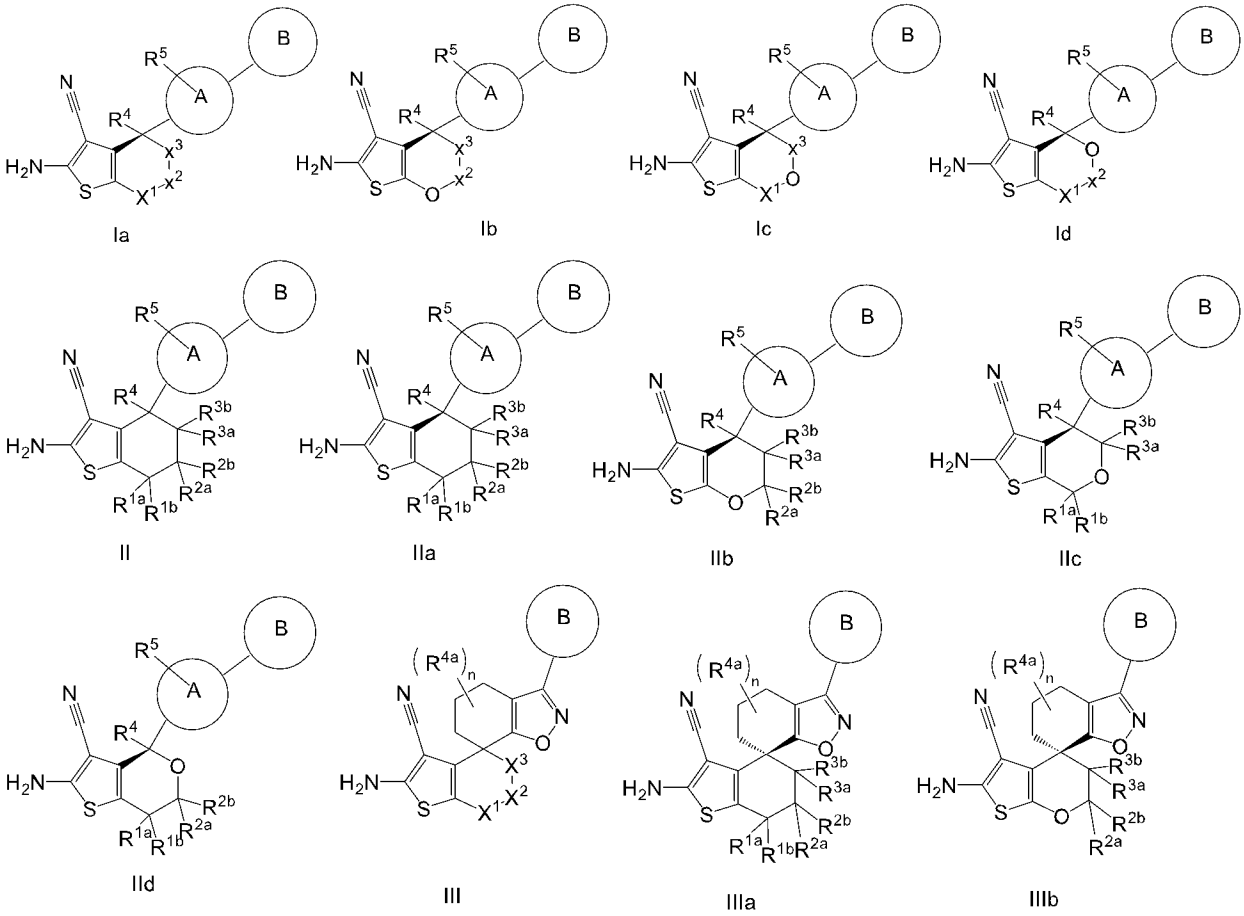
[0039] In some embodiments the compounds disclosed herein may have a Ring A selected from:

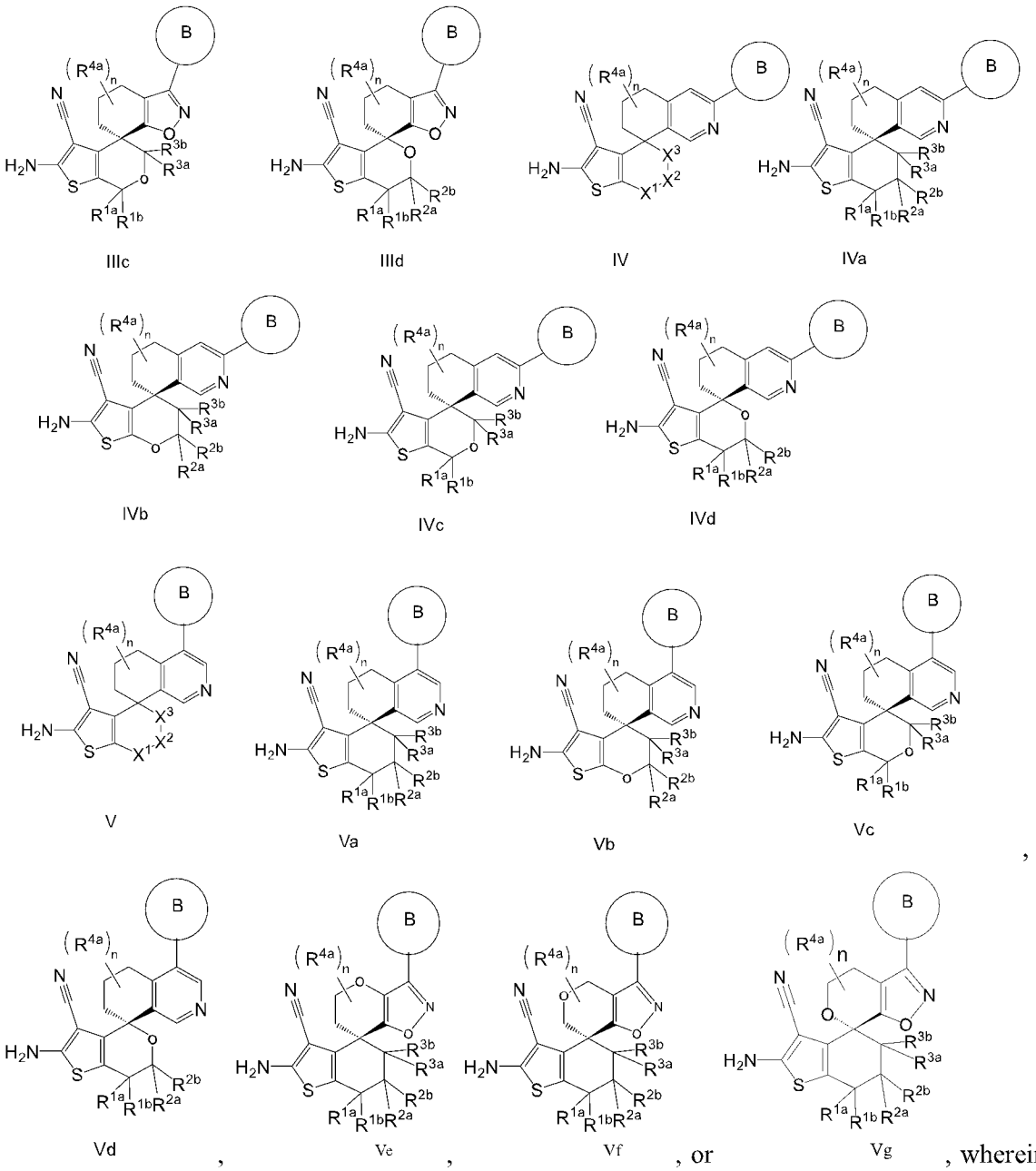




, and wherein each hydrogen on a ring atom is independently and optionally replaced by a R^A group.

[0040] In some embodiments the compounds disclosed herein may have a structure of:

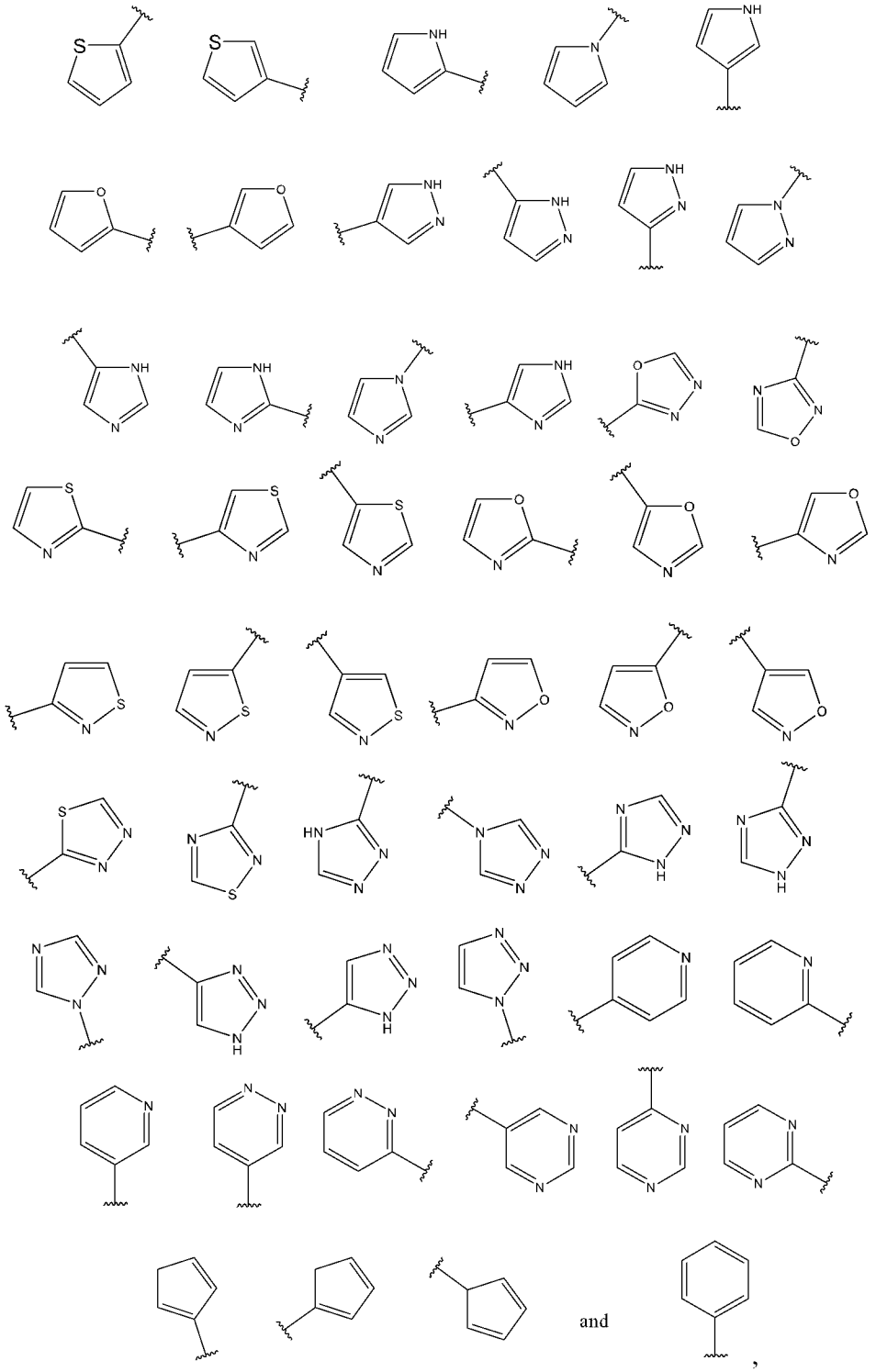




, , , , or , wherein each n is independently 0, 1, 2, or 3. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

[0041] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), or (Vg), wherein Ring B is a 5-8 membered ring substituted with 1-3 R^B. In some embodiments, ring B is optionally substituted 5-6 membered heteroaryl. In some embodiments, ring B is optionally substituted 5 membered heteroaryl. In some embodiments, ring B is optionally substituted thiazolyl. In some embodiments, ring B is optionally substituted 6 membered heteroaryl. In some embodiments, ring B is optionally substituted pyrimidinyl. In some embodiments, ring B is optionally substituted pyridinyl.

[0042] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), or (Vg), wherein Ring B is selected from:

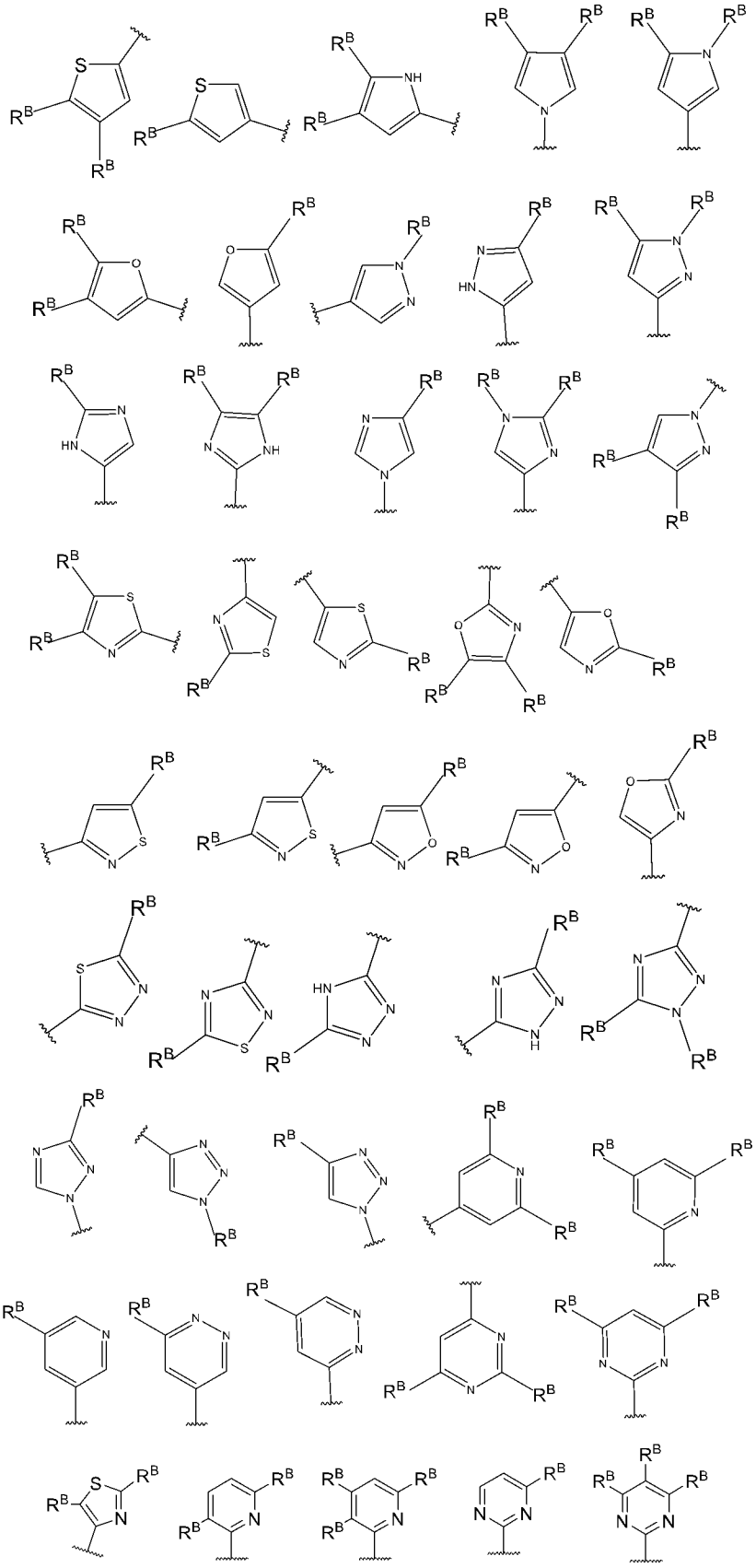


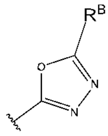
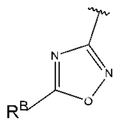
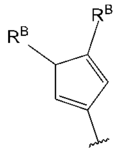
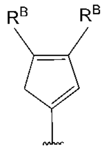
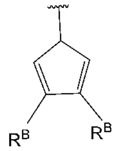
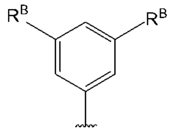
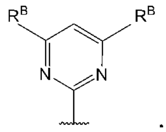
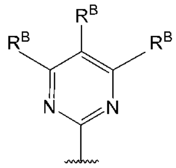
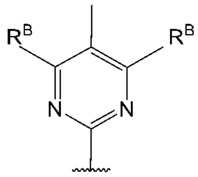
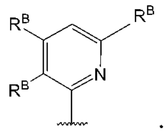
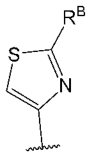
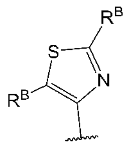
and

,

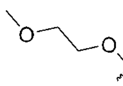
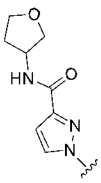
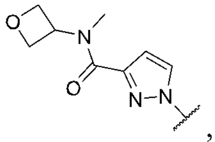
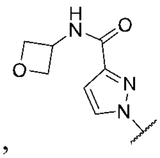
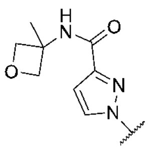
wherein each hydrogen on a ring atom is independently and optionally replaced by a R^B group.

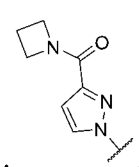
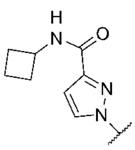
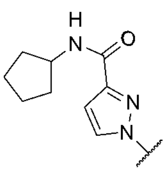
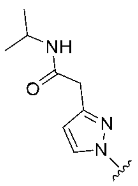
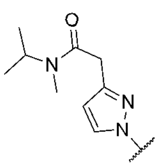
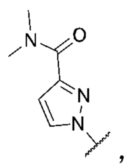
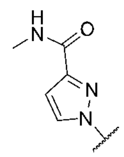
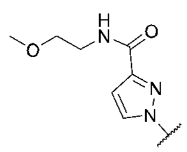
[0043] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), or (Vg), wherein Ring B is selected from:

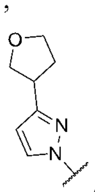
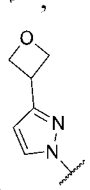
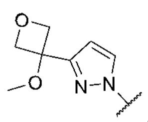
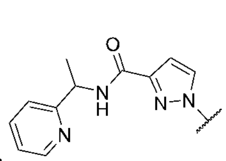
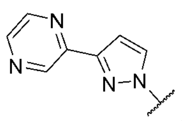
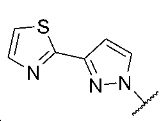
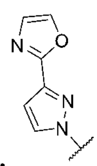


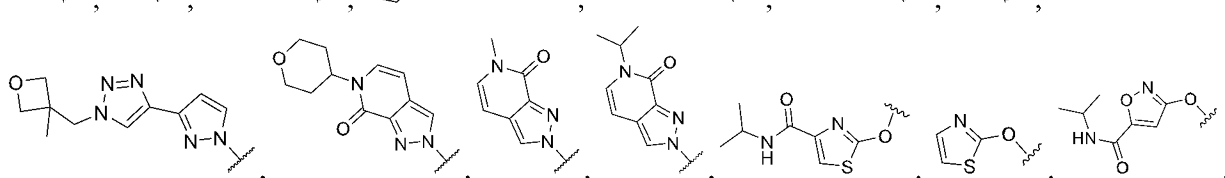
     and  . In some embodiments, Ring B is  . In some embodiments, Ring B is  . In some embodiments, Ring B is  . In some embodiments, Ring B is  . In some embodiments, Ring B is  . In some embodiments, Ring B is  .

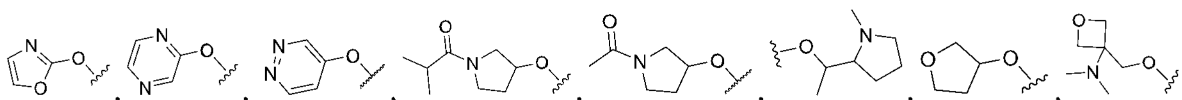
[0044] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), or (Vg), wherein each R^B independently is selected from:

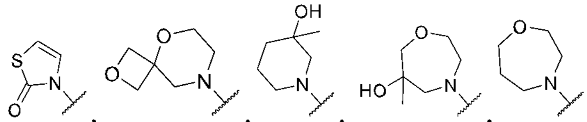
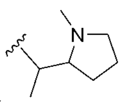
hydrogen, halogen, methyl, -OCHF$_2$,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

 ,

 ,

 ,and  .

[0045] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9) or (VI-10), each R^B is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$,$-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$.

[0046] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7) (VI-8), (VI-9) or (VI-10) wherein:

(1) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{B10}$, $-SR^{B10}$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2N(R^{10})(R^{11})$-, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

(2) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2N(R^{10})(R^{11})$-, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, -

$S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

(3) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2N(R^{10})(R^{11})$-, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl,

each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; and

each R^{11} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{10} and R^{11}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

(4) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})(R^{11})$;

(5) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{B10}$, $-SR^{B10}$, $-N(R^{10})(R^{11})$;

(6) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{2-9}heterocycloalkyl, and $-OR^{10}$;

(6) at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{2-9}heterocycloalkyl, and $-OR^{B10}$;

(7) at least one R^B is $R^{B''}$, wherein $R^{B''}$ is C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, -

CH_2-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and -CH_2-C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; and

each R^{11} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{10} and R^{11}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy;

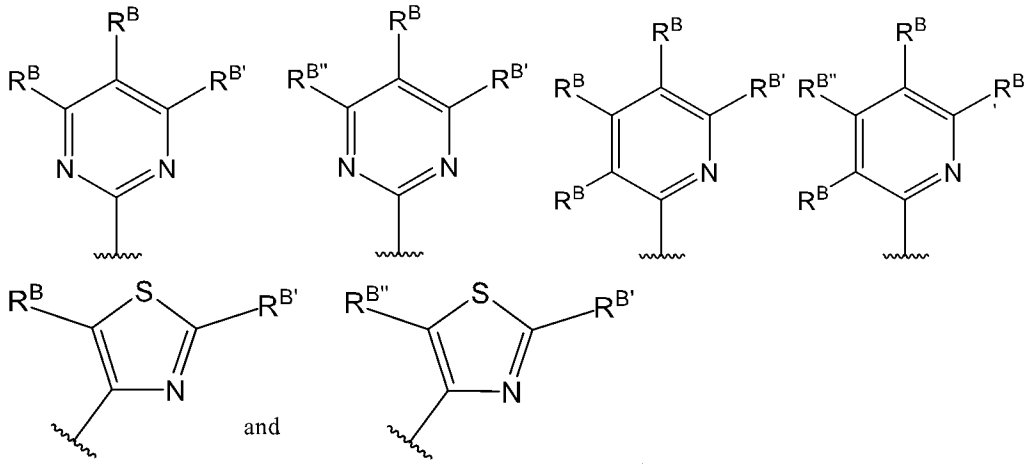
(8) at least one R^B is $R^{B''}$, wherein $R^{B''}$ is optionally substituted C_{1-9}heteroaryl;

(9) at least one R^B is $R^{B''}$, wherein $R^{B''}$ is optionally substituted thiazolyl;

(10) at least one R^B is $R^{B'}$ and at least one R^B is $R^{B''}$;

(11) Ring B is substituted by one, two, or three R^B that is not hydrogen; and/or

(12) Ring B is selected from:



and

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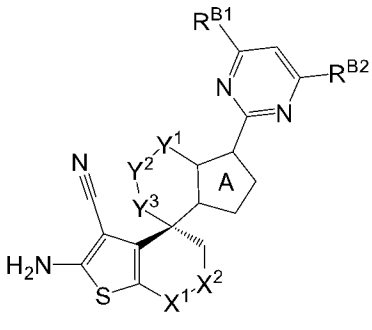
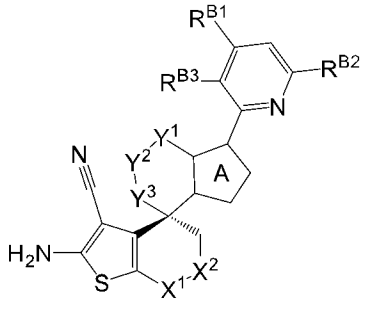
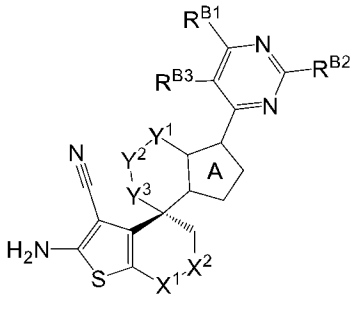
[0047] In some embodiments disclosed herein is a compound having a structure of:



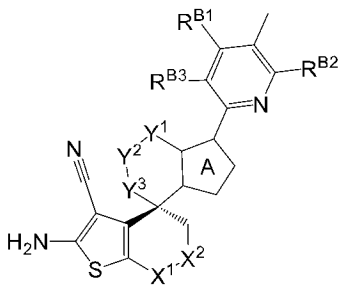
VI-1 ,



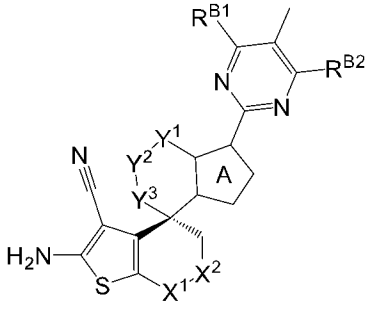
VI-2 ,



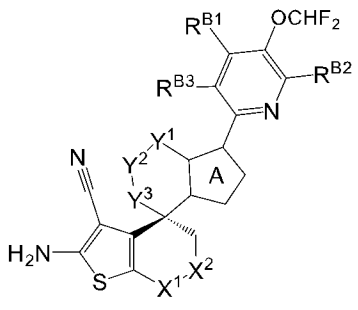
VI-3 ,



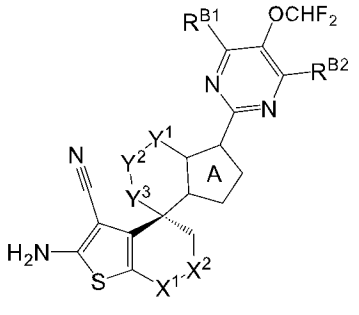
VI-4 ,

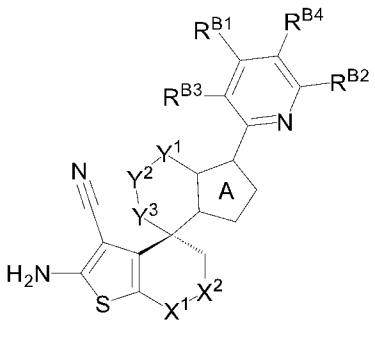


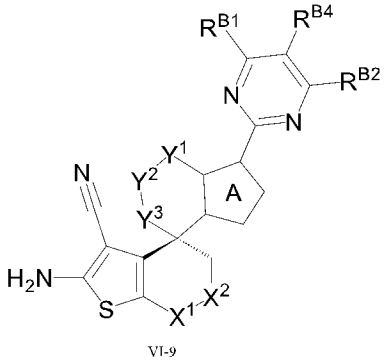
VI-5 ,

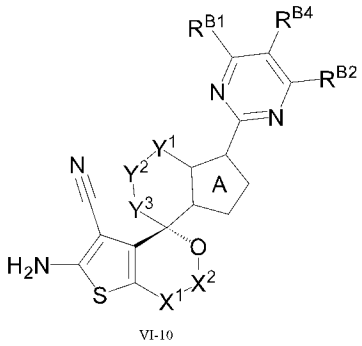


VI-6 ,


VI-7


VI-8


VI-9


VI-10

R^{B1}, R^{B2}, R^{B3}, and R^{B4} are independently selected from R^B;

X^1 is $C(R^{1a})(R^{1b})$, O, S, or $N(R^{1c})$;

X^2 is $C(R^{2a})(R^{2b})$, O, S, or $N(R^{2c})$;

Y^1 is $C(R^{1Ya})(R^{1Yb})$, O, S, or $N(R^{1Yc})$;

Y^2 is $C(R^{2Ya})(R^{2Yb})$, O, S, or $N(R^{2Yc})$;

Y^3 is $C(R^{3Ya})(R^{3Yb})$, O, S, or $N(R^{3Yc})$;

R^{1Ya}, R^{2Ya} and R^{3Ya} are independently selected from R^{1a};

R^{1Yb}, R^{2Yb} and R^{3Ya} are independently selected from R^{1b}; and

R^{1Yc}, R^{2Yc} and R^{3Yc} are independently selected from R^{1c}.

[0048] In some embodiments of a compound of Formula (VI-8) or (VI-9), when X^1 is $C(R^{1a})(R^{1b})$, X^2 is $C(R^{2a})(R^{2b})$, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$ and Y^3 is $C(R^{3Ya})(R^{3Yb})$, then R^{B4} is not hydrogen, halogen and OMe.

[0049] In some embodiments of a compound of Formula (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), or (VI-9), at least one of X^1, X^2, Y^1,Y^2 and Y^3 is not $C(R^{1a})(R^{1b})$.

[0050] In some embodiments of a compound of Formula (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), or (VI-9), at least one of X^1, X^2, Y^1,Y^2 and Y^3 is O. In some embodiments, at least one of X^1, X^2, Y^1,Y^2 and Y^3 is S. In some embodiments, at least one of Y^1,Y^2 and Y^3 is O. In some embodiments, at least one of Y^1 and Y^2 is O. In some embodiments, at least one of the following conditions are satisfied: (i) X^1 is not $C(R^{1a})(R^{1b})$; (ii) X^2 is not $C(R^{2a})(R^{2b})$; (iii) Y^1 is not $C(R^{1Ya})(R^{1Yb})$; (iv) Y^2 is not $C(R^{2Ya})(R^{2Yb})$; or (v) Y^3 is not $C(R^{3Ya})(R^{3Yb})$. In some embodiments, X^1 is not $C(R^{1a})(R^{1b})$. In some embodiments, X^2 is not $C(R^{2a})(R^{2b})$. In some embodiments, Y^1 is not $C(R^{1Ya})(R^{1Yb})$. In some embodiments, Y^2 is not $C(R^{2Ya})(R^{2Yb})$. In some embodiments, Y^3 is not $C(R^{3Ya})(R^{3Yb})$. In some embodiments, Y^1 is O or S, Y^2 is $C(R^{2Ya})(R^{2Yb})$, and Y^3 is $C(R^{3Ya})(R^{3Yb})$. In some embodiments, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is O or S, and Y^3 is $C(R^{3Ya})(R^{3Yb})$. In some embodiments, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$, and Y^3 is O or S. In some embodiments, X^1 is O or S and X^2 is $C(R^{2a})(R^{2b})$. In some embodiments, X^1 is $C(R^{1a})(R^{1b})$ and X^2 is O or S. In some embodiments, Y^1 is O, Y^2 is $C(R^{2Ya})(R^{2Yb})$, Y^3 is $C(R^{3Ya})(R^{3Yb})$, X^1 is $C(R^{1a})(R^{1b})$ and X^2 is $C(R^{2a})(R^{2b})$. In some embodiments, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is O, Y^3 is $C(R^{3Ya})(R^{3Yb})$, X^1 is $C(R^{1a})(R^{1b})$ and X^2 is $C(R^{2a})(R^{2b})$. In some embodiments, Y^1 is

$C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$, Y^3 is O, X^1 is $C(R^{1a})(R^{1b})$ and X^2 is $C(R^{2a})(R^{2b})$. In some embodiments, X^1 is O, X^2 is $C(R^{2a})(R^{2b})$, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$ and Y^3 is $C(R^{3Ya})(R^{3Yb})$. In some embodiments, X^1 is $C(R^{1a})(R^{1b})$, X^2 is O, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$ and Y^3 is $C(R^{3Ya})(R^{3Yb})$.

[0051] In some embodiments of a compound of Formula (VI-10), X^1 is $C(R^{1a})(R^{1b})$, X^2 is $C(R^{2a})(R^{2b})$, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$ and Y^3 is $C(R^{3Ya})(R^{3Yb})$.

[0052] In some embodiments of a compound of Formula (VI-8), (VI-9) or (VI-10), R^{B4} is halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{B10}$, $-SR^{B10}$, $-SF_5$, or $-N(R^{10})(R^{11})$. In some embodiments, R^{B4} is -F, -Cl, -Br, -I, -Me, -Et, -Pr, -i-Pr, -c-Pr, -c-Butyl, $-CF_3$, $-CH_2CF_3$, $-CF_2H$, $-CH_2CHF_2$, $-CH=CH_2$, $-CH=CHCH_3$, $-CH=C(CH_3)_2$, $-C\equiv CH$, $-C\equiv C-CH_3$, -CN, -OH, -OMe, -OEt, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_2H$, $-OCH_2CF_3$, -SH, -SMe, $-SCHF_2$, $-SCF_3$, -SCN, $-SF_5$, $-NH_2$, $-NHCH_3$, or $-N(CH_3)_2$.

[0053] In some embodiments disclosed herein is a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9) or (VI-10) wherein:

(i) R^4 is selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, -OH, -SH, $-SF_5$, and $-NH_2$;

(ii) R^4 together with one of R^{1a}, R^{1b}, and R^{1c} form a group selected from $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-CH_2CH_2CH_2CH_2-$ optionally substituted by one, two, or three groups selected from halogen, oxo, -CN, -OH, -SH, $-SF_5$, and $-NH_2$;

(iii) R^4 together with one of R^{2a}, R^{2b}, and R^{2c} form a group selected from $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-CH_2CH_2CH_2CH_2-$ optionally substituted by one, two, or three groups selected from halogen, oxo, -CN, -OH, -SH, $-SF_5$, and $-NH_2$;

(iv) R^4 together with one of R^{3a}, R^{3b}, and R^{3c} form a group selected from $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-CH_2CH_2CH_2CH_2-$ optionally substituted by one, two, or three groups selected from halogen, oxo, -CN, -OH, -SH, $-SF_5$, and $-NH_2$;

(v) R^5 is absent;

(vi) R^5 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OH, -SH, $-SF_5$, and $-NH_2$; and/or

(vii) R^4 and R^5 together with the atoms they are attached to form a C5-7cycloalkyl or a 5-7 membered heterocyclyl optionally substituted with 1-3 R^{4a}, wherein each R^{4a} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OH, -SH, $-SF_5$, and $-NH_2$.

[0054] In some embodiments, disclosed herein is a compound having a structure of Formula (VI-5), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, disclosed herein is a compound having a structure of Formula (VI-1), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, disclosed herein is a compound having a structure of Formula (Ve), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, disclosed herein is a compound having a structure of Formula (Vf), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, disclosed herein is a compound having a structure of Formula (Vg), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, disclosed herein is a compound having a structure of Formula (Vb), or a pharmaceutically acceptable salt or stereoisomer

thereof. In some embodiments, disclosed herein is a compound having a structure of Formula (Vc), or a pharmaceutically acceptable salt or stereoisomer thereof.

[0055] In some embodiments, X^1 is $C(R^{1a})(R^{1b})$. In some embodiments, X^1 is CH_2. In some embodiments, X^1 is O. In some embodiments, X^2 is $C(R^{2a})(R^{2b})$. In some embodiments, X^2 is CH_2. In some embodiments, X^2 is O. In some embodiments, X^3 is $C(R^{3a})(R^{3b})$. In some embodiments, X^3 is CH_2. In some embodiments, X^3 is O. In some embodiments, R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, R^{2c}, R^{3a}, R^{3b}, and R^{3c} are hydrogen.

[0056] In some embodiments, Y^1 is $C(R^{1Ya})(R^{1Yb})$. In some embodiments, Y^1 is CH_2. In some embodiments, Y^1 is O. In some embodiments, Y^1 is S. In some embodiments, Y^1 is $N(R^{1Yc})$. In some embodiments, Y^2 is $C(R^{2Ya})(R^{2Yb})$. In some embodiments, Y^2 is CH_2. In some embodiments, Y^2 is O. In some embodiments, Y^2 is S. In some embodiments, Y^2 is $N(R^{2Yc})$. In some embodiments, Y^3 is $C(R^{3Ya})(R^{3Yb})$. In some embodiments, Y^1 is CH_2. In some embodiments, Y^3 is O. In some embodiments, Y^3 is S. In some embodiments, Y^3 is $N(R^{3Yc})$. In some embodiments, at least one of Y^1, Y^2 and Y^3 is O.

[0057] In some embodiments, R^{1a} is hydrogen. In some embodiments, R^{1a} is $C_{1\text{-}6}$alkyl. In some embodiments, R^{1b} is hydrogen. In some embodiments, R^{1b} is $C_{1\text{-}6}$alkyl. In some embodiments, R^{1a} and R^{1b} together with the carbon atom they are attached to form an optionally substituted $C_{3\text{-}6}$cycloalkyl (e.g., a cyclopropyl) or optionally substituted 3- to 6- membered heterocycloalkyl.

[0058] In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2a} is $C_{1\text{-}6}$alkyl. In some embodiments, R^{2b} is hydrogen. In some embodiments, R^{2b} is $C_{1\text{-}6}$alkyl. In some embodiments, R^{2a} and R^{2b} together with the carbon atom they are attached to form an optionally substituted $C_{3\text{-}6}$cycloalkyl (e.g., a cyclopropyl) or optionally substituted 3- to 6- membered heterocycloalkyl.

[0059] In some embodiments, R^{3a} is hydrogen. In some embodiments, R^{3a} is $C_{1\text{-}6}$alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is $C_{1\text{-}6}$alkyl. In some embodiments, R^{3a} and R^{3b} together with the carbon atom they are attached to form an optionally substituted $C_{3\text{-}6}$cycloalkyl (e.g., a cyclopropyl) or optionally substituted 3- to 6- membered heterocycloalkyl.

[0060] In some embodiments, R^{1a} and R^{3a} together form a $C_{1\text{-}4}$alkylene. In some embodiments, R^{1a} and R^{3a} together form $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$.

[0061] In some embodiments, R^4 is hydrogen, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$haloalkyl. In some embodiments, R^4 is hydrogen, R^4 is $C_{1\text{-}3}$alkyl. In some embodiments, R^4 is hydrogen. In some embodiments, R^4 and R^{1a} together form a $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. In some embodiments, R^4 is hydrogen. In some embodiments, R^4 and R^{1a} together form a $-CH_2CH_2-$.

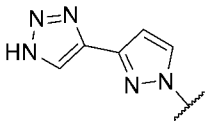
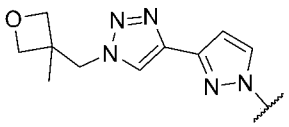
[0062] In some embodiments, R^5 is absent. In some embodiments, R^4 and R^5 together with the atoms they are attached to form a $C_{5\text{-}7}$cycloalkyl or a 5-7 membered heterocyclyl, each of which is optionally substituted with 1-3 R^{4a}. In some embodiments, R^4 and R^5 together with the atoms they are attached to form an optionally substituted $C_{5\text{-}7}$cycloalkyl. In some embodiments, R^4 and R^5 together with the atoms they are attached to form an optionally substituted C_6cycloalkyl.

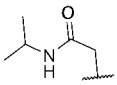
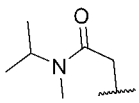
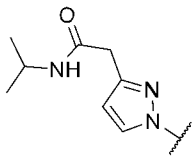
[0063] In some embodiments, R^4 and R^5 together with the atoms they are attached to form an optionally substituted 5-7 membered heterocycloalkyl. In some embodiments, R^4 and R^5 together with the atoms they are attached to form an optionally substituted 6 membered heterocycloalkyl. In some embodiments, R^4 and R^5 together with the atoms they are attached to form an optionally substituted 6 membered heterocycloalkyl comprising an oxygen.

[0064] In some embodiments, ring A is substituted. In some embodiments, each R^A is independently selected from hydrogen, halogen, -CN, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$haloalkyl. In some embodiments, ring A is unsubstituted.

[0065] In some embodiments, ring A is 5-6 membered heteroaryl. In some embodiments, ring A is 5 membered heteroaryl. In some embodiments, ring A is isoxazole. In some embodiments, ring A is oxadiazole. In some embodiments, ring A is furan.

[0066] In some embodiments, ring A is 6 membered heteroaryl. In some embodiments, ring A is pyridine.

[0067] In some embodiments, ring B is substituted with one or two R^B. In some embodiments, ring B is substituted by 1-3 R^B. In some embodiments, each R^B is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, or $-OR^{B10}$, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted. In some embodiments, each R^B is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, or $-OR^{10}$, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted. In some embodiments, each R^B is independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or $-OR^{10}$, wherein the C_{1-6}alkyl is optionally substituted. In some embodiments, each R^B is independently selected from halogen, C_{1-6}alkyl and $-OR^{10}$. In some embodiments, each R^B is independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or $-OR^{B10}$, wherein the C_{1-6}alkyl is optionally substituted. In some embodiments, each R^B is independently selected from halogen, C_{1-6}alkyl and $-OR^{B10}$. In some embodiments, each R^B is independently selected from halogen, C_{1-6}alkyl, $-OR^{B10}$, and optionally substitued C_{1-9}heteroaryl. In some embodiments, each R^B is independently selected from C_{1-6}alkyl and $-OR^{B10}$. In some embodiments, each R^B is independently selected from $-OR^{B10}$ and optionally substitued C_{1-9}heteroaryl. In some embodiments, one or more R^B is halogen. In some embodiments, one or more R^B is optionally substituted C_{1-6}alkyl. In some embodiments, one or more R^B is optionally substituted C_{1-3}alkyl. In some embodiments, one or more R^B is methyl. In some embodiments, one or more R^B is optionally substituted C_{1-9}heteroaryl. In some embodiments, one or more R^B is optionally substituted 5-6 membered heteroaryl. In some embodiments, one or more R^B is optionally substituted 5 membered heteroaryl. In some embodiments, one or more R^B is optionally substituted bicyclic heteroaryl. In some embodiments, one or more R^B is optionally substituted -C_{1-9}heteroaryl-C_{1-9}heteroaryl. In some embodiments, one or more R^B is optionally substituted -5 to 6 membered heteroaryl-5 to 6-membered heteroaryl (e.g., optionally substituted ). In some embodiments, one or more R^B is optionally substituted -5 membered heteroaryl-5-membered heteroaryl (e.g., ). In some embodiments, one or more R^B is $-OR^{10}$. In some embodiments, one or more R^B is $-OR^{B10}$. In some embodiments, one or more R^B is optionally substituted C_{2-9}heterocycloalkyl. In some embodiments, one or more R^B is optionally substituted 5-7 membered heterocycloalkyl. In some embodiments, one or more R^B is optionally substituted bicyclic heterocycloalkyl. In some embodiments, two or more R^B are independently $-OR^{B10}$. In some embodiments, two R^B are independently $-OR^{B10}$. In some embodiments, R^B is substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}heteroalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-C(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, wherein the C_{1-6}alkyl, C_{1-6}heteroalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{1-9}heteroaryl, or $-CH_2-C_{1-9}$heteroaryl is optionally subsituted, e.g., optionally substituted with one, two, or

three groups selected from halogen, -CN, hydroxy, oxo, C_{1-6}alkyl, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$,C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy. In some embodiments, R^B is substituted with one or more C_{1-6}heteroalkyl, which is optionaly substituted. In some embodiments, R^B is substituted with one or more C_{1-6}heteroalkyl, which is optionaly substituted with one, two, or three groups selected from halogen, -CN, hydroxy, oxo, C_{1-6}alkyl, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$,C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy. In some embodiments, the C_{1-6}heteroalkyl is  or  . In some embodiments, R^B is  . In some embodiments, R^B is substituted with one or more -CH_2-C_{2-9}heterocycloalkyl, which is optionaly substituted.

[0068] In some embodiments, each R^B is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{B10}, -SR^{B10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$. In some embodiments, the -OR^{B10} is -OR^{10}, and the -SR^{B10} is -SR^{10}.

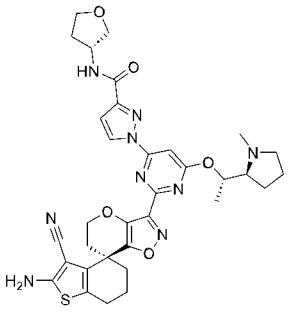
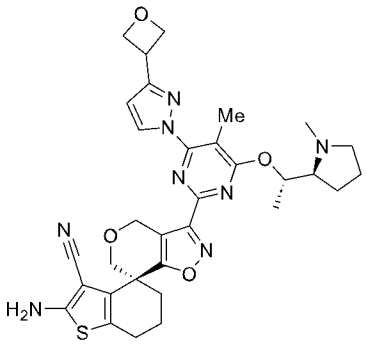
[0069] In some embodiments, each R^B is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{B10}, -SR^{B10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$, and wherein the C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-}

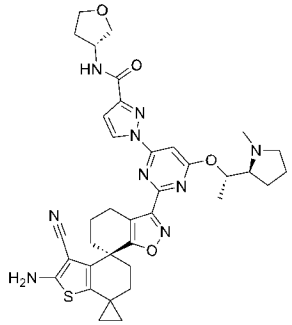
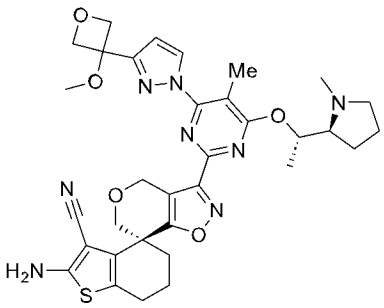
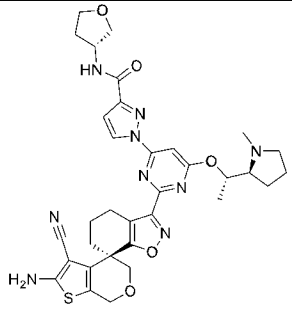
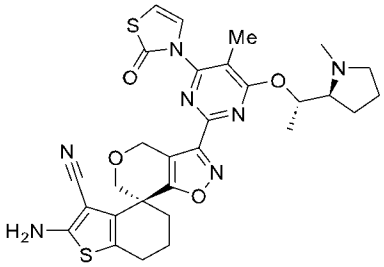
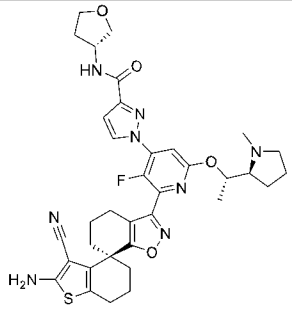
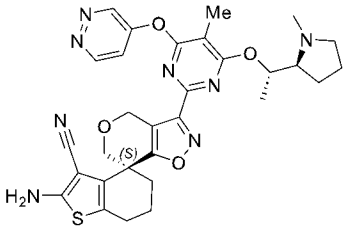
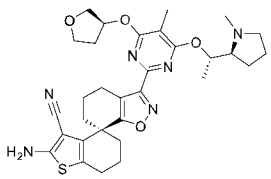
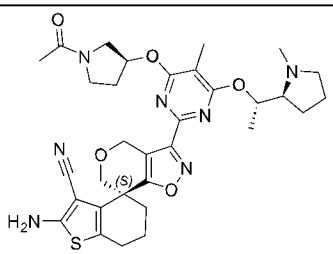
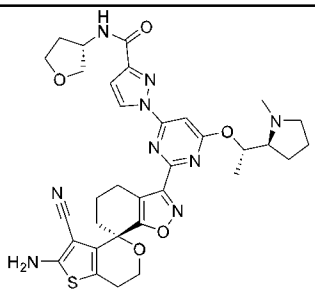
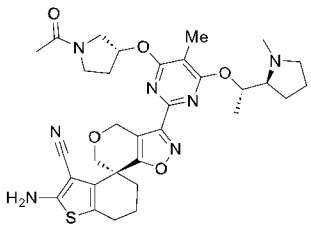
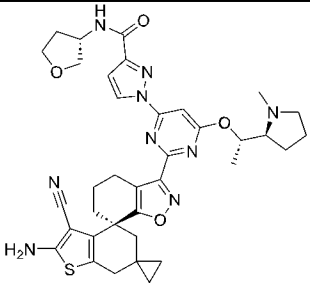
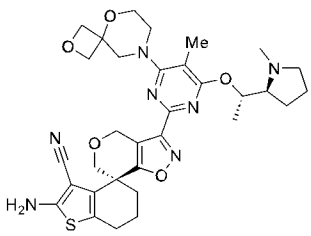
$_{9}$heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, or -CH_2-C_{1-9}heteroaryl is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, oxo, C_{1-6}alkyl, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$,C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy.

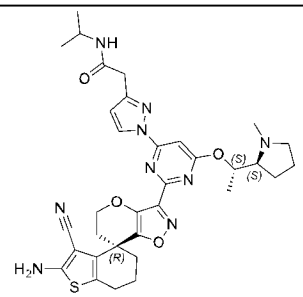
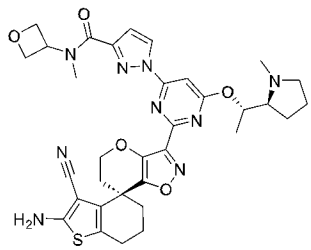
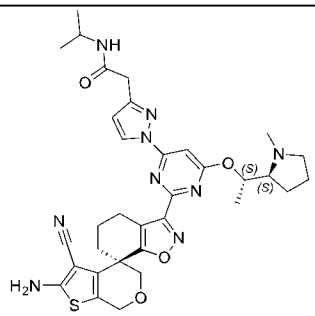
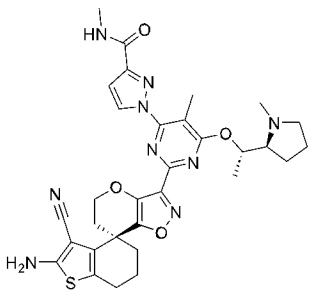
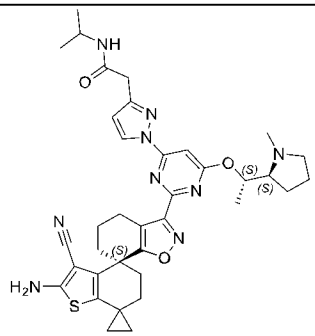
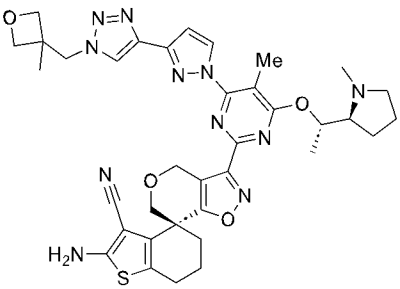
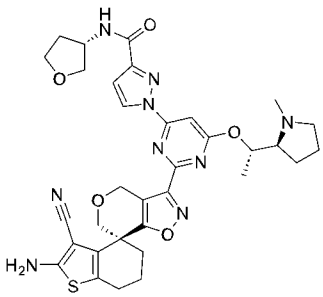
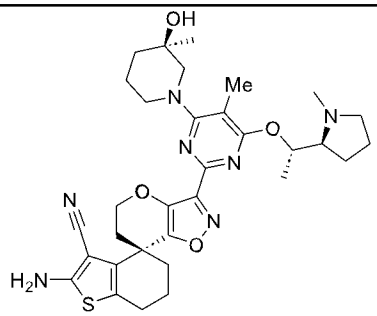
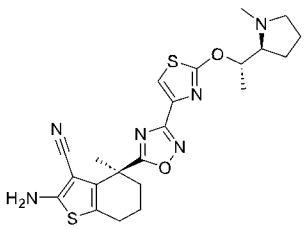
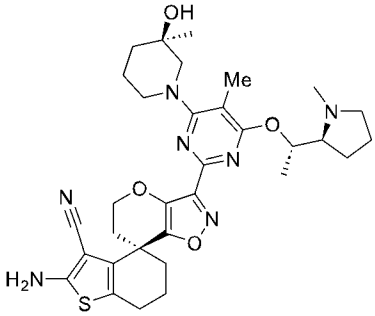
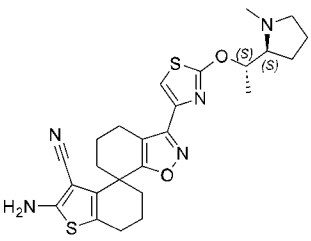
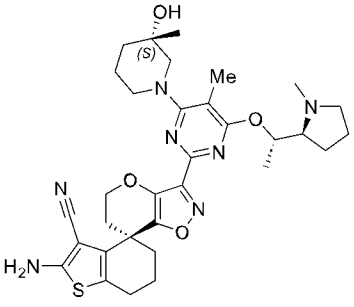
[0070] In some embodiments, each R^{B10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, -C_{1-3}alkylene-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -C_{1-3}alkylene-C_{2-9}heterocycloalkyl, -C_{1-3}alkylene-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and -C_{1-3}alkylene-C_{1-9}heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, -C_{1-3}alkylene-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -C_{1-3}alkylene-C_{2-9}heterocycloalkyl, -C_{1-3}alkylene-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and -C_{1-3}alkylene-C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, -$C(O)R^{13}$, oxo, C_{1-6}alkyl, C_{1-6}heteroalkyl, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{12})S(O)_2R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein each of the C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, and C_{2-9}heterocycloalkyl is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, oxo, C_{1-6}alkyl, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$,C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy. In some embodiments, R^{B10} is optionally substituted C_{1-6}alkyl. In some embodiments, R^{B10} is optionally substituted C_{1-6}heteroalkyl. In some embodiments, R^{B10} is optionally substituted C_{3-6}cycloalkyl or -C_{1-3}alkylene-C_{3-6}cycloalkyl. In some embodiments, R^{B10} is optionally substituted C_{2-9}heterocycloalkyl. In some embodiments, R^{B10} is optionally substituted 5-6 membered heterocycloalkyl. In some embodiments, R^{B10} is optionally substituted -C_{1-3}alkylene-C_{2-9}heterocycloalkyl. In some embodiments, R^{B10} is optionally substituted -CH_2-C_{2-9}heterocycloalkyl. In some embodiments, R^{B10} is optionally substituted -CH_2-5-6 membered heterocycloalkyl. In some embodiments, R^{B10} is optionally substituted -C_{1-3}alkylene-C_{6-10}aryl or C_{6-10}aryl. In some embodiments, R^{B10} is optionally substituted C_{1-9}heteroaryl. In some embodiments, R^{B10} is optionally substituted 5-6 membered heteroaryl. In some embodiments, R^{B10} is optionally substituted -C_{1-3}alkylene-C_{1-9}heteroaryl. In some embodiments, R^{B10} is substituted with one or more selected from halogen, -CN, hydroxy, -$C(O)R^{13}$, oxo, C_{1-6}alkyl, C_{1-6}heteroalkyl, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, and -OR^{10}.

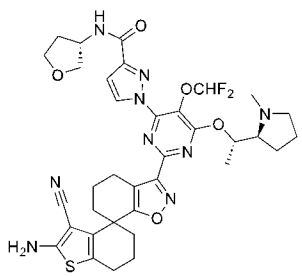
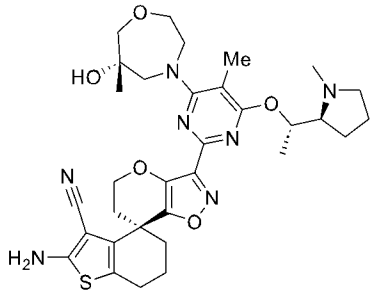
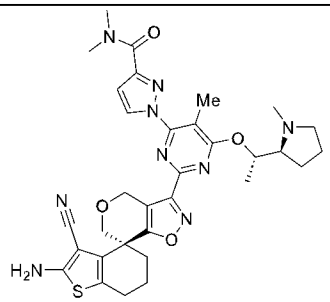
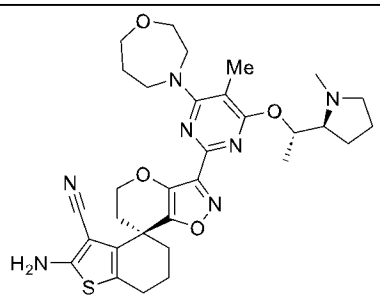
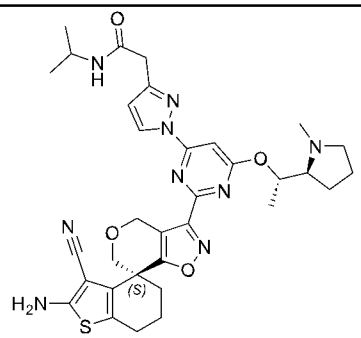
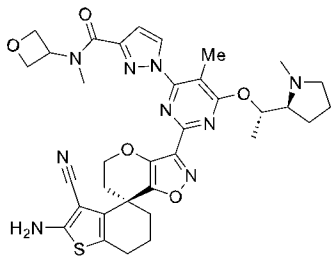
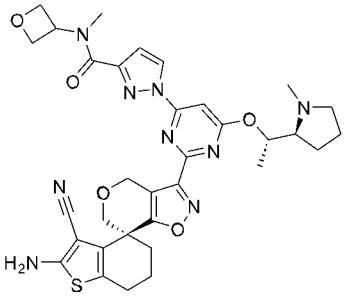
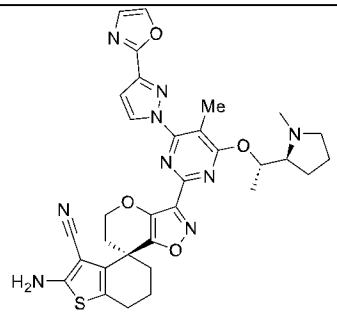
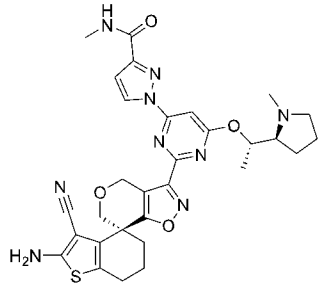
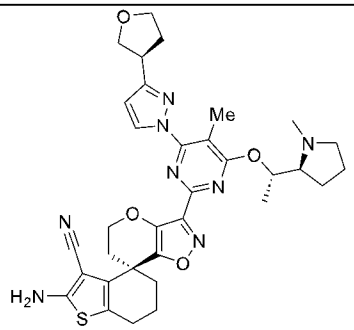
[0071] In some embodiments disclosed herein is a compound of Table 1 or a pharmaceutically acceptable salt or stereoisomer thereof.

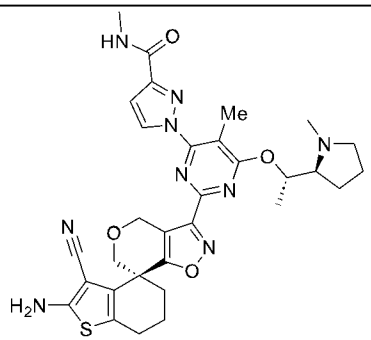
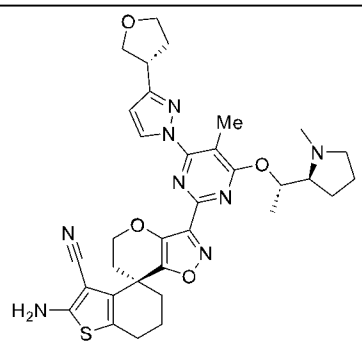
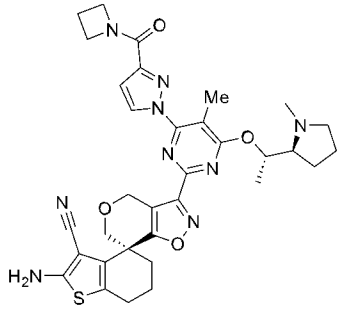
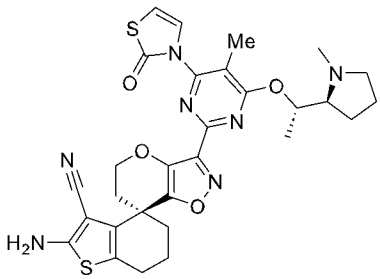
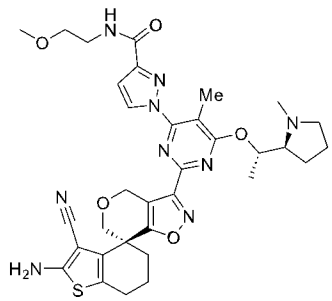
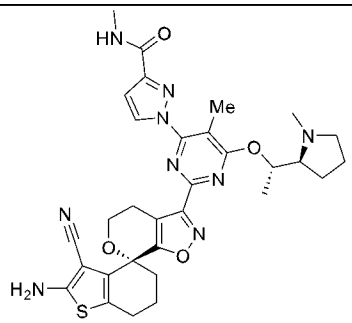
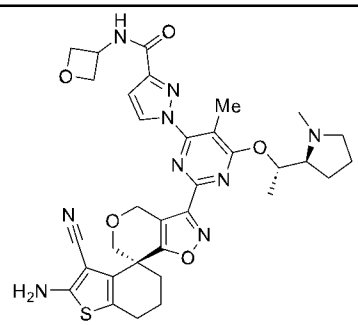
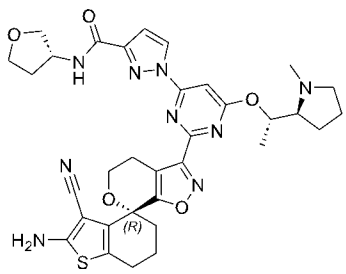
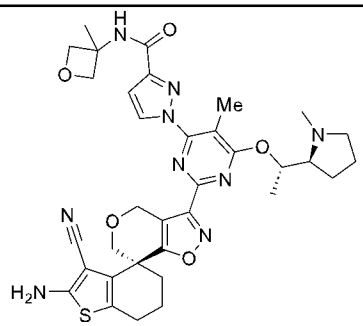
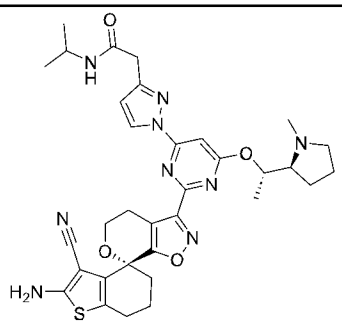
Table 1

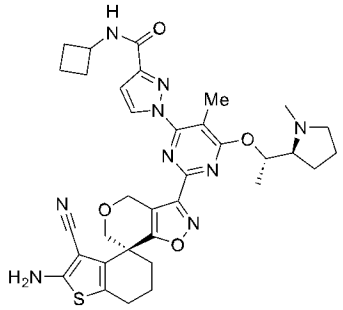
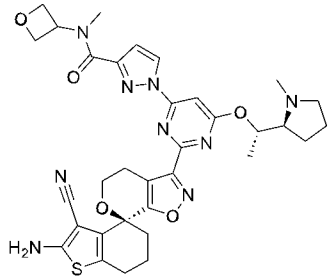
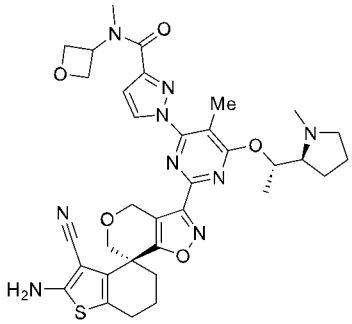
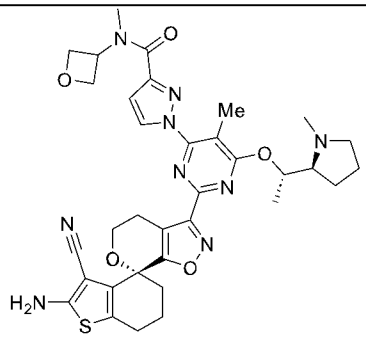
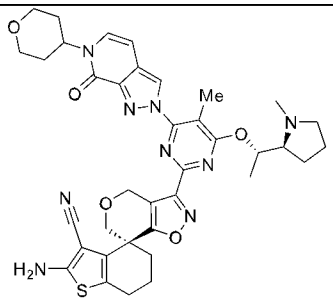
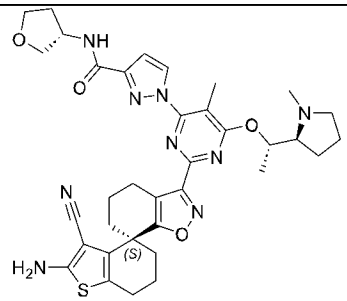
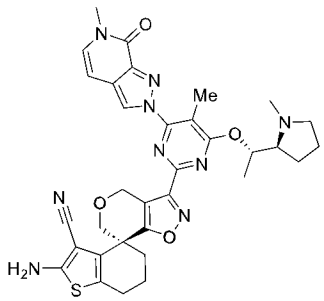
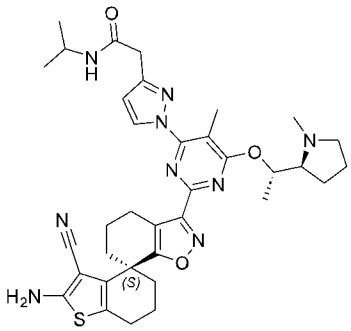
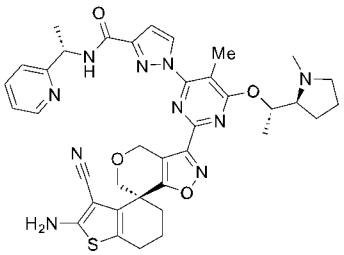
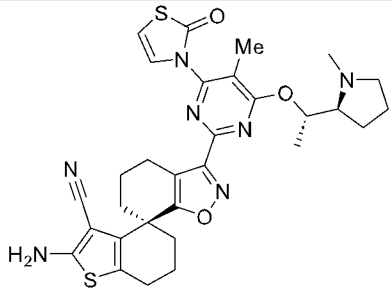
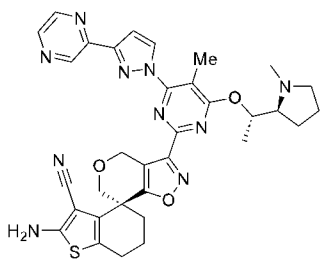
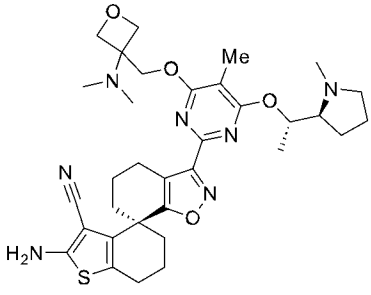
Cmpd ID	Structure	Cmpd ID	Structure
1A		31B	

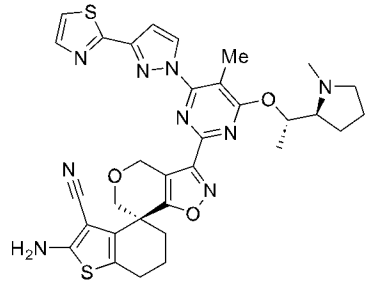
2A		32B	
3A		33B	
4A		34A	
5A		35B	
6A		36B	
7A		37B	

8A		38B	
9A		39B	
10A		40B	
11A		41A	
12A		41B	
13		42B	

14		43B	
15B		44A	
16B		45B	
17B		46B	
18B		47B	

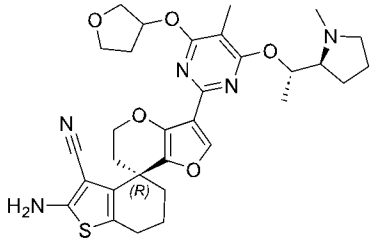
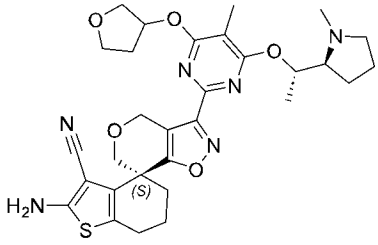
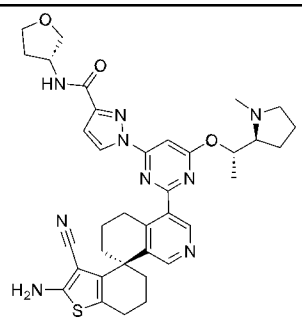
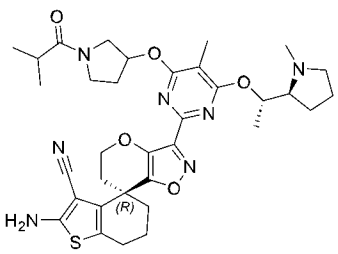
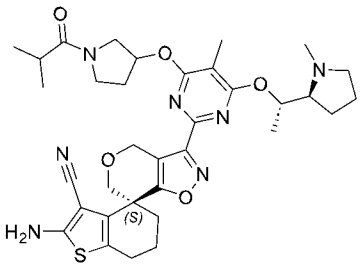
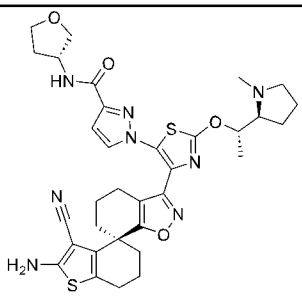
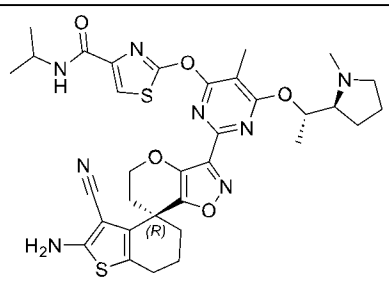
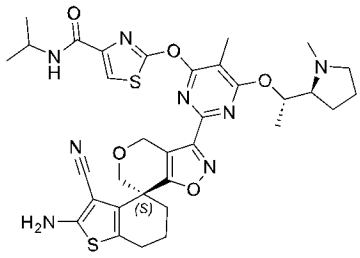
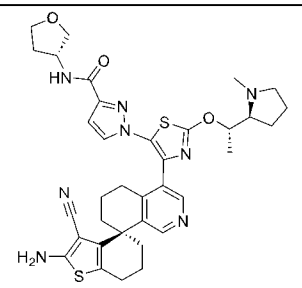
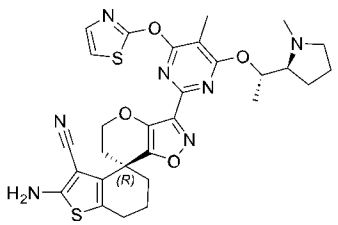
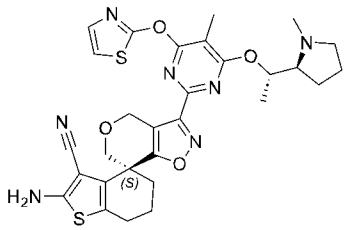
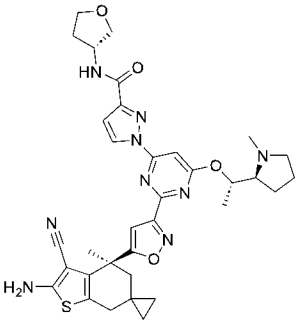
19B		48B	
20B		49B	
21B		50B	
22B		51B	
23B		52A	

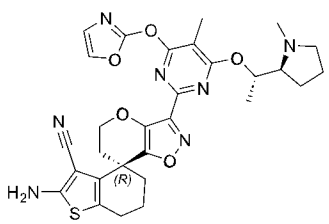
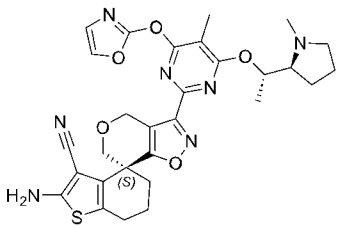
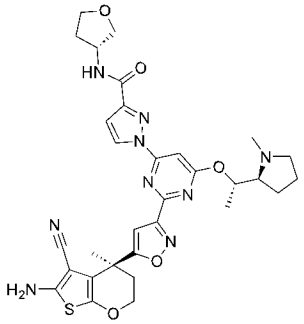
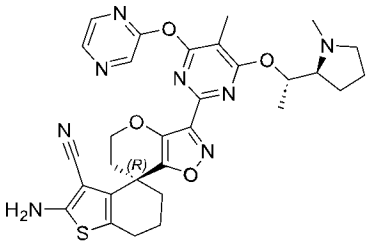
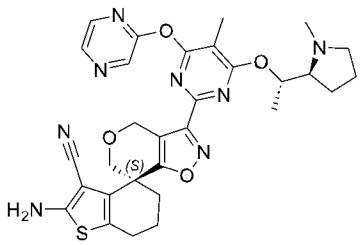
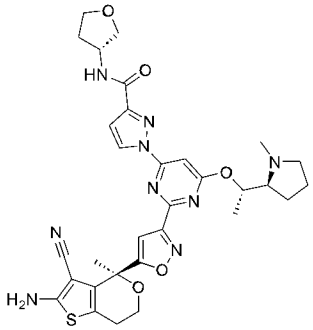
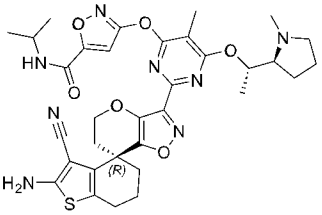
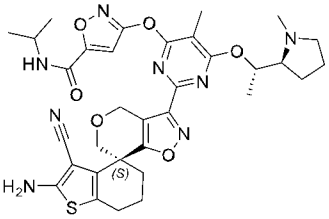
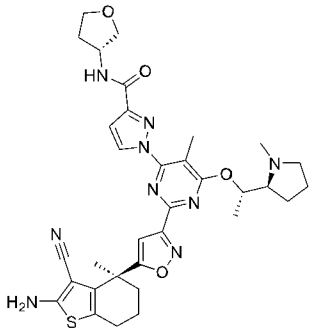
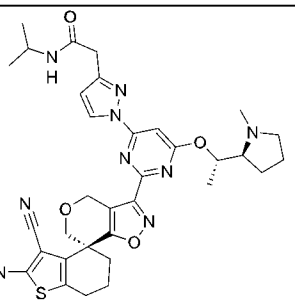
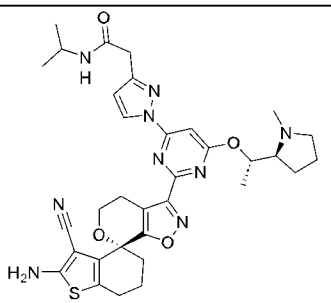
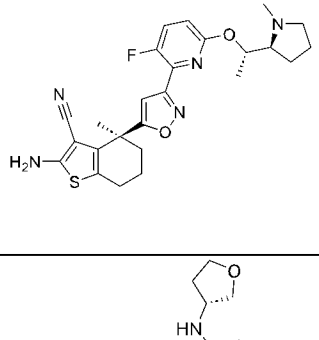
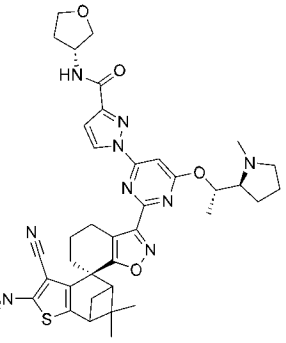
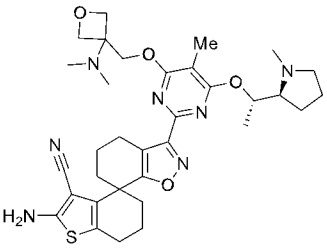
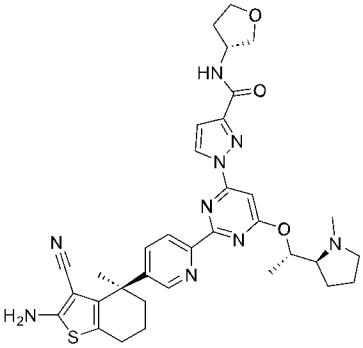
24B		53B	
25B		54B	
26B		55B	
27A		56B	
28B		57B	
29B		58B	

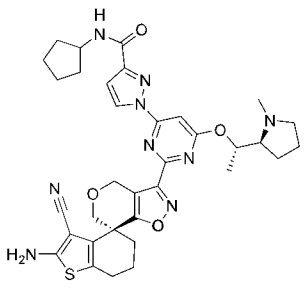
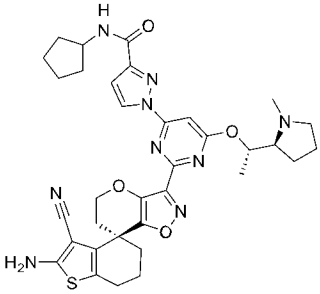
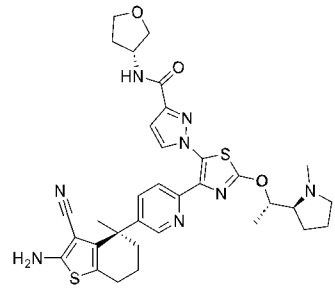
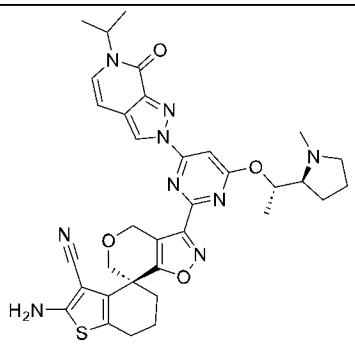
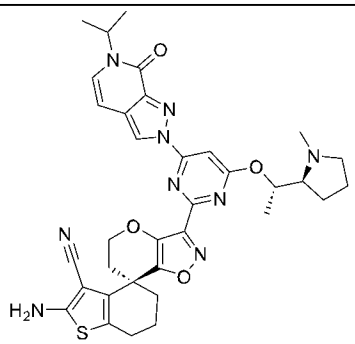
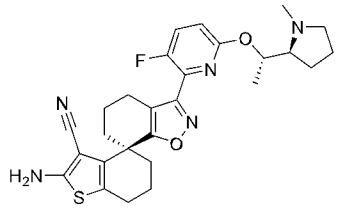
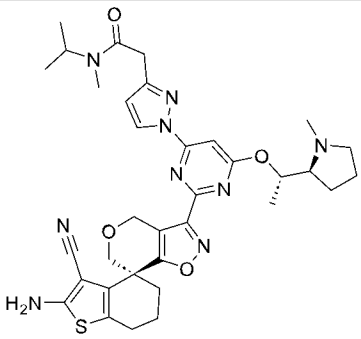
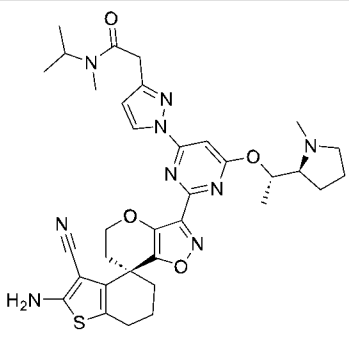
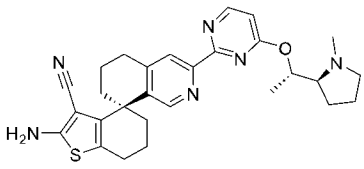
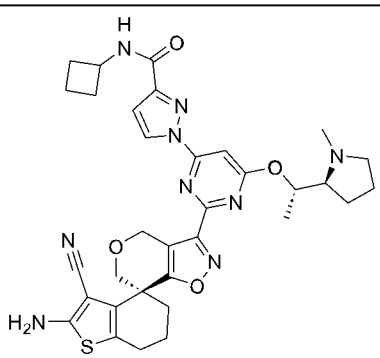
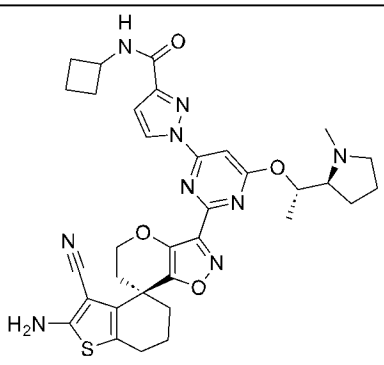
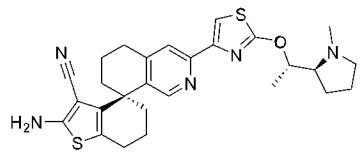
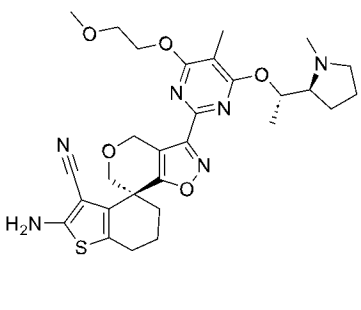
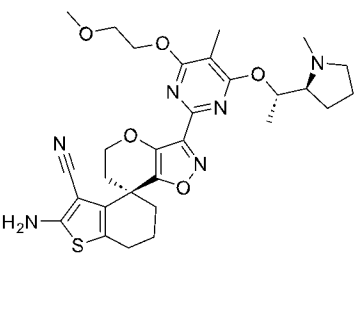
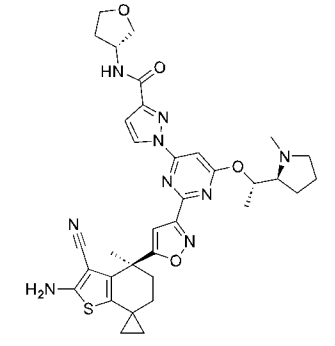
30A			

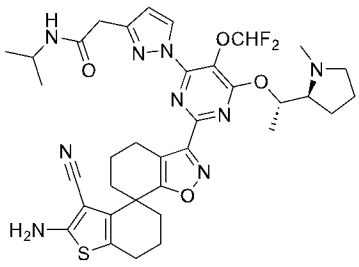
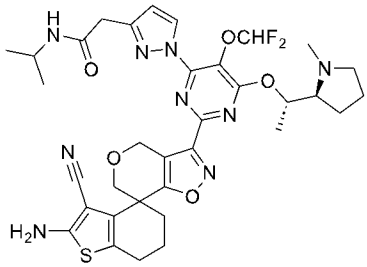
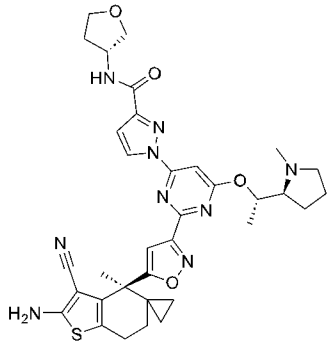
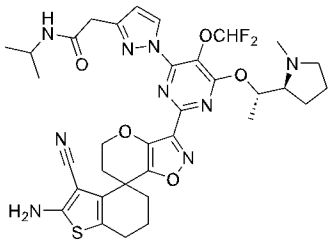
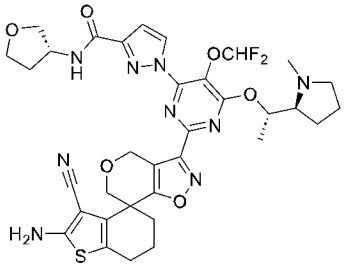
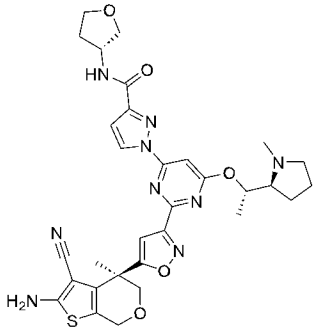
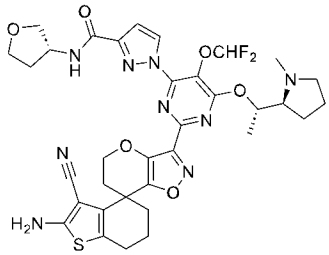
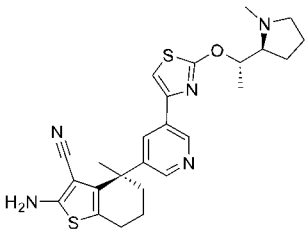
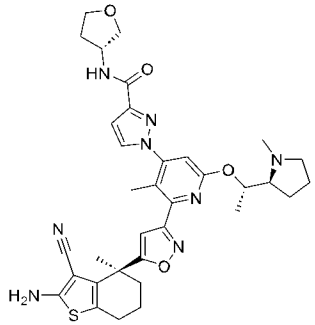
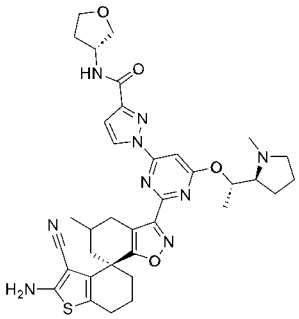
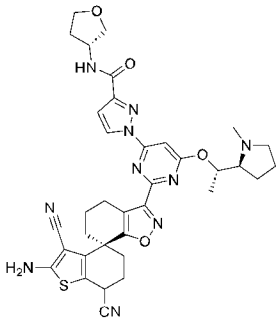
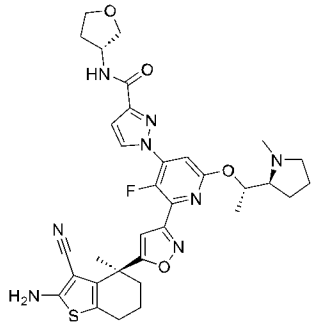
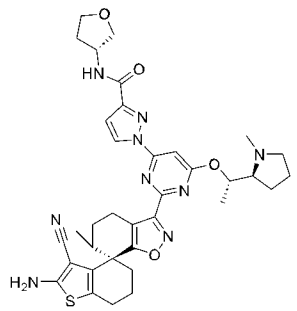
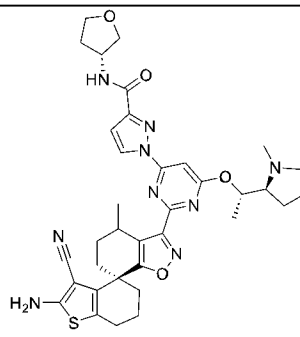
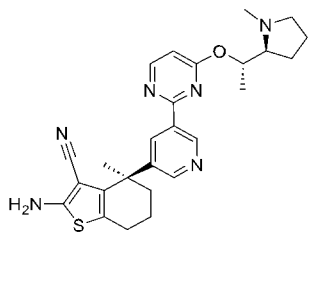
[0072] In some embodiments disclosed herein is a compound of Table 2 or a pharmaceutically acceptable salt or stereoisomer thereof.

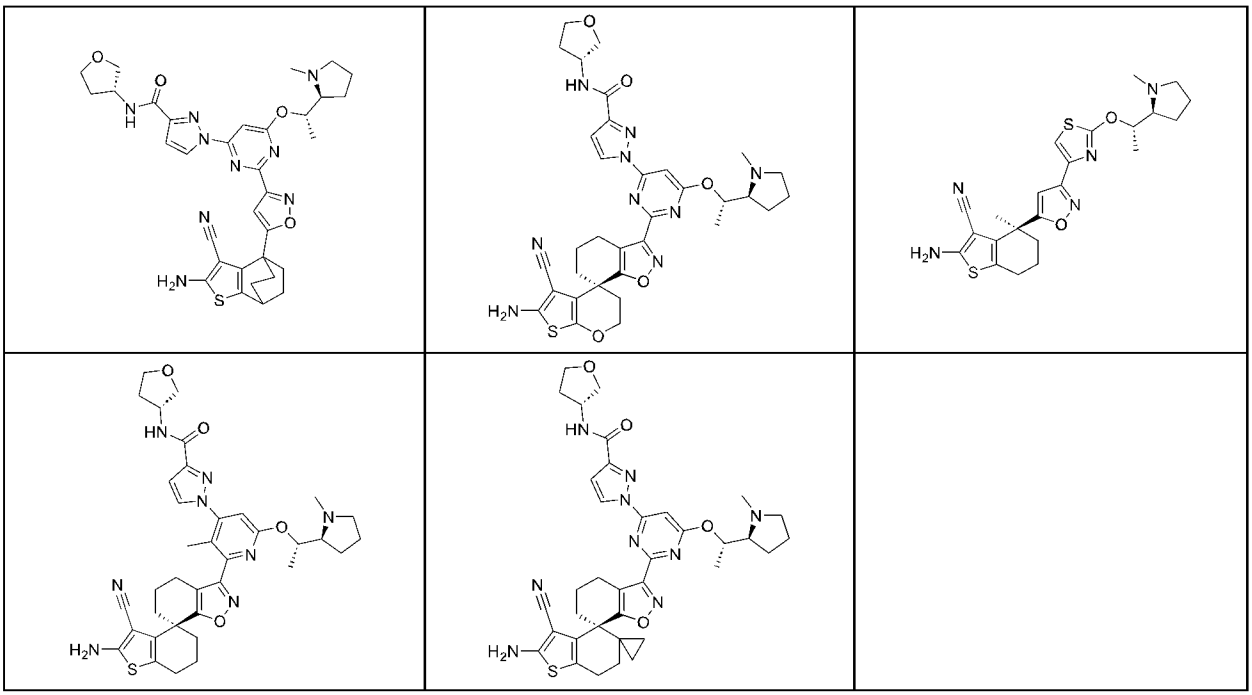
Table 2



Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[0073] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[0074] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic

mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^{2}H (D), ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the pharmaceutically acceptable salts or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability.

[0075] In some embodiments, the abundance of deuterium in each of the substituents disclosed herein is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar. In some embodiments, one or more of the substituents disclosed herein comprise deuterium at a percentage higher than the natural abundance of deuterium. In some embodiments, one or more ^{1}H are replaced with one or more deuteriums in one or more of the substituents disclosed herein.

[0076] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[0077] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0078] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0079] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[0080] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or

organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

[0081] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[0082] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Tautomers

[0083] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Method of Treatment

[0084] Disclosed herein is a method of treating a disease in which inhibition of KRAS mutation is beneficial, the method comprising administering a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments disclosed herein is a method of treating a disease in which inhibition of KRAS mutation is beneficial, the method comprising administering a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments disclosed herein is a method of treating a disease in which inhibition of KRAS mutation is beneficial, the method comprising administering a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId),

(IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments disclosed herein is a method of treating a disease in which inhibition of KRAS mutation is beneficial, the method comprising administering a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0085] Disclosed herein is a method of treating a disease or disorder associated with KRAS mutation, the method comprising administering to the subject a compound disclosed herein, e.g., a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), , or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments disclosed herein is a method of treating a disease or disorder associated with KRAS mutation, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments disclosed herein is a method of treating a disease or disorder associated with KRAS mutation, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments disclosed herein is a method of treating a disease or disorder associated with KRAS mutation, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0086] Disclosed herein is a method of treating cancer in a subject, the method comprising administering to the subject a compound disclosed herein, e.g., a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the cancer is selected from intra-hepatic cholangiocarcinoma, urothelial cancer, gastric cancer, bladder cancer, breast cancer, endometrial cancer, kidney cancer, liver cancer, lung cancer, melanoma, pancreatic cancer, prostate cancer, or thyroid cancer. In some embodiments is a method of treating intra-hepatic cholangiocarcinoma in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating urothelial cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating gastric cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating bladder cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating breast cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating endometrial cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating kidney cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method

of treating liver cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating lung cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating melanoma in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating pancreatic cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating prostate cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments is a method of treating thyroid cancer in a subject, the method comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof.

Dosing

[0087] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[0088] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder, or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of or risk factor for the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

Routes of Administration

[0089] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

Pharmaceutical Compositions/Formulations

[0090] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds of this disclosure may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, and topical routes of administration.

[0091] In another aspect, provided herein are pharmaceutical compositions comprising a compound disclosed here, e.g., a compound of Formula (I), (A-1), (A-2), (A-3), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId),(III), (IIIa), (IIIb), (IIIc), (IIId), (IV), (IVa), (IVb), (IVc), (IVd), (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), (VI-7), (VI-8), (VI-9), (VI-10), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf) or (Vg), or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. In some embodiments is a pharmaceutical compositions comprising a compound of Formula (I) described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. In some embodiments is a pharmaceutical compositions comprising a compound of Formula (Ia) described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. In some embodiments is a pharmaceutical compositions comprising a compound of Formula (Ib) described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. In some embodiments is a pharmaceutical compositions comprising a compound of Formula (Ic) described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. In some embodiments is a pharmaceutical compositions comprising a compound of Formula (Id) described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient.

[0092] Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

EXAMPLES

[0093] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

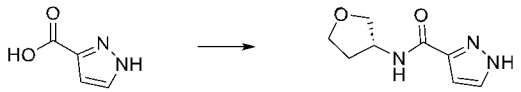
[0094] For the purpose of illustration, the following examples are included. The Examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. However, it is to be understood that these examples do not limit the present disclosure and are only meant to suggest a method of practicing the present disclosure. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds of the present disclosure, and alternative methods for preparing the compounds of the present disclosure are deemed to be within the scope of the present disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents and building blocks known in the art other than those described, and/or by making routine modifications of reaction conditions. Besides, persons skilled in the art will also understand that individual steps described herein or in the separate batches of a compound may be combined. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure. The following description is, therefore, not intended to limit the scope of the present disclosure, but rather is specified by the claims appended hereto..

[0095] As used above, and throughout the description of the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN acetonitrile
AcOH acetic acid
Ac acetyl
Bn benzyl
BOC or Boc *tert*-butyl carbamate
i-Bu *iso*-butyl
t-Bu *tert*-butyl
CDI 1,1-carbonyldiimidazole
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE dichloroethane ($ClCH_2CH_2Cl$)
DCM dichloromethane (CH_2Cl_2)
DIBAL-H diisobutylaluminum hydride
DIPEA or DIEA diisopropylethylamine
DMAP 4-(*N,N*-dimethylamino)pyridine
DME 1,2-dimethoxyethane
DMF *N,N*-dimethylformamide
DMA *N,N*-dimethylacetamide
DMPU *N,N'*-dimethylpropyleneurea
DMSO dimethylsulfoxide
DPPA diphenyl phosphoryl azide
Dppf or dppf 1,1'-bis(diphenylphosphino)ferrocene
EDC or EDCI *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
eq equivalent(s)
Et ethyl
Et_2O diethyl ether
EtOH ethanol
EA or EtOAc ethyl acetate
HATU 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOBt 1-hydroxybenzotriazole
HPLC high performance liquid chromatography
KOAc potassium acetate
KOtBu potassium *tert*-butoxide
KHMDS potassium bis(trimethylsilyl)amide
NaHMDS sodium bis(trimethylsilyl)amide
LiHMDS lithium bis(trimethylsilyl)amide
LAH/$LiAlH_4$ lithium aluminum anhydride
LCMS liquid chromatography mass spectrometry
Me methyl
MeOH methanol
MS mass spectroscopy
MTBE methyl *tert*-butyl ether
NBS *N*-bromosuccinimide

NMP *N*-methyl-pyrrolidin-2-one
NMR nuclear magnetic resonance
PE petroleum ether
Ph phenyl
iPr/i-Pr *iso*-propyl
PyAOP 7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RP-HPLC reverse-phase high-pressure liquid chromatography
rt room temperature
SEM 2-(trimethylsilyl)ethoxymethyl
TBS *tert*-butyldimethylsilyl
TEA triethylamine
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMS trimethylsilyl

[0096] Synthetic route of Fragment SC-1

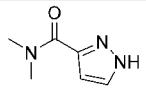
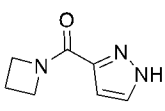
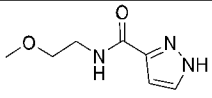


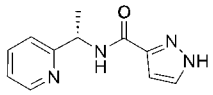
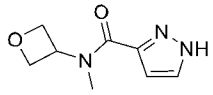
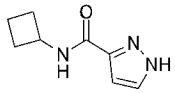
SC-1-1 SC-1

[0097] To a solution of 1H-pyrazole-3-carboxylic acid (5.0 g, 44.60 mmol, 1.00 eq) in DCE (100.0 ml) was added (R)-tetrahydrofuran-3-amine hydrochloride (6.0 g, 49.10 mmol, 1.10 eq), DIEA (23.1 g, 178.00 mmol, 4.00 eq) and HATU (22.1 g, 58.00 mmol, 1.30 eq) at 0 °C. The mixture was allowed to rt and stirred for 4 hr. The reaction mixture was directly concentrated in vacuum to give a residue. The residue was purified by column chromatography (DCM: MeOH = 20: 1) to afford **fragment SC-1** as a white solid. LC-MS (ESI+): *m/z* = 182.1 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.23 (s, 1H), 8.13 (d, *J* = 6.8 Hz,1H), 7.81 (s, 1H), 6.63 (s, 1H), 4.48-4.38 (m, 1H), 3.88 – 3.78 (m, 2H), 3.74 – 3.64 (m, 1H), 3.59 – 3.49 (m, 1H), 2.16 – 1.86 (m, 2H).

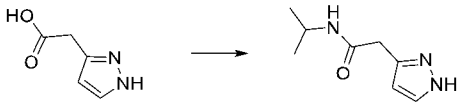
[0098] **The following compounds** in Table 3 were prepared using similar procedures as described in **fragment SC-1**.

Table 3

Structure	MS	HNMR
 **SC-3**	LC-MS (ESI+): *m/z* = 140.2 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 3.32 (s, 3H), 3.14 (s, 3H).
 **SC-4**	LC-MS (ESI+): *m/z* = 152.1 $[M+H]^+$.	^{1}H NMR (400 MHz, D_2O) δ 7.71 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 4.47 (t, *J* = 8.0 Hz, 2H), 4.13 (t, *J* = 7.6 Hz, 2H), 2.38 - 2.26 (m, 2H).
 **SC-5**	LC-MS (ESI+): *m/z* = 170.2 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 3. 72 - 3.59 (m, 4H), 3.49 (s, 3H).

 **SC-6**	LC-MS (ESI+): *m/z* = 217.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.60 - 13.16 (m, 1H), 8.63 - 8.39 (m, 2H), 7.89 - 7.72 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.33 - 7.22 (m, 1H), 6.72 - 6.58 (m, 1H), 5.26 - 5.09 (m, 1H), 1.58 - 1.36 (m, 3H).
 **SC-7**	LC-MS (ESI+): *m/z* = 182.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 7.81 (s, 1H), 6.63 - 6.45 (m, 1H), 5.82 - 5.04 (m, 1H), 4.73 - 4.52 (m, 4H), 3.31 - 3.13 (m, 3H)
 **SC-8**	LC-MS (ESI+): *m/z* = 166.1 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.95 - 12.07 (m, 1H), 8.45 - 8.09 (m, 1H), 7.80 - 7.63 (m, 1H), 6.71 - 6.56 (m, 1H), 4.45 - 4.27 (m, 1H), 2.22 - 2.00 (m, 4H), 1.69 - 1.56 (m, 2H).

[0099] Synthetic route of Fragment SC-2

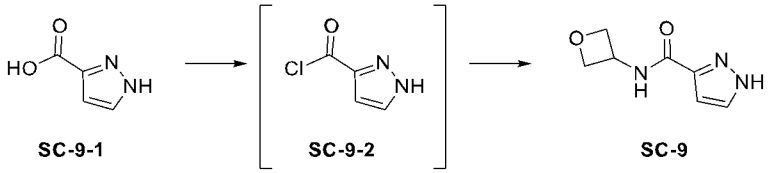


SC-2-1 SC-2

[00100] To a solution of compound **SC-2-1** (1.2 g, 9.52 mmol), propan-2-amine (0.844 g, 14.3 mmol) and TEA (2.65 mL, 19.0 mmol) in DCM (20.0 mL) was added EDCI (2.19 g, 11.4 mmol) and HOBt (1.75 g, 11.4 mmol) and the reaction mixture was stirred at rt for 12 hours. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Column: PC18 150×30mm, Mobile Phase: water (FA)-ACN, Mobile Phase B: acetonitrile Flow rate: 25 mL/min, gradient condition from 1% B to 30%) and lyophilized to give **fragment SC-2** as a white solid. LC-MS (ESI+): *m/z* = 168.7 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 – 7.70 (m, 2H), 6.42 (s, 1H), 6.26 (s, 1H), 4.10 – 3.99 (m, 1H), 3.67 (s, 2H), 1.20 – 1.05 (m, 6H).

[00101] Synthetic route of Fragment SC-9



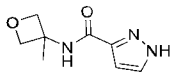
SC-9-1 SC-9-2 SC-9

To a solution of **SC-9-1** (500 mg, 4.46 mmol, 1.00 eq) in $SOCl_2$ (2.0 mL) was added DMF (0.017 mL, 0.22 mmol, 0.05 eq), then the reaction mixture was stirred at 80 ℃ for 1 h. The reaction mixture was cooled to rt and concentrated in vacuum to afford crude **SC-9-2**. To a solution of oxetan-3-amine (252.0 mg, 3.45 mmol, 0.90 eq) and DIEA (1.0 mL, 5.75 mmol, 1.50 eq) in DCM (5.0 mL) was added a solution of the above mentioned **SC-9-2** in DCM (5.0 mL) dropwise at 0 °C, then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was directly concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 25/1) to afford **SC-9** as a light yellow solid. LC-MS (ESI+): *m/z* = 168.2 $[M+H]^+$.

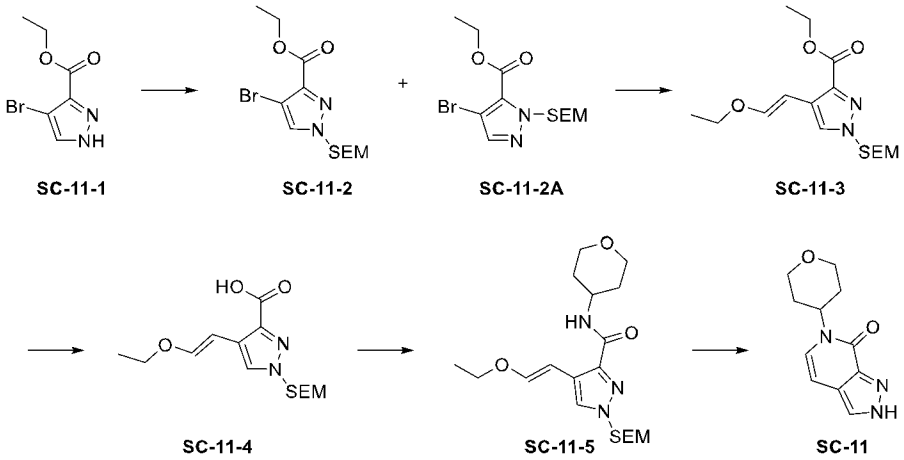
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.56 - 13.25 (m, 1H), 9.08 - 8.02 (m, 1H), 7.82 - 7.54 (m, 1H), 6.92 - 6.64 (m, 1H), 5.08 - 4.90 (m, 1H), 4.82 - 4.54 (m, 4H).

[00102] The following compounds in Table 4 were prepared using similar procedures as described in **fragment SC-9**.

Table 4

Structure	MS	HNMR
 **SC-10**	LC-MS (ESI+): *m/z* = 182.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.51 - 13.24 (m, 1H), 8.82 - 8.60 (m, 1H), 7.82 -7.53 (m, 1H), 6.82 - 6.61 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 1H), 4.37 - 4.31 (m, 2H), 1.57 (s, 3H).

[00103] Synthetic route of Fragment SC-11



Step 1:

To a mixture of **compound SC-11-1** (10.0 g, 45.7 mmol) in THF (100 mL) was added sodium hydride (2.92 g, 73.0 mmol, 60% purity) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 0.5 h, then SEM-Cl (9.72 ml, 54.8 mmol) was added and the reaction mixture was stirred at rt for 7 h. The reaction mixture was dropwise quenched with NH_4Cl (15 mL), diluted with H_2O (30 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give residue. The residue was purified by flash column chromatography (SiO2, PE/EA = 9/1) to give **compound SC-11-2** as a colorless oil and **compound SC-11-2A** as a colorless oil too.

SC-11-2

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.47 (s, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.64 - 3.47 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 0.96 - 0.85 (m, 2H), -0.01 (s, 9H).

SC-11-2A

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 5.82 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.67 - 3.59 (m, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.02 - 0.92 (m, 2H), 0.09 - 0.01 (m, 9H).

Step 2:

To a mixture of **compound SC-11-2** (14.5 g, 41.5 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.04 g, 45.7 mmol) and K_2CO_3 (17.2 g, 125 mmol) in 1,4-Dioxane (80 mL) and water (20 mL) was added Pd(dppf)Cl_2 (3.04 g, 4.15 mmol) and the reaction mixture was stirred at 110 ℃ under N2 atmosphere for 3 h. The reaction mixture was cooled to rt and filtered with celite. The filtrate was diluted with EA (150 mL) and washed with water (100 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The reside was purified by flash column chromatography (SiO2, PE/EA = 3/1) to afford **compound SC-11-3** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.92 (d, *J* = 13.2 Hz, 1H), 6.21 (d, *J* = 13.2 Hz, 1H), 5.45 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.91 (q, *J* = 7.2 Hz, 2H), 3.65 - 3.46 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 0.99 - 0.87 (m, 2H), 0.01 - -0.04 (m, 9H).

Step 3:

To a solution of **compound SC-11-3** (11.9 g, 34.9 mmol) in MeOH (30 mL) was added NaOH aq. (2M, 87 mL, 174 mmol). The reaction mixture was stirred at rt for 12 h, then heated to 50 ℃ and stirred for 1 h. 2N HCl was added to the reaction mixture until pH = 5 and the reaction mixture was extracted with ethyl acetate (100 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford crude **compound SC-11-4** as a white solid. The crude compound 5 was directly used in the next step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 6.99 (d, *J* = 13.2 Hz, 1H), 6.23 (d, *J* = 13.2 Hz, 1H), 5.35 (s, 2H), 3.80 (q, *J* = 7.2 Hz, 2H), , 3.55 - 3.45 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.89 - 0.76 (m, 2H), -0.04 (s, 9H).

Step 4:

To a solution of **compound SC-11-4** (800 mg, 2.56 mmol), HATU (1.17 g, 3.07 mmol) and DIPEA (1.34 mL, 7.68 mmol) in DMF (5 mL) was added tetrahydro-2*H*-pyran-4-amine (311 mg, 3.07 mmol) and the reaction mixture was stirred at 50 ℃ for 1 h. The reaction mixture was diluted with EA (20 mL) and washed with sat. $NaHCO_3$ aq. (15 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SIO2, PE/EA = 1/1) to afford **compound SC-11-5** as a yellow oil. LC-MS (ESI+): *m/z* = 396.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.97 (d, *J* = 13.2 Hz, 1H), 6.88 - 6.80 (m, 1H), 6.34 (d, *J* = 13.2 Hz, 1H), 5.35 (s, 2H), 4.27 - 4.08 (m, 1H), 4.04 - 3.94 (m, 2H), 3.91 (q, *J* = 7.2 Hz, 2H), 3.65 - 3.41 (m, 4H), 2.03 - 1.90 (m, 2H), 1.64 - 1.51 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.00 - 0.84 (m, 2H), 0.00 (s, 9H).

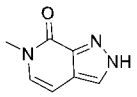
Step 5:

TFA (2.16 mL, 28.1 mmol) was added to a solution of **compound SC-11-5** (740 mg, 1.87 mmol) in THF (2 mL) and the reaction mixture was stirred at 70 ℃ for 1 h. The reaction mixture was cooled to rt and directly concentrated in vacuo to give a residue. The residue was purified by liquid chromatography (Claricep flash C18 column, 20-35 μm, 40 g, 14 -34% (v/v) (at 18% of MeCN, a peak begins to find) MeCN/water (0.5% NH_3•H_2O)) to give a **compound SC-11** as a pale yellow solid. LC-MS (ESI+): *m/z* = 219.8 $[M+H]^+$.

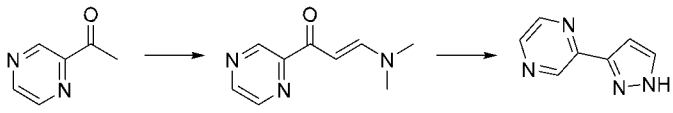
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 5.42 - 5.25 (m, 1H), 4.22 - 4.07 (m, 2H), 3.76 - 3.55 (m, 2H), 2.14 - 1.79 (m, 4H).

[00104] The following compounds in Table 5 were prepared using similar procedures as described in **fragment SC-11**.

Table 5

Structure	MS	HNMR
 **SC-12**	LC-MS (ESI+): m/z = 149.7 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-d_6) δ 14.15 - 13.89 (m, 1H), 7.95 - 7.84 (m, 1H), 7.25 - 7.12 (m, 1H), 6.62 - 6.50 (m, 1H), 3.54 - 3.45 (m, 3H).

[00105] Synthetic route of Fragment SC-13



Step 1:

A solution of **compound SC-13-1** (2.00 g, 16.4 mmol) in DMF-DMA (4.39 mL, 32.8 mmol) and TEA (2.28 mL, 16.4 mmol) was heated to 110℃ and stirred for 16 h. The reaction mixture was then cooled to room temperature and a precipitate was formed. The suspension was diluted with tert-butyl methyl ether (20 mL) and filtrated. The filter cake was collected and washed with tert-butyl methyl ether (30 mL). This filtered cake was triturated with tert-butyl methyl ether (30 mL) to afford **compound SC-13-2** as a yellow solid. LC-MS (ESI+): m/z = 178.2 $[M+H]^+$.

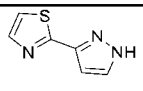
Step 2:

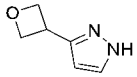
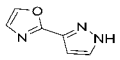
To a solution of **compound SC-13-2** (2.24 g, 12.6 mmol) in ethanol (20 mL) was added hydrazine hydrate (0.819 g, 13.90 mmol) at 25 ℃. The reaction mixture was stirred at 90 ℃ for 16 h. The reaction mixture was cooled to rt, quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, DCM/MeOH = 4/1) to afford **compound SC-13** as a yellow solid. LC-MS (ESI+): m/z = 147.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 1.0 Hz, 1H), 8.60 (s, 1H), 8.53 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H).

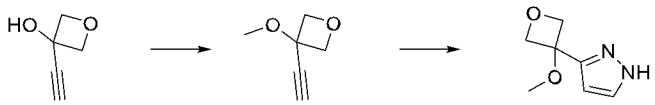
[00106] The following compounds in Table 6 were prepared using similar procedures as described in **fragment SC-13**.

Table 6

Structure	MS	HNMR
 **SC-14**	LC-MS (ESI+): m/z = 152.2 $[M+H]^+$.	^{1}H NMR (400 MHz, DMSO-$d6$) δ 13.21 (brs, 1H), 7.88 (s, 1H), 7.84 (d, J = 3.2 Hz, 1H), 7.66 (d, J = 2.8 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H).

 **SC-15**	LC-MS (ESI+): *m/z* = 125.2 $[M+H]^+$.	^{1}H NMR (400 MHz, D_2O) δ 7.63 (d, *J* = 2.0 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 5.08 - 4.96 (m, 2H), 4.82 – 4.68 (t, *J* = 6.4 Hz, 2H), 3.88 - 3.76 (m, 1H).
 **SC-16**	LC-MS (ESI+): *m/z* = 136.1 $[M+H]^+$.	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.74 (m, 1H), 7.73 - 7.70 (m, 1H), 7.28 - 7.24 (m, 1H), 7.24 - 7.18 (m, 1H), 6.90 - 6.84 (m, 1H).

[00107] Synthetic route of Fragment SC-17



SC-17-1 **SC-17-2** **SC-17**

Step 1:

To a solution of **compound SC-17-1** (500.0 mg, 5.10 mmol, 1.00 eq) in THF (5.0 mL) was added NaH (306.0 mg, 7.65 mmol, 1.50 eq, 60% in oil) at 0 ℃. The reaction mixture was stirred at rt for 20 min, then iodomethane (1.4 g, 10.19 mmol, 1.50 eq) was added at 0 ℃ and the resulting mixture was stirred at room temperature for 8 hr. The reaction mixture was quenched with water (15. mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude **compound SC-17-2** as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 6.4 Hz, 0.8 Hz, 2H), 4.67 (dd, *J* = 6.8 Hz, 0.8 Hz, 2H), 3.36 (s, 3H), 2.71 (s, 1H).

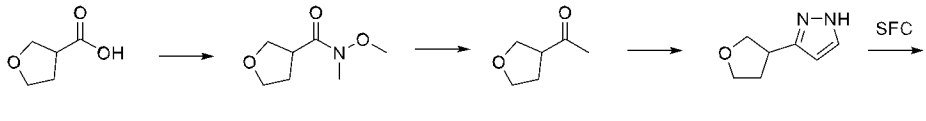
Step 2:

A solution of **compound SC-17-2** (350.0 mg, 3.12 mmol, 1.00 eq) in (trimethylsilyl)diazomethane (5.5 ml, 10.93 mmol, 3.50 eq, 2M in hexane) was stirred at 50 ℃ for 18 hrs under Ar protection in a sealed tube. The reaction mixture was cooled to room temperature and directly concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 8/1) to afford **compound SC-17** as a colorless oil.

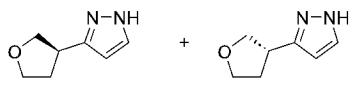
LC-MS (ESI+): *m/z* = 155.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (brs, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 4.92 (s, 4H), 3.21 (s, 3H).

[00108] Synthetic route of Fragment SC-18



SC-18-1 **SC-18-2** **SC-18-3** **SC-18-4**



SC-18-4A **SC-18-4B**

Step 1:

To a solution of **SC-18-1** (5.00 g, 43.1 mmol) in DCM (100 mL) was added oxalyl dichloride (4.01 mL, 47.4 mmol) and DMF (315 mg, 4.31 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 2 h, then the reaction mixture was directly concentrated under reduced pressure to give a residue. The residue dissolved in DCM (100 mL) and *N,O*-dimethylhydroxylamine hydrochloride (6.30 g, 64.6 mmol) and triethylamine (18.0 mL, 129 mmol) was added. The reaction mixture was stirred at rt for 16 h. The reaction mixture was acidified with 1N HCl aq. until pH = 3-4 and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, PE/EA = 1/1) to afford **SC-18-2** as a yellow oil. LC-MS (ESI+): *m/z* = 160.2 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) 4.03 (t, *J* = 8.2 Hz, 1H), 3.91 - 3.73 (m, 3H), 3.69 (s, 3H), 3.46 - 3.33 (m, 1H), 3.18 (s, 3H), 2.27 - 2.15 (m, 1H), 2.12 - 1.98 (m, 1H).

Step 2:

To a solution of **SC-18-2** (3.90 g, 24.5 mmol) in THF (200 mL) was added methylmagnesium bromide (24.5 mL, 1 M in THF) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with sat. $NaHCO_3$ aq. (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, PE/EA = 1/1) to afford **SC-18-3** as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) 3.93 - 3.81 (m, 3H), 3.80 - 3.65 (m, 1H), 3.23 - 3.11 (m, 1H), 2.18 (s, 3H), 2.15 - 2.01 (m, 2H).

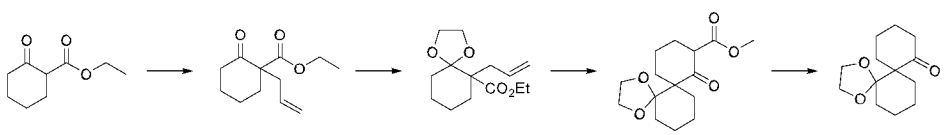
Step 3:

A solution of **SC-18-3** (1.00 g, 8.76 mmol) in DMF-DMA (10 mL, 76 mmol) was stirred at 100 °C for 16 h. The reaction mixture was cooled to room-temperature and concentrated under reduced pressure to give a residue which was dissolved in EtOH (40 mL). The resulting mixture was added $N_2H_4 \cdot H_2O$ (1 mL, 85% in H_2O) and stirred at 90 ℃ for 3 h. The reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (Column: Xtimate C18 150*40mm*10um, Mobile Phase: water (NH_3H_2O+NH_4HCO_3)-ACN, Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition from 0% B to 30%) to afford **SC-18-4** as a yellow oil. LC-MS (ESI+): *m/z* = 138.8 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) 7.52 (s, 1H), 6.10 (d, *J* = 2.0 Hz, 1H), 3.98 (t, *J* = 7.8 Hz, 1H), 3.87 - 3.72 (m, 2H), 3.57 (t, *J* = 7.8 Hz, 1H), 3.46 - 3.34 (m, 1H), 2.30 - 2.16 (m, 1H), 2.04 - 1.90 (m, 1H).

SC-18-4 was separated by SFC (DAICEL CHIRALPAK AS (250mm*30mm,10um) (eluent: 15% to 15% (v/v) CO_2-i-PrOH (0.1%NH_3H_2O) to **SC-18-4A** (peak with earlier retention time, single unknown configuration) and **SC-18-4B** (peak with later retention time, single unknown configuration) both as colorless oil.

[00109] Synthetic route of intermediate A



A-1 A-2 A-3 A-4 A

[00110] To a solution of compound A-1 (50.0 g, 293.77 mmol, 1.00 eq) in THF (300 mL) were added 3-bromoprop-1-ene (39.1 g, 323.15 mmol, 1.10 eq) and Potassium tert-butoxide (323.1 mL, 323.15 mmol, 1.10 eq, 1.0 M in THF) at 0 °C. The reaction mixture was heated to 70 °C and stirred for 16 hr. The reaction mixture was cooled to rt, the pH was adjusted to 3~4 with 1N HCl and extracted with DCM (600 mL x 3). The combined organic layers were washed with saturated NaCl solution (400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 20/1) to afford compound A-2 as a colorless oil.

[00111] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 – 5.69 (m, 1H), 5.04 (dd, J = 13.2 Hz, 1.2 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 2.61 (q, J = 6.8 Hz, 1H), 2.51 – 2.44 (m, 3H), 2.36 – 2.31 (m, 1H), 2.04 – 1.99 (m, 1H), 1.77 – 1.60 (m, 3H), 1.50 – 1.43 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H).

[00112] To a solution of compound A-2 (40.6 g, 193.06 mmol, 1.00 eq) in ethylene glycol (150 mL) was added TMSCl (61 mL, 482.64 mmol, 2.50 eq) at 10 °C. The reaction mixture was stirred at room temperature for 2 hr. Then a solution of NaOH (20.1 g, 501.95 mmol, 2.60 eq) in water (150 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water (300 mL) and extracted with EA (300 mL x 3). The combined organic layers were washed with saturated NaCl solution (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 20/1) to afford compound A-3 as a colorless oil.

[00113] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 – 5.49 (m, 1H), 4.95 – 4.89 (m, 2H), 4.06 – 4.00 (m, 2H), 3.84 – 3.76 (m, 4H), 2.69 (dd, J = 14.0 Hz, 6.4 Hz, 1H), 2.23 (dd, J = 14.0 Hz, 8.0 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.63 – 1.26 (m, 7H), 1.14 (t, J = 7.2 Hz, 3H).

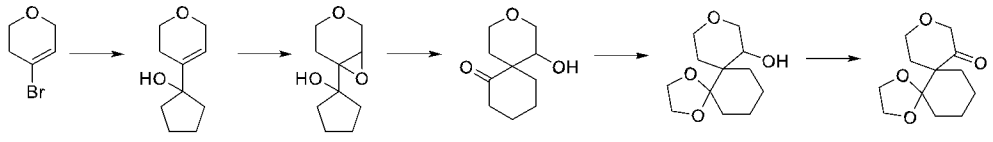
[00114] To a solution of 9-BBN (226.0 mL, 113.05 mmol, 1.25 eq, 0.5M in THF) was added the solution of compound A-3 (23.0 g, 90.44 mmol, 1.00 eq) in THF (12.0 mL) at 5°C. The reaction mixture was stirred at room temperature for 3 h, then the reaction mixture was cooled to -45°C and methyl 2-chloroacetate (10.3 mL, 117.58 mmol, 1.30 eq) and LiHMDS (298.5 mL, 298.47 mmol, 3.30 eq, 1M in THF) was added. The reaction mixture was allowed to warm to rt and stirred for 18 hr. The reaction mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with EA (200 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 30/1) to afford compound A-4 as a pale yellow oil. LC-MS (ESI+): m/z = 283.1 $[M+H]^+$.

[00115] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 – 3.88 (m, 4H), 3.74 (s, 3H), 2.45 – 1.68 (m, 9H), 1.67 – 1.27 (m, 6H).

[00116] To a solution of compound A-4 (22.0 g, 77.93 mmol, 1.00 eq) in EtOH (120 mL) was added the solution of NaOH (3.4 g, 85.72 mmol, 1.10 eq) in water (50 mL). The reaction mixture was heated to 70 °C and stirred for 18 hr. The reaction mixture was cooled to rt, concentrated in vacuum to remove EtOH and extracted with EA (200 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 30/1) to afford Intermediate A as a pale yellow oil. LC-MS (ESI+): m/z = 225.1 $[M+H]^+$.

[00117] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 – 3.80 (m, 4H), 2.52 – 2.44 (m, 1H), 2.39 – 2.34 (m, 1H), 2.28 – 2.23 (m, 1H), 2.11 – 2.05 (m, 1H), 1.99 – 1.80 (m, 2H), 1.79 – 1.67 (m, 3H), 1.66 – 1.53 (m, 3H), 1.52 – 1.37 (m, 3H), 1.24 – 1.16 (m, 1H).

[00118] Synthetic route of intermediate B



[00119] To a solution of 4-bromo-3,6-dihydro-2H-pyran (10.0 g, 0.061 mol, 1.0 equiv.) in THF (150 mL) was added n-butyllithium solution (2.5 M in hexanes, 49.1 mL, 0.123 mol, 2.0 equiv.) in 10 min at -78 °C under argon atmosphere. The mixture was stirred at -78 °C for 0.5 h. Cyclopentanone (5.16 g, 0.061 mol, 1.0 equiv.) in dry THF (40 mL) was then added and the mixture was stirred at -78 °C for 0.5 h. The mixture was allowed to warm to rt. Water (100 mL) was added to quench the reaction and the aqueous layer was extracted with DCM (80 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by flash chromatography on neutral alumina to afford **B-2.**

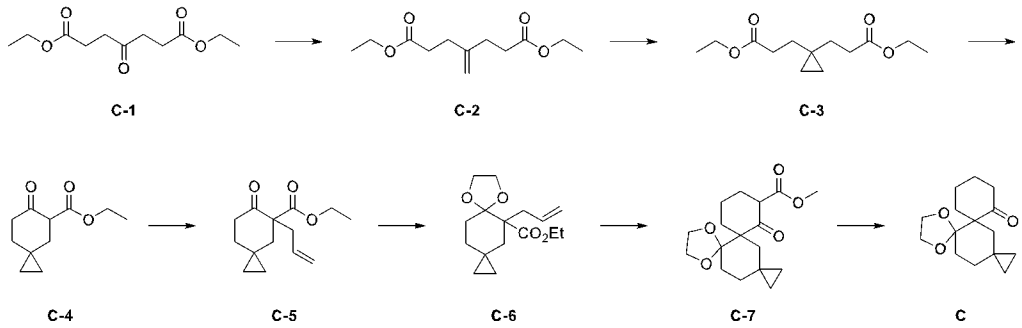
[00120] To a solution of B-2 (5.00 g, 0.030 mol, 1.0 equiv.) in benzene (100 mL) was added vanadyl acetylacetonate (0.788 g, 0.003 mol, 0.1 equiv.) at 0 °C under argon atmosphere, followed by dropwise addition of t-BuOOH (10.7 g, 0.036 mol, 1.2 equiv.). Benzene (100 mL) was added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was warmed to rt, diluted with saturated NaHCO3 (100 ml x 2) aq. and by extracted with EA (80 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **B-3.**

[00121] To a solution of B-3 (4.00 g, 0.022 mol, 1.0 equiv.) in dry DCM (400 mL) was added a solution of BF3.OEt2 (2.68 mL, 0.022 mol, 1.0 equiv.) in DCM (20 mL) dropwise at -78 °C under argon atmosphere. Then reaction mixture was stirred at -78 °C for 3 h. After the reaction was completed, the mixture was concentrated to give a residue. The residue was purified by liquid chromatography to afford **B-4**. LC-MS (ESI+): *m/z* = 185.1 $[M+H]^+$.

[00122] To a solution of B-4 (3.10 g, 0.017 mol, 1.0 equiv.) in benzene (62 mL) was added p-TsOH (960 mg, 0.005 mol, 0.3equiv.) and ethane-1 ,2-diol (9.49 mL, 0.17 mol, 10.0 equiv.). The reaction mixture was stirred for 10 min at rt, then heated to 80-90°C with use of dean stark setup and stirred for 20 h. After the reaction was completed. the reaction mixture was cooled to rt, quenched with 5% NaHCO3 aq. (60 mL) and extracted with EA (60 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **B-5**. LC-MS (ESI+): *m/z* = 229.1 $[M+H]^+$.

[00123] To a solution of B-5 (1.35 g, 0.006 mol, 1.0 equiv.) in dry DCM (54 mL) was added Dess-Martin periodinane (2.76 g, 0.007 mol, 1.1 equiv.) at 0 °C. The reaction mixture was stirred at rt for 1 h. After the reaction was completed. The reaction mixture was quenched with aq. 5% NaHCO3 aq. (20 mL) and washed with water. The organic layer was dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **Intermediate B**. LC-MS (ESI+): *m/z* = 227.1 $[M+H]^+$.

[00124] Synthetic route of intermediate C



[00125] To a solution of methyltriphenylphosphonium bromide (124.1 g, 347.37 mmol, 1.60 eq) in THF (1.3 L) was added t-BuOK (130 mL, 130.27 mmol, 1.50 eq, 1.0 M in THF) dropwise at 0 ℃. The reaction mixture was stirred at 0 ℃ for 10 min, then a solution of **compound C-1** (50.0 g, 217.11 mmol, 1.00 eq) in THF (200 mL) was added dropwise. The reaction mixture was spontaneously warmed to rt and stirred for 18 hr. The reaction was quenched with NH_4Cl aq. (2000 mL) at 0 ℃ and extracted with EA (1000 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 50/1) to afford **compound C-2** (32.0 g, 140.17 mmol, 64.6% yield) as a colorless oil. LC-MS (ESI+): *m/z* = 229.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.13 – 4.00 (dd, *J* = 14.0 Hz, 6.0 Hz, 4H), 2.45 – 2.35 (m, 4H), 2.33 – 2.25 (m, 4H), 1.19 (t, *J* = 6.8 Hz, 6H).

[00126] To a solution of **compound C-2** (32.0 g, 140.17 mmol, 1.00 eq) in toluene (250 mL) was added diethylzinc (350 mL, 350.42 mmol, 4.00 eq, 1M in THF) dropwise at -40 ℃ under Ar atmosphere. The reaction mixture was stirred at -40 ℃ for 10 min and then Diiodomethane (187.7 g, 700.83 mmol, 4.00 eq) was added. The reaction mixture was allowed to stirred at room temperature for 18 hr. The reaction was quenched with NH_4Cl aq. (500 mL) at 0 ℃ and extracted with EA (300 mL x 3). The combined organic layers were dried over Na2SO4 anhydrous, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 50/1) to afford **compound C-3** (30.8 g, 126.91 mmol, 90.5% yield) as a colorless oil. LC-MS (ESI+): *m/z* = 243.2 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 4.8 Hz, 4H), 2.40 – 2.30 (m, 4H), 1.62 – 1.54 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 6H), 0.31 (s, 4H).

[00127] To a solution of **compound C-3** (35.0 g, 144.45 mmol, 1.00 eq) in THF (400 mL) was added t-BuOK (288.9 mL, 288.9 mmol, 2.0 equiv. 1M in THF) dropwise at 0 ℃. The reaction mixture was stirred at 0 ℃ for 1 h. The reaction mixture was quenched with NH_4Cl aq. (500 mL) at 0 ℃ and extracted with EA (300 mL x 3). The organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 100/1) to afford **compound C-4** (25.0 g, 127.42 mmol, 88.2% yield) as a colorless oil. LC-MS (ESI+): *m/z* = 197.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 12.23 (s, 0.7H), 4.29 – 4.13 (m, 2H), 3.50 (dd, *J* = 8.8, 4.4 Hz, 0.3H), 2.60 – 2.44 (m, 0.7H), 2.42 – 2.32 (m, 2H), 2.04 – 1.93 (m, 0.3H), 1.65 – 1.54 (m, 1H), 1.52 – 1.40 (m, 2H), 1.33 – 1.23 (m, 3H), 0.62 – 0.30 (m, 4H).

[00128] To a solution of ethyl **compound C-4** (25.0 g, 127.00 mmol, 1.00 eq) in THF (500 mL) was added potassium t-BuOK (140.0 ml, 127.00 mmol, 1.10 eq, 1.0 M in THF) and 3-bromoprop-1-ene (17.0 g, 140.00 mmol, 1.10 eq). The reaction mixture was stirred at 70 ℃ for 18 h. The reaction mixture was diluted with Water (500 mL) and extracted with EA (300 mL x 3). The combined organic layers were

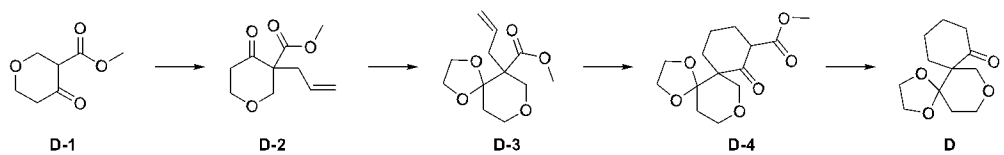
dried over Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 50/1) to afford **compound C-5** (25.1 g, 106.00 mmol, 83.0% yield) as a colorless oil. LC-MS (ESI+): *m/z* = 237.2 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.71 (m, 1H), 5.07 – 4.98 (m, 2H), 4.30 – 4.08 (m, 2H), 2.87 – 2.75 (m, 1H), 2.61 – 2.50 (m, 1H), 2.49 – 2.40 (m, 1H), 2.39 – 2.29 (m, 1H), 2.13 – 2.00 (m, 1H), 2.00 – 1.93 (m, 1H), 1.90 – 1.80 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26 – 1.20 (m, 1H), 0.69 – 0.62 (m, 1H), 0.49 – 0.42 (m, 1H), 0.42 – 0.35 (m, 2H).

[00129] To a solution of **compound C-5** (25.0 g, 106.00 mmol, 1.00 eq) in ethylene glycol (125 mL) was added TMSCl (57.5 g, 529.00 mmol, 5.00 eq) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The reaction was diluted with ice-water (300 mL) and extracted with EA (100 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 20/1) to afford **compound C-6** (28.7 g, 102.00 mmol, 97.0% yield) as a colorless oil. LC-MS (ESI+): *m/z* = 281.2 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 5.69 – 5.59 (m, 1H), 5.09 – 4.96 (m, 2H), 4.20 – 4.06 (m, 2H), 4.01 – 3.90 (m, 4H), 2.84 – 2.75 (m, 1H), 2.61 – 2.50 (m, 1H), 2.10 (d, *J*=14.0 Hz, 1H), 1.90 – 1.75 (m, 2H), 1.65-1.55 (m, 1H), 1.50-1.40 (m, 1H), 1.26 (t, *J* = 2.8 Hz, 3H), 1.24 – 1.16 (m, 1H), 0.42 – 0.18 (m, 4H).

[00130] To a solution of 9-BBN (178 mL, 89.00 mmol, 1.30 eq, 0.5 M in THF) in THF (50 mL) was added a solution of **compound C-6** (20.0 g, 71.30 mmol, 1.00 eq) in THF (50 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h, then methyl 2-chloroacetate (10.1 g, 93.00 mmol, 1.30 eq) and LiHMDS (235 mL, 235.00 mmol, 3.30 eq) dropwise at -45 °C. The reaction mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was diluted with water (500 mL) and extracted with EA (200 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 20/1) to afford **compound C-7** (15.9 g, 51.40 mmol, 72.1% yield) as a light yellow oil. LC-MS (ESI+): *m/z* = 309.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 4.17 – 3.84 (m, 5H), 3.78-3.68 (m, 3H), 2.67 – 2.59 (m, 1H), 2.15 – 2.03 (m, 2H), 2.02 – 1.76 (m, 4H), 1.75 – 1.50 (m, 4H), 1.31 – 1.22 (m, 1H), 0.50 – 0.20 (m, 4H).

[00131] To a solution of **compound C-7** (15.9 g, 51.40 mmol, 1.00 eq) in EtOH (120 mL) was added a solution of sodium hydroxide (2.3 g, 56.50 mmol, 1.10 eq) in water (40 mL). The reaction mixture was heated to 70 °C and stirred for 18 hr. The reaction mixture was cooled to rt, diluted with iced-water (300 mL) and extracted with EA (200 mL x 3). The combined organic layers were dried over Na2SO4 anhydrous, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 10/1) to afford **intermediate C** (11.2 g, 44.80 mmol, 87.0% yield) as a colorless oil. LC-MS (ESI+): *m/z* = 251.2 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 4.02 – 3.85 (m, 4H), 2.57 – 2.29 (m, 4H), 2.01 – 1.61 (m, 10H), 0.29 – 0.14 (m, 4H).

[00132] Synthetic route of intermediate D



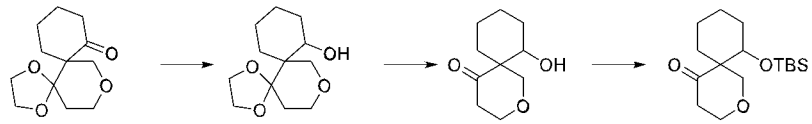
[00133] To a solution of methyl **compound D-1** (19.6 g, 123.89 mmol, 1.00 eq) in THF (250 mL) were added 3-bromoprop-1-ene (16.5 g, 136.28 mmol, 1.10 eq) and potassium tert-butoxide (15.3 g, 136.28 mmol, 1.10 eq). Then the reaction mixture was heated to 70 °C and stirred for 18 hr. The reaction mixture was cooled to rt, acidified with 3N HCl until pH = 3~4 and extracted with EA (300 mL x 2). The combined organic layers were washed with saturated NaCl aq.(200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 20/1) to afford **compound D-2** as a colorless oil. LC-MS (ESI+): *m/z* = 199.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.70 (m, 1H), 5.13 – 5.07 (m, 1H), 5.06 (s, 1H), 4.48 (dd, *J* = 11.6 Hz, 1.2 Hz, 1H), 4.24 – 4.12 (m, 1H), 3.75 (s, 3H), 3.73 – 3.66 (m, 1H), 3.46 (d, *J* = 11.6 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.63 – 2.53 (m, 1H), 2.50 – 2.40 (m, 1H), 2.39 – 2.29 (m, 1H).

[00134] To a solution of **compound D-2** (17.0 g, 85.77 mmol, 1.00 eq) in ethylene glycol (70 mL) was added TMSCl (27.1 mL, 214.43 mmol, 2.50 eq) at 10 °C and the reaction mixture was stirred at room temperature for 2 hr. Then a solution of NaOH (8.9 g, 223.01 mmol, 2.60 eq) in water (70 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water (300 mL) and extracted with EA (120 mL x 2). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 10/1) to afford **compound D-3** as a colorless oil.
^1H NMR (400 MHz, $CDCl_3$) δ 5.58 – 5.43 (m, 1H), 5.05 – 4.90 (m, 2H), 3.92 – 3.72 (m, 4H), 3.71 (s, 3H), 3.56 (s, 3H), 3.55 – 3.45 (m, 1H), 2.67 – 2.56 (m, 1H), 2.46 – 2.35 (m, 1H), 1.83 – 1.72 (m, 1H), 1.55 – 1.44 (m, 1H).

[00135] To a solution of **compound D-3** (19.0 g, 78.42 mmol, 1.00 eq) in THF (10.0 mL) was added a solution of 9-BBN (188.2 mL, 94.10 mmol, 1.20 eq, 0.5M in THF) at 5 °C. The reaction mixture was stirred at room temperature for 3 h, then methyl 2-chloroacetate (11.1 g, 101.94 mmol, 1.30 eq) and a solution of LiHMDS (259.0 mL, 258.78 mmol, 3.30 eq, 1M in THF) was added at -45°C. The reaction mixture was allowed to warm to room temperature and stirred for 18 hr. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EA (120 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 10/1) to afford **compound D-4** as a pale yellow oil. LC-MS (ESI+): *m/z* = 285.1 $[M+H]^+$.
^1H NMR (400 MHz, DMSO-d_6) δ 4.05 – 3.73 (m, 6H), 3.73 – 3.59 (m, 3H), 3.39 (d, *J* = 11.2 Hz, 2H), 2.25 – 2.10 (m, 1H), 2.10 – 1.90 (m, 2H), 1.90 – 1.40 (m, 6H).

[00136] To a solution of **compound D-4** (13.0 g, 45.73 mmol, 1.00 eq) in EtOH (65 mL) was added a solution of NaOH (3.8 g, 96.03 mmol, 2.10 eq) in water (25 mL). The reaction mixture was heated to 70 °C and stirred for 16 hr. The reaction mixture was cooled to rt, concentrated under reduced pressure to remove most of EtOH and extracted with EA (100 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 10/1) to afford **intermediate D** as a pale yellow oil. LC-MS (ESI+): *m/z* = 227.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 11.6 Hz, 1H), 4.03 – 3.88 (m, 4H), 3.82 – 3.65 (m, 2H), 3.54 (d, *J* = 12.0 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.25 – 2.00 (m, 2H), 1.93 – 1.66 (m, 4H), 1.64 –1.50 (m, 2H).

[00137] Synthetic route of intermediate E

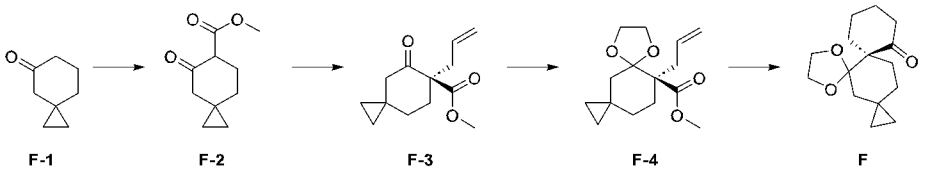


[00138] To a solution of **intermediate D** (4.2 g, 18.56 mmol, 1.00 eq) in THF (50.0 mL) was added $LiAlH_4$ (14.9 mL, 37.12 mmol, 2.00 eq, 2.5 M in THF) at 0 °C. The reaction mixture was allowed to warm to rt and for 2 hr. Then the reaction mixture was diluted with EA (100 mL), quenched with water (100 mL) at -20 °C and extracted with EA (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 4/1) to afford **compound E-1** as a colorless oil.
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 4.06 – 3.73 (m, 6H), 3.66 – 3.49 (m, 4H), 1.83 – 1.51 (m, 4H), 1.51 – 1.34 (m, 4H), 1.34 – 1.28 (m, 2H).

[00139] A solution of **compound E-1** (1.0 g, 4.38 mmol, 1.00 eq) in HCl/EtOH (8.8 mL, 87.6 mmol, 20.00 eq, 10 M in EtOH) was stirred at room temperature for 1 h. The reaction mixture was directly concentrated in vacuum, diluted with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 4/1) to afford **compound E-2** as a colorless oil.
^{1}HNMR (400 MHz, DMSO-*d6*) δ 4.54 (d, *J* = 5.2 Hz, 1H), 4.24 – 4.05 (m, 3H), 3.65 – 3.53 (m, 1H), 3.18 (d, *J* = 12.0 Hz, 1H), 2.85 – 2.71 (m, 1H), 2.19 – 2.08 (m, 1H), 2.06 – 1.93 (m, 1H), 1.78 – 1.68 (m, 1H), 1.67 – 1.59 (m, 1H), 1.55 – 1.45 (m, 1H), 1.44 – 1.23 (m, 2H), 1.22 – 1.12 (m, 1H), 1.08 – 0.97 (m, 1H).

[00140] To a solution of **compound E-2** (1.4 g, 7.82 mmol, 1.00 eq) in DCM (15.0 ml) was added 2,6-dimethylpyridine (1.7 g, 15.63 mmol, 2.00 eq) at -40 °C. The reaction mixture was stirred at -40 °C for 10 min, then TBSOTf (2.9 g, 10.55 mmol, 1.35 eq) was added and the reaction mixture was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was directly concentrated in vacuum, diluted with water (20 mL) and extracted with EA (20 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 40/1) to afford **intermediate E** as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41-4.31 (m, 1H), 4.27-4.13 (m, 2H) 3.65 – 3.54 (m, 1H), 3.19 (d, *J* = 12.0 Hz, 1H), 2.85 – 2.70 (m, 1H), 2.26 – 2.08 (m, 2H), 1.78 – 1.65 (m, 2H), 1.62 – 1.45 (m, 2H), 1.36 – 1.26 (m, 1H), 1.15 – 1.00 (m, 2H), 0.77 (s, 9H), 0.00 (s, 3H), – 0.04 (s, 3H).

[00141] Synthetic route of intermediate F



[00142] Sodium hydride (15.46 g, 387.0 mmol, 60% in mineral oil) was added to the solution of **compound F-1** (12.0 g, 97.0 mmol) and dimethyl carbonate (34.8 g, 387.0 mmol) in THF (360 mL) at 0 °C. The reaction mixture was heated to 70 °C and stirred for 16 hours. The reaction mixture was cooled to room temperature, quenched with water (50 mL) and extracted with EA (200 mL x 3). The combined

organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **compound F-2** as a yellow oil. LC-MS (ESI+): *m/z* = 182.9 $[M+H]^+$.

[00143] 1,1,3,3-tetramethylguanidine (22.76 g, 198.0 mmol), **compound F-2** (18.0 g, 99.0 mmol) and allyl acetate (12.86 g, 128.0 mmol) were dissolved in a mixed solvent of toluene (180 ml) and water (60 mL). The resulting mixture was degassed, charged with N2 and cooled to 10 °C before (*S*,*S*)-DACH-phenyl Trost ligand (1.37 g, 1.98 mmol) and allylpalladium(II) chloride dimer (0.36 g, 0.99 mmol) were added and the reaction mixture was stirred at rt for 2 hours. After that, a solution of *N*-acetyl-*L*-cysteine (0.48 g, 2.96 mmol) in water (40 ml) was added and the reaction mixture was stirred at 25 °C for another 2 hours. The reaction mixture was diluted with water (100 mL), concentrated under reduced pressure to remove toluene and extracted with ethyl acetate (300 mL x 2). The combined organic layers were washed with saturated NaCl aq. (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE:EA = 9:1) to afford **compound F-3** as a yellow oil. LC-MS (ESI+): *m/z* = 222.9 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.68 (m, 1H), 5.13 – 5.01 (m, 2H), 3.72 (s, 3H), 2.87 – 2.75 (m, 1H), 2.72 – 2.61 (m, 1H), 2.50 – 2.41 (m, 1H), 2.41 – 2.32 (m, 1H), 2.14 – 2.04 (m, 1H), 1.80 – 1.70 (m, 1H), 1.70 – 1.60 (m, 1H), 1.08 – 0.99 (m, 1H), 0.46 – 0.39 (m, 1H), 0.39 – 0.31 (m, 2H), 0.29 – 0.22 (m, 1H).

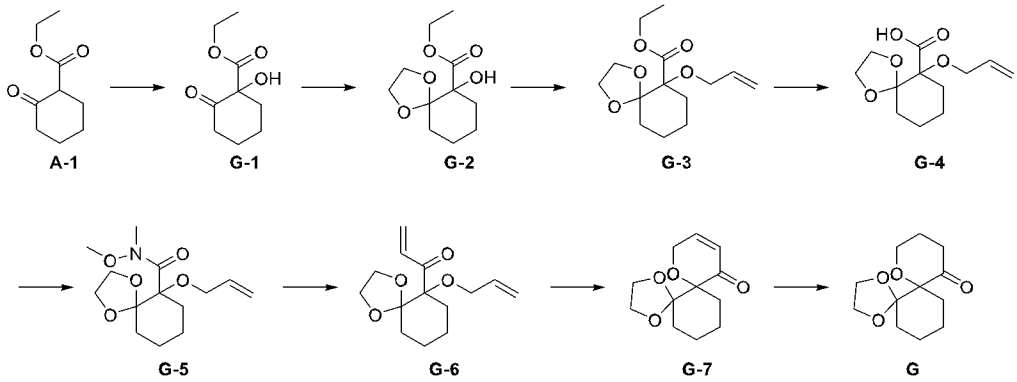
[00144] To a solution of **compound F-3** (11.8 g, 53.1 mmol) in ethane-1,2-diol (118 mL, 53.1 mmol) was added chlorotrimethylsilane (14.42 g, 133 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 hr. The reaction mixture was diluted with ethyl acetate (500 mL) and washed with water (100 mL x 3). The layers were separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 6/1) to afford **compound F-4** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 – 5.57 (m, 1H), 5.12 – 4.99 (m, 2H), 3.99 – 3.84 (m, 4H), 3.69 (s, 3H), 2.91 – 2.81 (m, 1H), 2.47 – 2.35 (m, 1H), 2.21 – 2.10 (m, 1H), 1.87 – 1.71 (m, 2H), 1.56 – 1.46 (m, 1H), 1.38 – 1.27 (m, 1H), 1.16 – 1.07 (m, 1H), 0.37 – 0.21 (m, 4H).

[00145] To a solution of **compound F-4** (6.7 g, 25.2 mmol) in THF (60 mL) was added 9-BBN (101.0 mL, 50.3 mmol, 0.5 M in THF) at 0 °C under N_2 atmosphere. The reaction mixture was warmed to rt and stirred for 2 hrs and then added methyl 2-chloroacetate (3.55 g, 32.7 mmol) and LiHMDS (75 mL, 75 mmol, 1.0 M in THF) dropwise while keeping temperature below -35 °C. The reaction mixture was allowed to warmed to rt and stirred for 16 hours. The reaction mixture was quenched with NH_4Cl aq. (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with saturated NaCl aq. (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was dissolved in EtOH (100 mL) and a solution of NaOH (2.21 g, 55.1 mmol) in H_2O (60 mL) was added. The reaction mixture was heated to 70 °C and stirred for 12 hours. The reaction mixture was cooled to rt, diluted with water (50 mL), concentrated under reduced pressure to remove EtOH and extracted with ethyl acetate (150 mL x 2). The combined organic layers were washed with saturated NaCl aq. (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude was purified by column chromatography (SiO2, PE/EA = 4/1) to afford **Intermediate F** as a colorless oil. LC-MS (ESI+): *m/z* = 251.0 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 – 3.82 (m, 4H), 2.56 – 2.44 (m, 1H), 2.42 – 2.32 (m, 2H), 2.32 – 2.24 (m, 1H), 2.06 – 1.95 (m, 1H), 1.94 – 1.86 (m, 2H), 1.71 – 1.62 (m, 4H), 1.55 – 1.52 (m, 1H), 1.20 – 1.11 (m, 1H), 0.98 – 0.87 (m, 1H), 0.37 – 0.16 (m, 4H).

[00146] Synthetic route of intermediate G



To a solution of compound **A-1** (20.0 g, 117.5 mmol, 1.00 eq) in toluene (200 ml) was added m-CPBA (28.6 g, 141.0 mmol, 1.20 eq) and the resulting mixture was stirred at 60 ℃ for 18 hr. The reaction mixture was cooled to rt, quenched with sat. $Na_2S_2O_3$ aq. (200 mL), and extracted with EA (500 mL x 3). The combined organic layers were washed with sat. Na_2CO_3 aq. (300 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 6/1) to afford **compound G-1** as a colorless oil. LC-MS (ESI+): *m/z* = 187.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d6*) δ 6.23 (s, 1H), 4.19 - 4.09 (m, 2H), 2.65 - 2.53 (m, 1H), 2.36 - 2.16 (m, 2H), 1.86 - 1.68 (m, 4H), 1.62 - 1.50 (m, 1H), 1.20 (t, *J* = 6.8 Hz, 3H).

To a solution of **compound G-1** (17.1 g, 91.8 mmol, 1.00 eq) in ethylene glycol (170 ml) was added TMSCl (58.7 ml, 459.0 mmol, 5.00 eq) at 0 ℃ and the reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was quenched with water (800. mL) and extracted with EA (500 mL x 3). The combined organic layers were washed with brine (500 ml), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 5/1) to afford **compound G-2** as a light yellow oil. LC-MS (ESI+): *m/z* = 231.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 4.89 (s, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.79 - 3.60 (m, 4H), 1.88 - 1.78 (m, 1H), 1.70 - 1.59 (m, 1H), 1.55 - 1.44 (m, 2H), 1.44 - 1.28 (m, 4H), 1.10 (t, *J* = 7.2 Hz, 3H).

To a solution of **compound G-2** (19.1 g, 82.9 mmol, 1.00 eq) in THF (300 ml) was added potassium tert-butoxide (166.0 mL, 166.0 mmol, 2.00 eq, 1M in THF) at 0 ℃ and the reaction mixture was stirred at 0 ℃ for 30 min. Then 3-bromoprop-1-ene (20.1 g, 166.0 mmol, 2.00 eq) was added to the reaction mixture at 0 ℃ and stirred at 0 ℃ for 1 h. The reaction mixture was diluted with water (500 mL) and extracted with EA (300 mL x 2). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by chromatography column (SiO2, PE/EA = 10/1) to afford **compound G-3** as a yellow colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 6.04 - 5.94 (m, 1H), 5.32 - 5.22 (m, 1H), 5.18 - 5.10 (m, 1H), 4.29 - 4.15 (m, 2H), 3.99 - 3.70 (m, 6H), 2.16 - 2.03 (m, 2H), 2.01 - 1.91 (m, 1H), 1.65 - 1.30 (m, 5H), 1.31 (t, *J* = 7.2 Hz, 3H).

To a solution of **compound G-3** (20.0 g, 74.0 mmol, 1.00 eq) in Ethanol (200 mL) and water (60 mL) was added KOH (41.5 g, 740.0 mmol, 10.00 eq) and the reaction mixture was stirred at 80 ℃ for 16 hr. The reaction mixture was cooled to rt, diluted with water (300 mL) and washed with EA (120 mL). The aqueous layer was adjusted pH to 4~5 with 2N HCl aqueous solution and extracted with EA (200 mL x 2). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford crude **compound G-4** as a colorless oil. LC-MS (ESI+): *m/z* = 241.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (brs, 1H), 5.99 - 5.84 (m, 1H), 5.32 – 5.22 (m, 1H), 5.21 (d, J = 10.4 Hz, 1H), 3.95 - 3.70 (m, 6H), 1.99 – 1.86 (m, 2H), 1.80 - 1.70 (m, 1H), 1.62 - 1.37 (m, 4H), 1.36 - 1.23 (m, 1H).

To a solution of **compound G-4** (17.5 g, 72.20 mmol, 1.00 eq) in DMF (200 mL) was added HATU (41.2 g, 108.31 mmol, 1.50 eq), DIEA (55.9 g, 433.21 mmol, 6.00 eq), N,O-dimethylhydroxylamine hydrochloride (21.1 g, 216.63 mmol, 3.00 eq) and DMAP (8.8 g, 72.23 mmol, 1.00 eq). The reaction mixture was stirred at 80 ℃ for 16 h. The reaction mixture was cooled to rt, diluted with water (800 mL) and extracted with EA (500 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 3/1) to afford **compound G-5** as a yellow oil. LC-MS (ESI+): m/z = 286.0 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.02 - 5.88 (m, 1H), 5.37-5.27 (m, 1H), 5.21 -5.11 (m, 1H), 4.02 – 3.53 (m, 6H), 3.57 (s, 3H), 3.51 (s, 3H), 2.13 - 1.75 (m, 3H), 1.64 - 1.30 (m, 4H), 1.28 - 1.10 (m, 1H).

To a solution of **compound G-5** (51.0 g, 179 mmol, 1.00 eq) in THF (250 ml) was added vinylmagnesium chloride (268 ml, 536 mmol, 3.00 eq) at -10 °C under Ar atmosphere, then the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was poured into ice-water (1000 mL) and extracted with EA (800 mL x 2). The combined organic layers were washed with brine (800 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 25/1) to afford **compound G-6** as a yellow oil. LC-MS (ESI+): m/z = 275.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 17.4, 10.4 Hz, 1H), 6.28 (dd, J = 17.4, 2.1 Hz, 1H), 6.04 – 5.88 (m, 1H), 5.58 (dd, J = 10.4, 2.0 Hz, 1H), 5.38 – 5.26 (m, 1H), 5.21 – 5.12 (m, 1H), 3.99 – 3.80 (m, 3H), 3.80 – 3.70 (m, 2H), 3.68 – 3.60 (m, 1H), 2.20 – 2.08 (m, 1H), 2.05 – 1.95 (m, 1H), 1.93 – 1.84 (m, 1H), 1.65 – 1.45 (m, 4H), 1.42 – 1.33 (m, 1H).

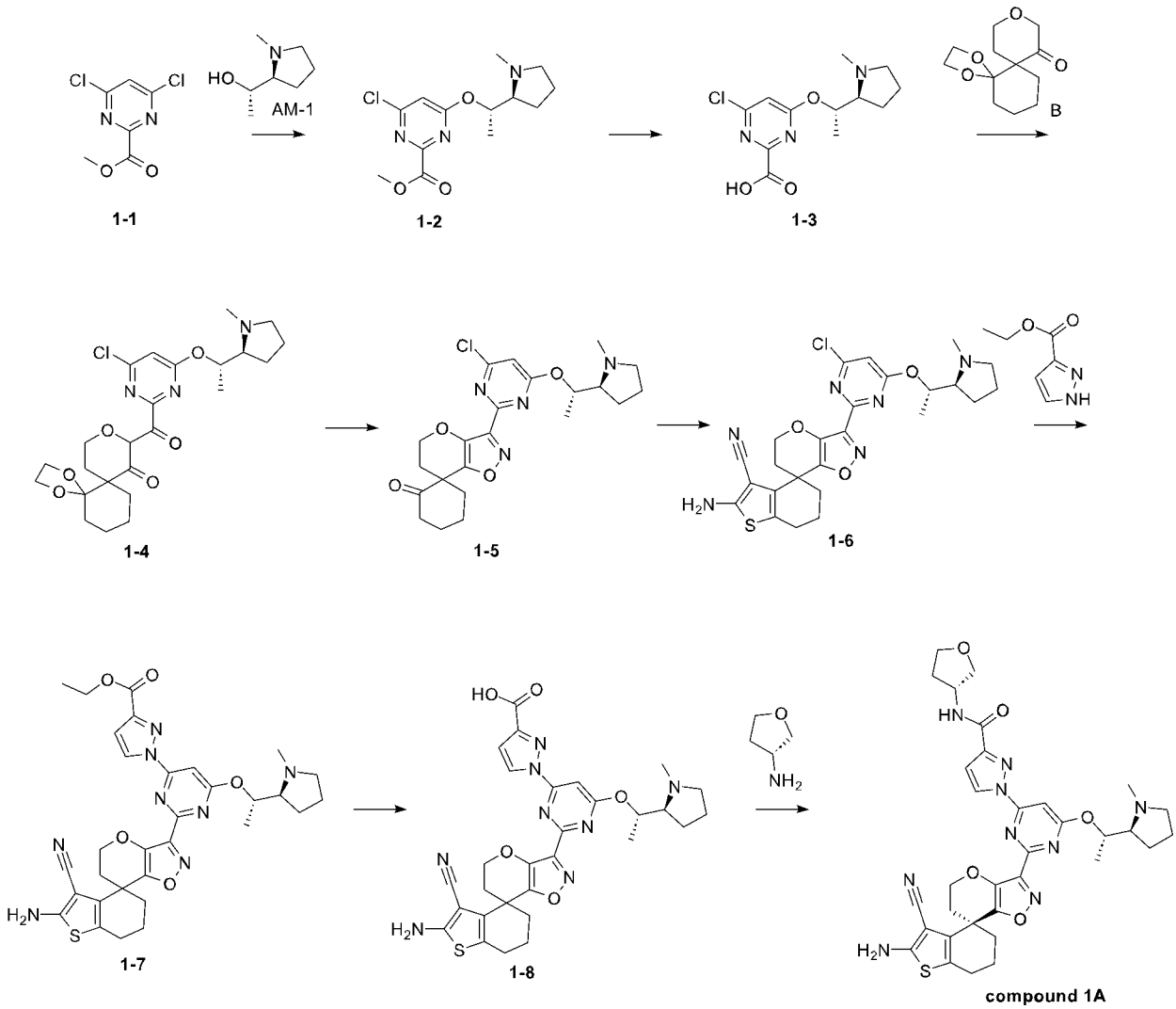
To a solution of **compound G-6** (32.0 g, 127 mmol, 1.0 eq) in DCM (640 mL) was added Grubbs II catalyst (3.77 g, 4.44 mmol, 0.03 eq), then the reaction mixture was stirred at room temperature for 7 h under Ar atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 15/1) to afford **compound G-7** as a yellow solid. LC-MS (ESI+): m/z = 225.0 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.94 (m, 1H), 6.07 (dt, J = 10.4, 2.2 Hz, 1H), 4.78 (dt, J = 18.8, 2.4 Hz, 1H), 4.43 – 4.33 (m, 1H), 3.98 – 3.77 (m, 3H), 3.76 – 3.69 (m, 1H), 2.27 – 2.17 (m, 1H), 1.97 – 1.87 (m, 1H), 1.76 – 1.60 (m, 4H), 1.60 – 1.45 (m, 2H).

To a solution of **compound G-7** (16.5 g, 73.6 mmol, 1.00 eq) in EA (180 mL) was added Pd/C (3.20 g, 10% wet). The reaction mixture was stirred at room temperature under H_2 (1 atm) atmosphere for 4 h. Then the reaction mixture was filtered and the filter cake was washed with DCM (300 mL). The filtrate was collected and concentrated under reduced pressure to afford crude **intermediate G** as a light yellow oil.

^{1}HNMR (400 MHz, $CDCl_3$) δ 4.26 – 4.15 (m, 1H), 3.97 – 3.74 (m, 5H), 2.70 – 2.58 (m, 1H), 2.51 – 2.40 (m, 1H), 2.25 – 2.05 (m, 2H), 2.05 – 1.93 (m, 1H), 1.93 – 1.83 (m, 1H), 1.74 – 1.42 (m, 6H).

[00147] Example 1



[00148] **Compound 1-1** (6.00 g, 29.0 mmol, 1.0 equiv.) was dissolved in DCM (60 mL) and DIPEA (10.7 mL, 58 mmol, 2.0 equiv.) and **fragment AM-1** (6.40 g, 43.6 mmol, 1.5 equiv.) was added. The reaction mixture was then stirred at rt for 18 h. After the reaction was completed, the reaction mixture was concentrated, diluted with water (60 mL) and extracted with EA (60 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **1-2**. LC-MS (ESI+): *m/z* = 300.1 $[M+H]^+$.

[00149] To a solution of **compound 1-2** (4.00 g, 13.41 mmol, 1.0 equiv.) in ACN (10 mL) was added a solution of sodium hydroxide (1 M in water, 20 mL, 20 mmol, 1.5 equiv.) and the resulting reaction mixture was stirred at rt for 1.5 h. After the reaction was completed, the reaction mixture was concentrated and neutralized with HCl (8 M in water). The mixture was purified by liquid chromatography to afford **compound 1-3**. LC-MS (ESI+): *m/z* = 286.1 $[M+H]^+$.

[00150] **compound 1-3** (2 g, 6.99 mmol, 1.00 equiv.) and CDI (2.27 g, 13.98 mmol, 2.00 equiv.) were dissolved in dry THF (12 mL) under argon atmosphere and stirred for 1 h. After complete activation of the acid, a solution of **intermediate B** (3.33 g, 13.98 mmol, 2.00 equiv.) and LiHMDS (1.0 M in THF, 14.7 mL, 14.7 mmol, 2.10 equiv.) were added to the reaction mixture and washed with THF (10 mL). The resulting mixture was stirred at 60 °C overnight. After the reaction was completed, the reaction mixture was cooled to rt, diluted with sat. NaHCO3 aq. (40 mL) and extracted with DCM (40 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to

give a residue. The residue was purified by liquid chromatography to afford **compound 1-4**. LC-MS (ESI+): *m/z* = 494.2 $[M+H]^+$.

[00151] To a solution of **compound 1-4** (1.32 g, 2.67 mmol, 1.0 equiv.) in dioxane (4.5 mL) was added hydroxylamine (50% in water, 200 μL, 3.21 mmol, 1.2 equiv). The reaction mixture was stirred at rt overnight. After the reaction was completed, the reaction mixture was diluted with sat. NaHCO3 aq. (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was dissolved in dioxane (10 mL) and HCl (4 M in water, 3 mL, 12.0 mmol. 4.5 equiv.) was added. The reaction mixture was stirred at rt for 3 h. After the reaction was completed, the reaction mixture was diluted with sat. NaHCO3 aq. (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **compound 1-5**. LC-MS (ESI+): *m/z* = 447.2 $[M+H]^+$.

[00152] **Compound 1-5** (1.0 g, 2.22 mmol, 1.0 equiv.), ammonium acetate (274 mg, 3.57 mmol, 1.60 equiv.) and sulfur (114 mg, 3.57 mmol, 1.60 equiv.) were dissolved in EtOH (10 mL) and stirred at 60 °C for 15 min. Malonitrile as a solution in EtOH (3.24 mL, 3.68 mmol, 1.65 equiv.) was added dropwise. The reaction was stirred at 80 °C for 5 h. After the reaction was completed, the reaction mixture was cooled to rt, filtered, diluted with sat. NaHCO3 aq. (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **compound 1-6**. LC-MS (ESI+): *m/z* = 527.2 $[M+H]^+$.

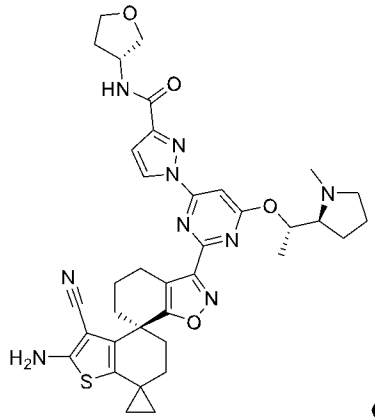
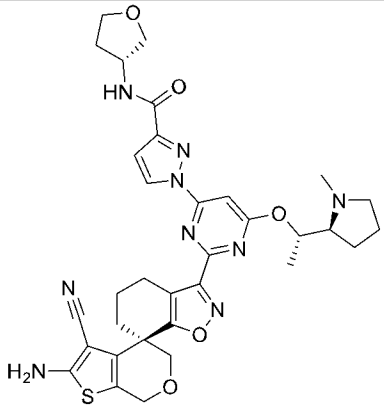
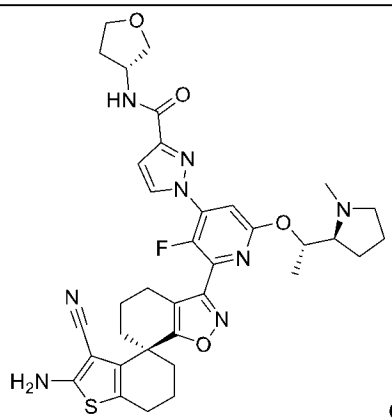
[00153] **Compound 1-6** (100 mg, 0.19 mmol, 1.0 equiv.) and ethyl 1H-pyrazole-3-carboxylate (53 mg, 0.38 mmol, 2.0 equiv.) were dissolved in THF (1.5 mL), cesium carbonate (153 mg, 0.48 mmol, 2.5 equiv.) was added and reaction mixture was stirred at 65 °C for 3 h. After the reaction was completed, the reaction mixture was diluted with sat. NaHCO3 aq. (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **compound 1-7**. LC-MS (ESI+): *m/z* = 631.7 $[M+H]^+$.

[00154] To a solution of **compound 1-7** (78 mg, 0.124 mmol, 1.0 equiv) in 1-propanol (1 mL) was added sodium hydroxide (4 M in water, 100 μL, 0.40 mmol, 3.2 equiv.) and the reaction mixture was stirred at rt for 30 min. After the reaction was completed, the reaction mixture was diluted with sat. NaHCO3 aq. (5 mL) and extracted with DCM (5 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by liquid chromatography to afford **compound 1-8**. LC-MS (ESI+): *m/z* = 603.2 $[M+H]^+$.

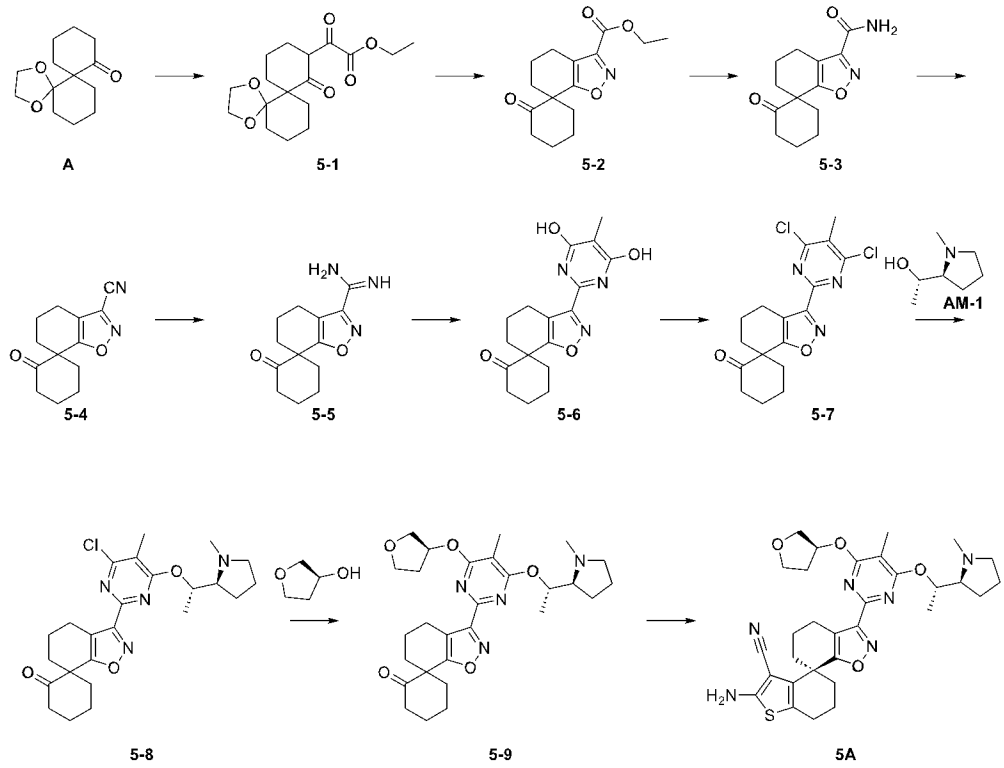
[00155] A solution of **compound 1-8** (35 mg, 0.059 mmol, 1.0 equiv) in DMF (0.4 mL) was added (*R*)-tetrahydrofuran-3-amine hydrochoride (14 mg, 0.116 mmol, 2.0 equiv.), DIPEA (20 μL, 0.15 mmol, 2.5 equiv.) and T3P (26 μL, 0.87 mmol, 1.5 equiv.) and the reaction mixture was stirred at rt for 3 h. After the reaction was completed, the reaction mixture was diluted with sat. NaHCO3 aq. (5 mL) and extracted with DCM (5 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by pre-HPLC followed by SFC to afford **compound 1A**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.32 (s, 1H), 8.15 (d, 1H), 7.10 (s, 1H), 6.93 (s, 2H), 6.77 (d, 1H), 4.12-3.60 (m, 8H), 2.82-2.70 (m, 3H), 2.43-1.41(m, 15H), 1.36 (d, 3H). LC-MS (ESI+): *m/z* = 672.2 $[M+H]^+$.

[00156] **The following compounds** in Table 7 were prepared using similar procedures as described in **Compound 1A**.

Table 7

Structure	$[M+H]^+$
 **Compound 2A**	696.3
 **Compound 3A**	672.4
 **Compound 4A**	687.2

[00157] Example 2



[00158] A mixture of sodium ethoxide (6.7 g, 98.08 mmol, 2.00 eq) in EtOH (40 mL) was stirred at 0 °C for 15 min. Then **Intermediate A** (11.0 g, 49.04 mmol, 1.00 eq) and a solution of diethyl oxalate (10.7 g, 73.56 mmol, 1.50 eq) in EtOH (10.0 mL) were added dropwise at 0 °C. The reaction mixture was warmed to rt an stirred for 18 h. The reaction mixture was neutralized with HCl/dioxane until pH = 7. To the resulting suspension was added hydroxylamine hydrochloride (2.4 g, 34.31 mmol, 0.70 eq) and the reaction mixture was heated to 70 °C and stirred for 6 hr. After that, the reaction mixture was acidified to pH = 1 with HCl/dioxane, heated to 80 °C again and stirred for another 6 hr. The reaction mixture was cooled to rt, quenched with water (400 mL) and extracted with EA (400 mL x 2). The combined organic layers were washed with brine (300 mL) and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 15/1) to afford **compound 5-2** as a colorless oil. LC-MS (ESI+): *m/z* = 278.1 $[M+H]^+$.
^{1}H NMR (400 MHz, CDCl3) δ 4.42 (q, *J* = 7.2 Hz, 2H), 2.76 – 2.69 (m, 1H), 2.67 – 2.62 (m, 1H), 2.59 – 2.48 (m, 2H), 2.45 – 2.31 (m, 2H), 2.08 – 1.97(m, 3H), 1.90 – 1.80 (m, 3H), 1.77 – 1.67 (m, 1H), 1.64 – 1.59 (m, 1H), 1.40 (t, *J* = 6.8 Hz, 3H).

[00159] To a solution of **compound 5-2** (4.7 g, 16.95 mmol, 1.00 eq) in EtOH (4.0 mL) was added ammonium hydroxide (19.8 mL, 514.29 mmol). The reaction mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with water (200 mL) and extracted with EA (200 mL x 2). The combined organic layers were washed with brine(100 mL) and concentrated in vacuum to afford crude **compound 5-3** as a white solid. The crude product was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 249.1 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.99 (s, 1H), 7.71 (s, 1H), 2.78 – 2.70 (m, 1H), 2.59 – 2.50 (m, 1H), 2.49 – 2.41 (m, 1H), 2.40 – 2.25 (m, 2H), 2.24 – 2.14 (m, 1H), 2.03 – 1.65 (m, 7H), 1.50 – 1.39 (m, 1H).

[00160] To a solution of crude **compound 5-3** (3.3 g, 13.29 mmol, 1.00 eq) in ACN (30 mL) was added pyridine (2.6 mL, 31.90 mmol, 2.40 eq) and the resulting mixture was stirred at room temperature for 20 min. Then TFAA (3.3 g, 15.95 mmol, 1.20 eq) was added dropwise and the reaction mixture was stirred at room temperature for 6 hr. The reaction mixture was diluted with H_2O (100 mL) and extracted with

EA (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 15/1) to afford **compound 5-4** as a white solid. LC-MS (ESI+): *m/z* = 231.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-*d6*) δ 2.83 – 2.73 (m, 1H), 2.60 – 2.51 (m, 1H), 2.50 – 2.38 (m, 2H), 2.33 – 2.17 (m, 2H), 2.07 – 1.71 (m, 7H), 1.52 – 1.40 (m, 1H).

[00161] To a solution of **compound 5-4** (2.6 g, 11.29 mmol, 1.00 eq) in MeOH (40.0 mL) was added sodium methoxide (0.2 g, 2.82 mmol, 0.25 eq) and the resulting mixture was stirred at room temperature for 2 hr. Then NH_4Cl (2.1 g, 39.51 mmol, 3.50 eq) was added and the reaction mixture was stirred at room temperature for 18 hr. The reaction mixture was directly concentrated in vacuum to give a residue. The residue was slurried with DCM (50 mL) and dried under reduce pressure to afford crude **compound 5-5** as a white solid. The crude product was not further purified and directly used in the next step. LC-MS (ESI+): *m/z* = 248.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-*d6*) δ 9.50 (brs, 3H), 2.86 – 2.75 (m, 1H), 2.60 – 2.50 (m, 2H), 2.48 – 2.39 (m, 1H), 2.35 – 2.18 (m, 2H), 2.06 – 1.97 (m, 1H), 1.97 – 1.89 (m, 1H), 1.89 – 1.74 (m, 5H), 1.53 – 1.42 (m, 1H).

[00162] To a solution of crude **compound 5-5** (2.8 g, 11.32 mmol, 1.00 eq) and diethyl 2-methylmalonate (15.8 g, 90.58 mmol, 8.00 eq) in DMF (10.0 mL) was added DBU (12.1 g, 79.26 mmol, 10.00 eq). Then the reaction mixture was heated to 100 °C and stirred for 16 hr. The reaction mixture was cooled to rt, diluted with water (200 mL), basified with 4N NaOH aq. until pH=11 and washed with EA (100 mL x 3). Then the aqueous layer was collected and acidified with 4N HCl aqueous solution until pH = 1 and then extracted with EA (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 50/1) to afford **compound 5-6** as a white solid. LC-MS (ESI+): *m/z* = 330.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-*d6*) δ 11.91 (brs, 2H), 2.80 – 2.70 (m, 2H), 2.63 – 2.52 (m, 1H), 2.45 – 2.35 (m, 1H), 2.35 – 2.20 (m, 2H), 2.06 – 1.85 (m, 3H), 1.84 (s, 3H), 1.83 – 1.72 (m, 4H), 1.54 – 1.45 (m, 1H).

[00163] To a solution of **compound 5-6** (1.1 g, 3.34 mmol, 1.00 eq) in $POCl_3$ (7.8 mL) was added DIEA (1.2 mL, 7.01 mmol, 2.10 eq) at 0 °C dropwise. Then the reaction mixture was heated to 80 °C and stirred for 3 hr. The reaction mixture was cooled to rt and directly concentrated in vacuum to remove $POCl_3$. The resulting mixture was diluted with water (100 mL) and extracted with EA (100 mL x 2). The combined organic layers were washed with saturated NaHCO3 solution (100 ml) and brine (100 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was slurried with PE (50 mL) to afford **compound 5-7** as a white solid. LC-MS (ESI+): *m/z* = 366.0 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-*d6*) δ 2.83-2.70 (m, 2H), 2.66-2.56 (m, 1H), 2.48 (s, 3H), 2.46-2.38 (m, 1H), 2.36-2.23 (m, 2H), 2.06-1.72 (m, 7H), 1.56 – 1.40 (m, 1H).

[00164] To a solution of **fragment AM-1** (355.6 mg, 2.75 mmol, 1.40 eq) in THF (3.0 mL) was added LiHMDS (3.5 mL, 3.54 mmol, 1.80 eq, 1M in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and then a solution of **compound 5-7** (720.0 mg, 1.97 mmol, 1.00 eq) in THF (3.0 mL) was added. The reaction mixture was heated to 65°C and stirred for 1.5 hr. The reaction mixture was cooled to rt, diluted with water (100 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na2SO4, filtered and concentrated in

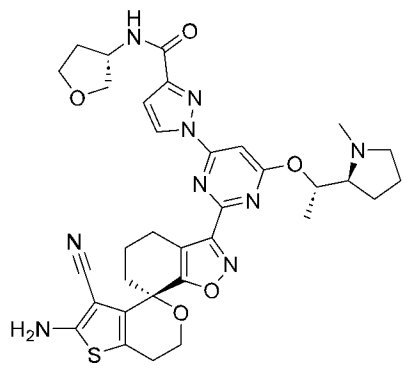
vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 30/1) to afford **compound 5-8** as a brown solid. LC-MS (ESI+): *m/z* = 459.1 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.40 – 5.30 (m, 1H), 3.03 – 2.93 (m, 1H), 2.82 – 2.70 (m, 2H), 2.69 – 2.60 (m, 2H), 2.48 – 2.38 (m, 1H), 2.37 (s, 3H), 2.33 – 2.23 (m, 2H), 2.22 (s, 3H), 2.10 – 1.60 (m, 12H), 1.56 – 1.40 (m, 1H), 1.28 (d, *J* = 6.0 Hz, 3H).

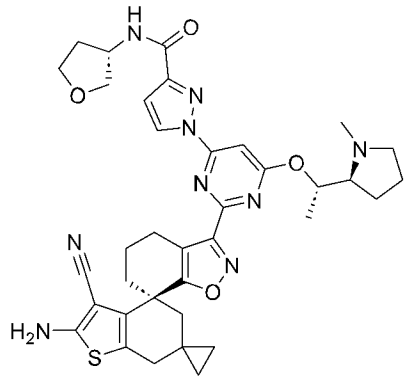
[00165] To a solution of (S)-tetrahydrofuran-3-ol (15.4 mg, 0.17 mmol, 2.00 eq) in THF (1.0 mL) was added t-BuOK (0.17 ml, 0.17 mmol, 2.00 eq, 1M in THF) dropwise at 0 °C under Ar atmosphere. Then the reaction mixture was stirred at 0 °C for 30 min and **compound 5-8** (40.0 mg, 0.09 mmol, 1.00 eq) was added at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 1 hr. The reaction was quenched with NH_4Cl aq. (5.0 mL) at 0 °C and extracted with EA (5 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. the residue was purified by prep-TLC (SiO2, DCM/MeOH = 15/1) to afford **compound 5-9** as a light yellow solid. LC-MS (ESI+): *m/z* = 511.3 $[M+H]^+$.
^{1}H NMR (400 MHz, methanol-*d4*) δ 5.77 – 5.71 (m, 1H), 5.50 – 5.38 (m, 1H), 4.10 – 3.85 (m, 4H), 3.30 – 3.23 (m, 1H), 3.23 – 3.08 (m, 1H), 2.98 – 2.89 (m, 1H), 2.84 – 2.70 (m, 3H), 2.71 (s, 3H), 2.54 – 2.45 (m, 2H), 2.44 – 2.26 (m, 2H), 2.25 – 2.13 (m, 2H), 2.08 (s, 3H), 2.05 – 1.90 (m, 8H), 1.90 – 1.76 (m, 2H), 1.74 – 1.60 (m, 1H), 1.39 (d, J = 6.0 Hz, 3H).

[00166] To a solution of **compound 5-9** (34.0 mg, 0.07 mmol, 1.00 eq) in EtOH (1.0 mL) was added malononitrile (13.2 mg, 0.20 mmol, 3.00 eq), β-Alanine (7.7 mg, 0.09 mmol, 1.30 eq) and sulfur (4.3 mg, 0.13 mmol, 2.00 eq), then the reaction mixture was heated to 80 °C and stirred for 18 h under Ar atmosphere. The reaction mixture was cooled to rt and directly concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 15/1) and prep-HPLC (column: SunFire Prep C18 OBD 10 um 19*250 mm Column; mobile phase: 0.1% FA in water, 7.82 min, 8.60 min, peak with later retention time) to afford **compound 5A** formic acid salt. LC-MS (ESI+): *m/z* = 591.2 $[M+H]^+$.
^{1}H NMR (400 MHz, methanol-*d4*) δ 8.53 (s, 1H), 5.80 – 5.73 (m, 1H), 5.50 – 5.41 (m, 1H), 4.10 – 3.84 (m, 4H), 3.23 – 3.10 (m, 2H), 2.97 – 2.87 (m, 1H), 2.87 – 2.74 (m, 1H), 2.72 – 2.49 (m, 5H), 2.42 – 2.27 (m, 1H), 2.23 – 2.08 (m, 5H), 2.07 (s, 3H), 2.06 – 1.71 (m, 9H), 1.36 (d, *J* = 6.0 Hz, 3H).

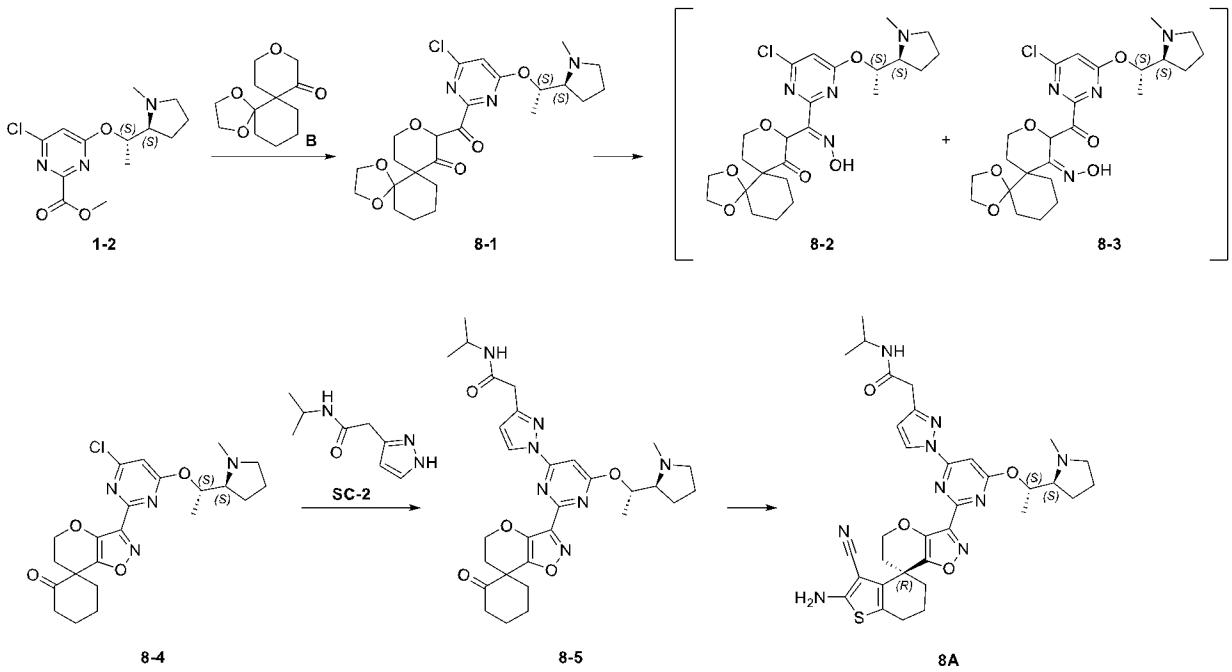
[00167] **The following compounds** in Table 8 were prepared using similar procedures as described in **Compound 5A**.

Table 8

Structure	Spectrum	HPLC/SFC
 **Compound 6A** FA salt	LC-MS (ESI+): *m/z* = 672.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, *J* = 2.8 Hz, 1H), 8.60 (d, *J*=6.8 Hz, 1H), 8.35 (s, 1H), 7.54 (s, 1H), 7.19 (s, 2H), 6.97 (d, *J* = 2.8 Hz, 1H), 5.54 – 5.42 (m, 1H), 4.55 – 4.45 (m, 1H), 4.06 – 3.90 (m, 2H), 3.90 – 3.80 (m, 2H), 3.78 – 3.68 (m, 1H), 3.63 (q, *J* = 4.4 Hz, 1H), 3.25 – 3.14 (m, 1H), 3.01 – 2.92 (m, 1H), 2.78 – 2.55 (m, 4H), 2.39 (s, 3H), 2.30 – 2.14 (m, 3H), 2.14 – 2.02 (m, 1H), 2.01 – 1.85 (m, 3H), 1.85 – 1.70 (m, 2H), 1.70 – 1.60 (m, 2H), 1.32 (d, *J* = 6.4 Hz, 3H).	column: Waters Xbridge C18 10 um OBD, 19*250mm; mobile phase: 0.1% FA in water, peak with later retention time

 **Compound 7A** FA salt	LC-MS (ESI+): *m/z* = 696.3 $[M+H]^+$. ^1H NMR (400 MHz, methanol-*d4*) δ 8.82 (d, *J* = 2.8 Hz, 1H), 8.52 (s, 1H), 7.54 (s, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.60-5.50 (m, 1H), 4.68 – 4.56 (m, 1H), 4.07 – 3.93 (m, 2H), 3.90 – 3.80 (m, 1H), 3.79 – 3.73 (m, 1H), 3.67 – 3.59 (m, 1H), 3.25 – 3.13 (m, 1H), 3.02 – 2.92 (m, 1H), 2.82 (s, 2H), 2.65 (s, 3H), 2.50 – 2.41 (m, 1H), 2.41 – 2.29 (m, 2H), 2.29 – 2.17 (m, 1H), 2.17 – 2.09 (m, 2H), 2.09 – 1.95 (m, 2H), 1.93 (s, 1H), 1.92 – 1.83 (m, 1H), 1.60 (d, *J* = 14.0 Hz, 1H), 1.48 (d, *J* = 6.0 Hz, 3H), 1.38 – 1.25 (m, 3H), 0.72-0.62 (m, 2H), 0.51-0.41 (m, 2H).	column: SunFire Prep C18 OBD 10 um, 19*250 mm Column; mobile phase: 0.1% FA in water, peak with later retention time

[00168] Example 3



[00169] **Compound 1-2** (600 mg, 2.00 mmol), **Intermediate B** (543 mg, 2.40 mmol), $MgBr_2 \cdot Et_2O$ (2.33 g, 9.01 mmol), 3A MS (600 mg) and DIPEA (1.57 mL, 9.01 mmol) was added to MeCN (6 mL) in glove box. The reaction mixture was heated to 60 °C and stirred for 4 hours. The reaction mixture was cooled to room temperature, quenched with water (30 mL) and extracted with DCM (30 mLx3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 1:1) to afford **compound 8-1** as a yellow solid. LC-MS (ESI+): *m/z* = 494.2 $[M+H]^+$.

[00170] To a solution of **compound 8-1** (550 mg, 1.11 mmol) in EtOH (6 ml) was added hydroxylamine hydrochloride (77 mg, 1.1 mmol). The reaction mixture was heated to 70 °C and stirred for 1.5 hr. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL),

dried over Na_2SO_4, filtered and the concentrated under reduced pressure to give a mixture of crude **compound 8-2** & **compound 8-3**. The crude product was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 509.1 $[M+H]^+$.

[00171] A mixture of crude **compound 8-2** & **compound 8-3** (350 mg, 0.688 mmol) was dissolved in TFA (4 mL) and stirred at 80 °C for 16 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ aq. (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: C18 150×30 mm, Mobile Phase: water (NH_3H_2O+NH_4HCO_3)-ACN, Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition from 75% B to 100%) to afford **compound 8-4** as a yellow solid. LC-MS (ESI+): *m/z* = 447.1 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.52 – 5.40 (s, 1H), 4.46 – 4.33 (m, 1H), 4.24 – 4.12 (m, 1H), 3.17 – 3.04 (m, 1H), 2.96 – 2.84 (m, 1H), 2.70 – 2.62 (m, 1H), 2.61 – 2.50 (m, 2H), 2.48 (s, 3H), 2.33 – 2.20 (m, 3H), 1.97 – 1.81 (m, 5H), 1.80 – 1.68 (m, 4H), 1.41 – 1.30 (m, 3H).

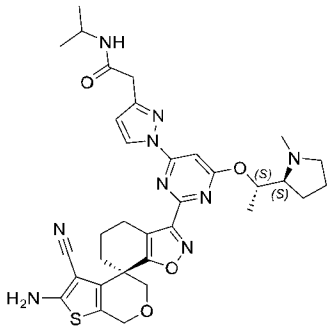
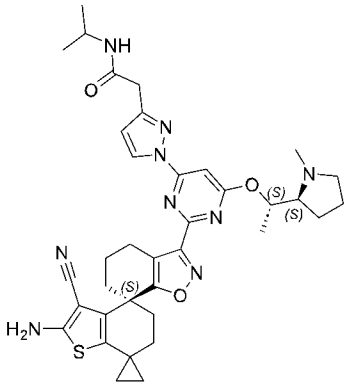
[00172] **Compound 8-4** (38 mg, 0.085 mmol) and **fragment SC-2** (42.7 mg, 0.255 mmol) were dissolved in THF (2 mL) and Cs_2CO_3 (139 mg, 0.425 mmol) was added. The reaction mixture was stirred at 50 °C for 5 hours. The reaction mixture was cooled to room temperature and directly concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 12/1) to afford **compound 8-5** as yellow solid. LC-MS (ESI+): *m/z* = 578.4 $[M+H]^+$.

[00173] **Compound 8-5** (40 mg, 0.069 mmol), 3-aminopropanoic acid (21 mg, 0.24 mmol), malononitrile (16 mg, 0.24 mmol), 3A MS (100 mg, 0.036 mmol) and sulfur (17 mg, 0.53 mmol) was added to EtOH (1 mL). The reaction mixture was heated to 80 °C and stirred for 16 hours. Then the reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ aq. (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: C18 150×30mm, Mobile Phase: water (NH_3H_2O+NH_4HCO_3)-ACN, Mobile Phase B: ACN, Flow rate: 25 mL/min, gradient condition from 65% B to 95%) and prep-SFC (Column: DAICEL CHIRALPAK AS (250mm*30mm,10um), Mobile Phase: CO_2-EtOH (0.1%NH_3•H_2O), Mobile Phase B: acetonitrile Flow rate: 80 mL/min, gradient condition from 40% B to 40%, peak with later retention time) to afford **compound 8A**. LC-MS (ESI+): *m/z* = 658.4 $[M+H]^+$.

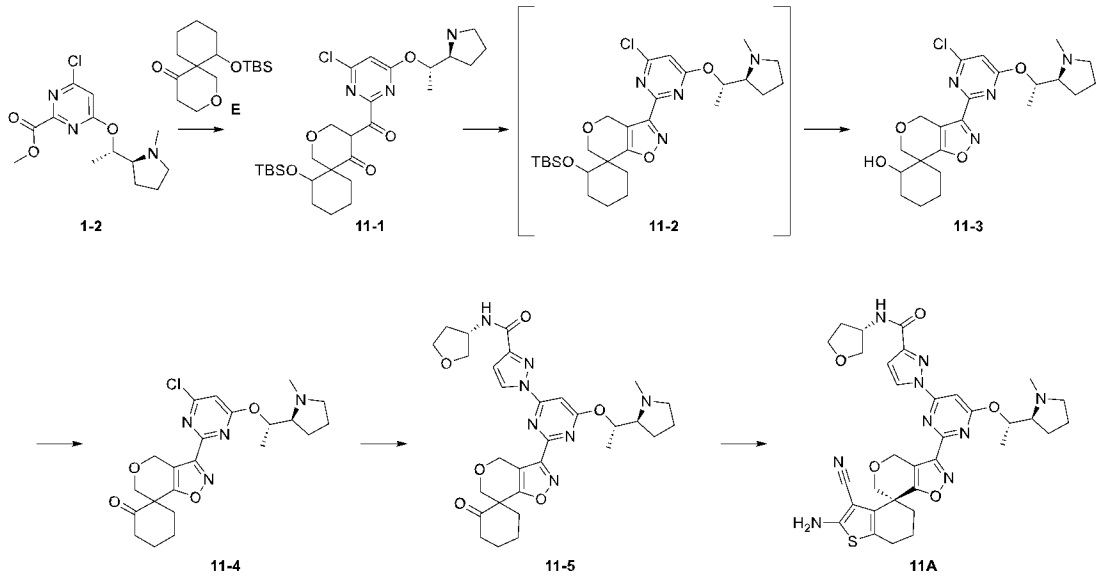
^1H NMR (400 MHz, $CDCl_3$): 8.67 (d, *J* = 2.8 Hz, 1H), 7.17 (s, 1H), 6.41 (d, *J* = 2.8 Hz, 1H), 6.15 – 6.01 (m, 1H), 5.73 – 5.57 (m, 1H), 4.72 (s, 2H), 4.55 – 4.48 (m, 1H), 4.30 – 4.20 (m, 1H), 4.13 – 4.03 (m, 1H), 3.66 (s, 2H), 3.39 – 3.10 (m, 1H), 2.78 – 2.57 (m, 5H), 2.54 – 2.36 (m, 2H), 2.26 – 2.18 (m, 1H), 2.13 – 1.96 (m, 4H), 1.95 – 1.78 (m, 5H), 1.51 – 1.42 (m, 3H), 1.17 – 1.07 (m, 6H).

[00174] **The following compounds** in Table 9 were prepared using similar procedures as described in **Compound 8A**.

Table 9

Structure	Spectrum	HPLC/SFC
 **Compound 9A**	LC-MS (ESI+): *m/z* = 658.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.4 Hz, 1H), 7.17 (s, 1H), 6.42 (d, *J* = 2.8 Hz, 1H), 6.11 – 6.01 (m, 1H), 5.55 – 5.43 (m, 1H), 4.85 – 4.76 (m, 2H), 4.75 – 4.63 (m, 2H), 4.13 – 4.03 (m, 2H), 3.93 – 3.83 (m, 1H), 3.66 (s, 2H), 3.26 – 3.08 (m, 2H), 2.97 – 2.83 (m, 1H), 2.74 – 2.64 (m, 1H), 2.51 (s, 3H), 2.43 – 2.24 (m, 2H), 2.14 – 1.95 (m, 3H), 1.95 – 1.85 (m, 4H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.18 – 1.08 (m, 6H).	REGIS(S,S)WHELK-O1 (250mm*25mm,10um), eluting with 60% (v) CO_2-EtOH with 0.1% NH_3 in H_2O at 80 mL/min, peak with earlier retention time
 **Compound 10A**	LC-MS (ESI+): *m/z* = 682.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.8 Hz, 1H), 7.16 (s, 1H), 6.47 – 6.38 (m, 1H), 6.19 – 6.02 (m, 1H), 5.56 – 5.44 (m, 1H), 4.62 (s, 2H), 4.14 – 4.03 (m, 1H), 3.66 (s, 2H), 3.26 – 3.15 (m, 1H), 3.15 – 3.05 (m, 1H), 2.97 – 2.86 (m, 1H), 2.72 – 2.63 (m, 1H), 2.49 (s, 3H), 2.38 – 2.28 (m, 2H), 2.24 – 2.13 (m, 3H), 2.12 – 2.00 (m, 3H), 1.94 – 1.89 (m, 3H), 1.80 – 1.76 (m, 2H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.18 – 1.09 (m, 6H), 0.96 – 0.82 (m, 4H).	Column: DAICEL CHIRALPAK IG (250mm*30mm,10um), Mobile Phase: CO_2-EtOH (0.1%NH_3•H_2O), Mobile Phase B: acetonitrile Flow rate: 80 mL/min, gradient condition from 55% B to 55%, peak with later retention time

[00175] Example 4



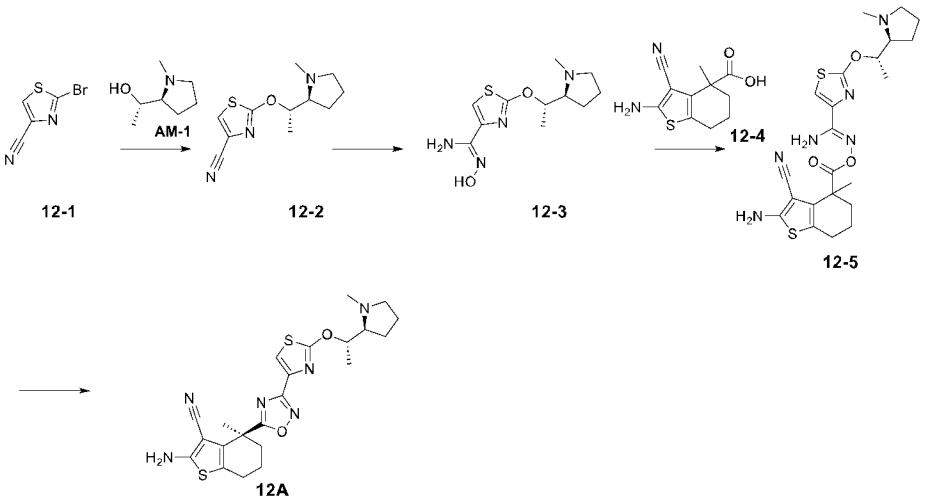
[00176] Magnesium bromide diethyl etherate (1.29 g, 5.00 mmol, 1.50 eq) and **intermediate E** (1.49 g, 5.00 mmol, 1.50 eq) was added to a solution of **compound 1-2** (1.0 g, 3.34 mmol, 1.00 eq) in THF (8.0 ml) at room temperature under Ar atmosphere, then the mixture was stirred at room temperature for 10 min. LiHMDS (8.34 ml, 8.34 mmol, 2.50 eq, 1.0 M in THF) was added to the reaction mixture dropwise and the reaction mixture was heated to 50 °C and stirred for 4h. The reaction mixture was cooled to rt, concentrated in vacuum and diluted with water (20 mL). The resulting mixture was adjusted to pH=6~7 with 1N HCl aqueous solution and extracted with EA (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 15/1) to afford **compound 11-1** as a light yellow oil. LC-MS (ESI+): *m/z* = 566.3 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.39 – 7.17 (m, 1H), 5.32 – 5.10 (m, 1H), 4.69 – 4.48 (m, 1H), 4.42 – 4.24 (m, 1H), 4.02 – 3.93 (m, 1H), 3.88 – 3.81 (m, 1H), 3.62 – 3.50 (m, 1H), 3.00 – 2.90 (m, 1H), 2.80 – 2.50 (m, 2H), 2.45 – 2.25 (m, 3H), 2.25 – 2.05 (m, 2H), 2.04 – 1.92 (m, 2H), 1.91 – 1.75 (m, 2H), 1.74 – 1.50 (m, 4H), 1.50 – 1.40 (m, 1H), 1.38 – 1.28 (m, 1H), 1.27 – 1.20 (m, 3H), 1.05-0.95 (m, 1H), 0.84-0.74 (m, 9H), 0.05 – 0.05 (m, 6H).

[00177] To a solution of **compound 11-1** (1.1 g, 1.94 mmol2, 1.00 eq) in EtOH (8.0 ml) was added hydroxylamine hydrochloride (94.0 mg, 1.36 mmol, 0.70 eq), then the reaction mixture was heated to 70 °C and stirred for 16 h. The reaction mixture was cooled to rt and concentrated in vacuum to give a residue. Then HCl/EtOH (10 M, 10 mL) was added to the residue and the resulting reaction mixture was heated to 70 °C again and stirred for 1 h. The reaction mixture was cooled to rt, concentrated in vacuum, diluted with water (20 mL) and extracted with EA (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 10/1) to afford **compound 11-3** as a light yellow oil.
[00178] To a solution of **compound 11-3** (600.0 mg, 1.34 mmol, 1.00 eq) in DCM (12.0 ml) was added PCC (576.0 mg, 2.67 mmol, 2.00 eq), the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by Prep-TLC (SiO2, DCM/MeOH = 10/1) to afford **compound 11-4** as a light brown oil. LC-MS (ESI+): *m/z* = 447.1 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.23 (s, 1H), 5.77 – 5.67 (m, 1H), 5.35 – 5.25 (m, 1H), 4.94 – 4.73 (m, 2H), 4.59 – 4.50 (m, 1H), 3.00 – 2.90 (m, 1H), 2.89 – 2.76 (m, 1H), 2.65 – 2.53 (m, 1H), 2.44 – 2.30 (m, 4H), 2.30 – 2.16 (m, 2H), 2.10 – 1.97 (m, 2H), 1.96 – 1.75 (m, 4H), 1.75 – 1.60 (m, 3H), 1.28 (d, *J* = 6.4 Hz, 3H).

[00179] To a solution of **compound 11-4** (240.0 mg, 0.54 mmol, 1.00 eq) in THF (5.0 ml) was added **fragment SC-1** (107.0 mg, 0.59 mmol, 1.10 eq) and Cs_2CO_3 (350 mg, 1.07 mmol, 2.00 eq). The reaction mixture was heated to 65 °C and stirred for 3 hr. The reaction mixture was cooled to rt, diluted with water (100 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by Prep-TLC (SiO2, DCM/MeOH = 10/1) to afford **compound 11-5** as a light yellow oil. LC-MS (ESI+): *m/z* = 592.3 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.65 (d, *J* = 2.4 Hz, 1H), 8.60 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 5.50 – 5.40 (m, 1H), 5.05 – 4.95 (m, 1H), 4.94 – 4.84 (m, 1H), 4.63 – 4.51 (m, 1H), 4.51 – 4.41 (m, 1H), 3.95 – 3.82 (m, 2H), 3.82 – 3.68 (m, 2H), 3.67 – 3.59 (m, 1H), 3.20 – 2.95 (m, 1H), 2.90 – 2.78 (m, 1H), 2.50 – 2.35 (m, 4H), 2.35 – 2.15 (m, 3H), 2.14 – 1.90 (m, 4H), 1.90 – 1.60 (m, 7H), 1.34 (d, *J* = 5.6 Hz, 3H).

[00180] A solution of **compound 11-5** (210.0 mg, 0.36 mmol, 1.00 eq), malononitrile (64.9 mg, 0.98 mmol, 2.77 eq), sulfur (21.16 mg, 0.66 mmol, 1.86 eq) and 3-aminopropanoic acid (38.6 mg, 0.43 mmol, 1.22 eq) in ethanol (2.0 ml) was heated to 80 °C and stirred for 16 h. Then the reaction mixture was cooled to rt, diluted with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed by brine (50 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 10/1) and SFC (AD, 250mm*30mm*10um Daicel, 65%CO2, 35%EtOH, Flow: 140ml/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time) to afford **compound 11A**. LC-MS (ESI+): *m/z* = 672.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.65 (s, 1H), 8.61 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 1.2 Hz, 1H), 7.06 (s, 2H), 6.97 (d, *J* = 2.8 Hz, 1H), 5.50 – 5.40 (t, *J* = 6.0 Hz, 1H), 5.18 (d, *J* = 15.2 Hz, 1H), 4.90 (d, *J* = 14.4 Hz, 1H), 4.54 – 4.45 (m, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 3.92 – 3.82 (m, 2H), 3.77 – 3.67 (m, 2H), 3.66 – 3.60 (m, 1H), 3.01 – 2.92 (m, 1H), 2.70 – 2.61 (m, 1H), 2.60 – 2.50 (m, 1H), 2.40 (s, 3H), 2.27 – 2.10 (m, 4H), 2.05 – 1.92 (m, 2H), 1.92 – 1.75 (m, 4H), 1.75 – 1.60 (m, 2H), 1.33 (d, *J* = 5.2Hz, 3H).

[00181] Example 5



[00182] To a solution of **fragment AM-1** (684 mg, 5.29 mmol) in THF (10 mL) was added NaH (318 mg, 7.94 mmol, 60% in mineral oil) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min. Then a solution of **compound 12-1** (1.00 g, 5.29 mmol) in THF (2 mL) was added and the reaction mixture was allowed to warm to rt and stirred for 1 hour. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 0/1) to give **compound 12-2** as a yellow gum. LC-MS (ESI+): *m/z* = 237.9 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.22 (s, 1H), 5.03 – 4.93 (m, 1H), 3.00 – 2.90 (m, 1H), 2.67 – 2.55 (m, 1H), 2.35 (s, 3H), 2.29 – 2.21 (m, 1H), 1.89 – 1.75 (m, 1H), 1.73 – 1.57 (m, 3H), 1.30 (d, *J* = 6.0 Hz, 3H).

[00183] To a solution of **compound 12-2** (500 mg, 2.107 mmol) in EtOH (10 mL) was added 50% NH_2OH aq. (0.594 mL, 9.90 mmol) and the reaction mixture was heated to 60 °C and stirred for 2 hours. The reaction mixture was cooled to rt and concentrated under reduced pressure to give crude **compound 12-3** as a white solid. The crude product was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 271.1 $[M+H]^+$.

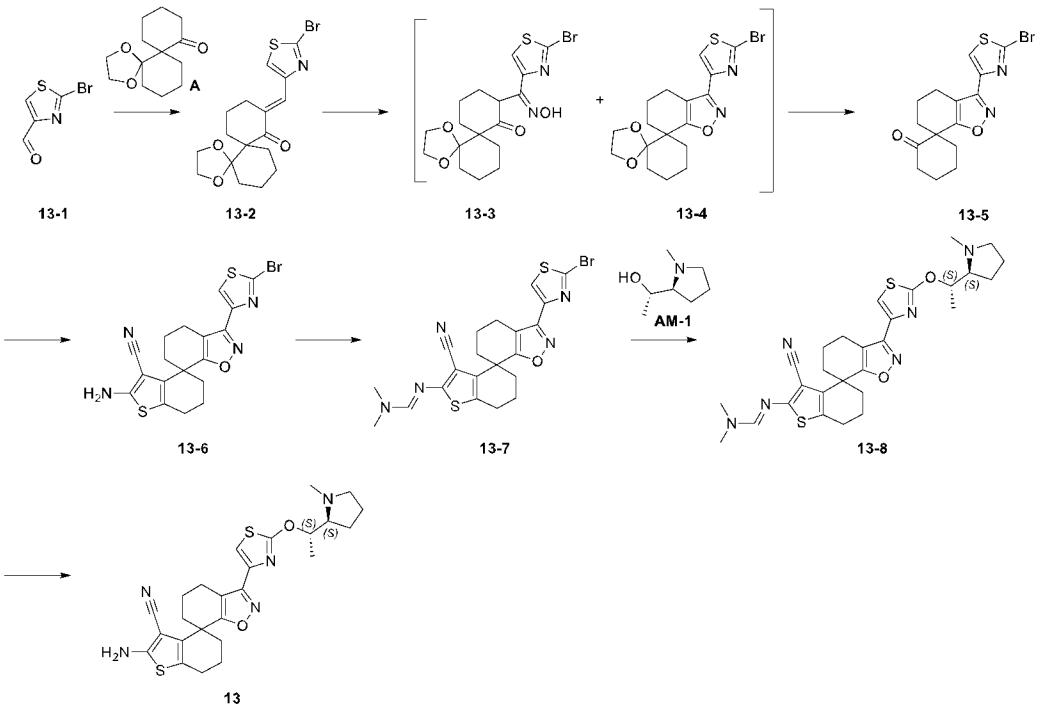
[00184] To a solution of **compound 12-3** (390 mg, 1.44 mmol) and **compound 12-4** (409 mg, 1.73 mmol) in DMF (5 mL) was added TEA (1.00 mL, 7.21 mmol) and HATU (823 mg, 2.16 mmol). The

reaction mixture was stirred at rt for 12 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 0/1) to give **compound 12-5** as a white solid. LC-MS (ESI+): *m/z* = 489.1 $[M+H]^+$.

[00185] To a mixture of compound **6** (600 mg, 1.23 mmol) in THF (5 mL) was added DBU (0.367 mL, 2.46 mmol) and the reaction mixture was heated to 70 °C and stirred for 12 hours. The reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Xtimate C18 150*40mm*10um, Mobile Phase: water (FA)-ACN, Mobile Phase B: acetonitrile Flow rate: 55mL/min, gradient condition from 12 % B to 42 %) and prep-SFC (Column: DAICEL CHIRALPAK IG (250mm*30mm, 10um), Mobile Phase: CO_2-MeOH, Mobile Phase B: acetonitrile Flow rate: 60 mL/min, gradient condition from 60% B to 60%, peak with earlier retention time) to afford **compound 12A**. LC-MS (ESI+): *m/z* = 471.1 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.07 (s, 2H), 5.10 – 4.95 (m, 1H), 2.98 – 2.88 (m, 1H), 2.65 – 2.55 (m, 1H), 2.55 – 2.47 (m, 2H), 2.35 (s, 3H), 2.25 – 2.15 (m, 1H), 2.10 – 2.00 (m, 1H), 1.90 – 1.75 (m, 4H), 1.76 (s, 3H), 1.72 – 1.55 (m, 3H), 1.40 – 1.25 (d, *J* = 6.4 Hz, 3H).

[00186] Example 6



[00187] To a solution of **intermediate A** (2.50 g, 11.2 mmol) and 2-bromothiazole-4-carbaldehyde (2.57 g, 13.3 mmol) in ethanol (15.0 mL) was added sodium hydroxide (1.78 g, 44.6 mmol) and the reaction mixture was stirred at rt for 1 hr. Then another potion of 2-bromothiazole-4-carbaldehyde (2.57 g, 13.3 mmol) was added and the resulting reaction mixture was stirred at rt for 2 hours. After that, the third portion of 2-bromothiazole-4-carbaldehyde (2.57 g, 13.3 mmol) was added and the reaction mixture was stirred at rt again for 16 hours. The reaction mixture was directly concentrated in vacuum to give a residue. The residue was purified by flash column chromatography (SiO2, PE/EA = 9/1) to afford **compound 13-2** as a yellow oil. LC-MS (ESI+): *m/z* = 397.9 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.07 (s, 1H), 3.99 – 3.87 (m, 3H), 3.86 – 3.74 (m, 1H), 3.42 – 3.28 (m, 1H), 2.84 – 2.62 (m, 1H), 2.18 – 2.06 (m, 3H), 1.93 – 1.80 (m, 2H), 1.72 – 1.58 (m, 4H), 1.50 – 1.43 (m, 3H).

[00188] To a solution of **compound 13-2** (400.0 mg, 1.00 mmol) and $NaHCO_3$ (422.0 mg, 5.02 mmol) in EtOH (8.0 mL) was added hydroxylamine hydrochloride (279.0 mg, 4.02 mmol) at rt. The reaction mixture was heated to 90 °C and stirred for 40 hours under O_2 atmosphere. The reaction mixture was cooled to room temperature, concentrated under reduced pressure to afford a mixture of crude **compound 13-3** & **compound 13-4** as a yellow solid. The crude product was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 411.0, 429.1 $[M+H]^+$.

[00189] The mixture of crude **compound 13-3** & **compound 13-4** (1.60 g, 1.40 mmol) in TFA (20.0 mL) was heated to 70 °C and stirred for 2 hours. The reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The residue was neutralized to pH = 7 with saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 3:1) to afford **compound 13-5** as a colorless oil. LC-MS (ESI+): *m/z* = 367.0 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 2.80 – 2.68 (m, 1H), 2.67 – 2.58 (m, 1H), 2.58 – 2.52 (m, 1H), 2.46 – 2.36 (m, 1H), 2.36 – 2.28 (m, 1H), 2.28 – 2.17 (m, 1H), 2.06 – 1.97 (m, 1H), 1.97 – 1.88 (m, 1H), 1.88 – 1.70 (m, 5H), 1.57 – 1.42 (m, 1H).

[00190] To a solution of **compound 13-5** (150.0 mg, 0.40 mmol), 3-aminopropanoic acid (138.0 mg, 1.55 mmol), malononitrile (105.0 mg, 1.59 mmol) and 4A MS (250.0 mg, 0.40 mmol) in EtOH (3.0 ml) was added sulfur (82.0 mg, 2.57 mmol) at rt and the reaction mixture was heated to 80 °C stirred for 16 hours under Ar atmosphere. The reaction mixture was cooled to rt, diluted with saturated $NaHCO_3$ aqueous solution (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, PE/EA = 3:1) to afford **compound 13-6** as a yellow solid. LC-MS (ESI+): *m/z* = 447.0 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 4.62 (s, 2H), 3.06 – 2.95 (m, 1H), 2.76 – 2.55 (m, 3H), 2.16 – 2.04 (m, 4H), 1.89 – 1.79 (m, 2H), 1.69 – 1.60 (m, 2H).

[00191] A solution of **compound 13-6** (45.0 mg, 0.10 mmol) in DMF-DMA (3.0 mL, 22.4 mmol) was stirred at rt for 3 hr. The reaction mixture was directly concentrated in vacuum to give crude **compound 13-7** as a brown oil. The crude product was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 502.1 $[M+H]^+$.

[00192] To a solution of **fragment AM-1** (64.3 mg, 0.49 mmol) in THF (2.0 ml) was added sodium hydride (19.9 mg, 0.49 mmol, 60%w) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hr under N_2 atmosphere. Then a solution of crude **compound 13-7** (50.0 mg, 0.10 mmol) in THF (1.0 ml) was added and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was quenched with water (10 mL) and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: 55-Boston Prime C18 150×30mm, 5μm, Mobile Phase: water ($0.05\%NH_3H_2O$+10mM NH_4HCO_3)-ACN, Mobile Phase B: acetonitrile Flow rate: 25 mL/min, gradient condition from 75% B to 100%) to afford **compound 13-8** as a yellow solid. LC-MS (ESI+): *m/z* = 551.3 $[M+H]^+$.

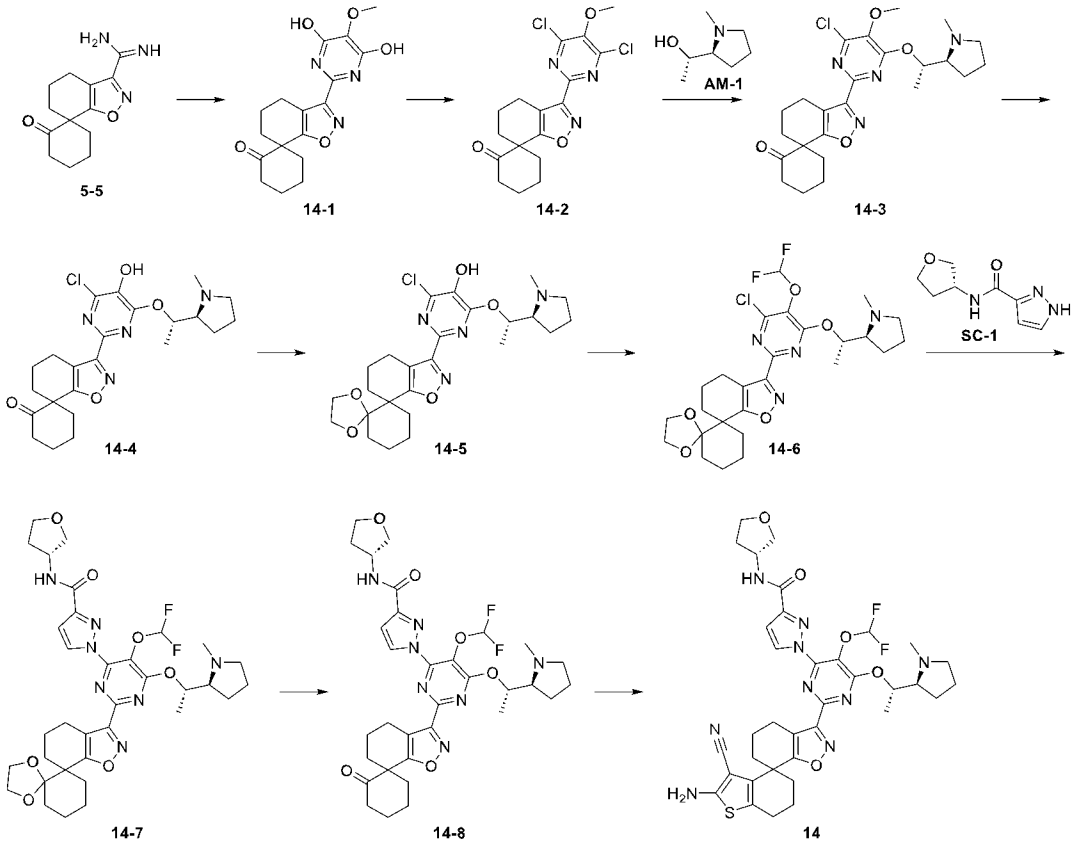
^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.18 (s, 1H), 5.38 – 5.24 (m, 1H), 3.08 – 3.01 (m, 6H), 3.00 – 2.91 (m, 2H), 2.79 – 2.69 (m, 2H), 2.69 – 2.60 (m, 2H), 2.60 – 2.53 (m, 2H), 2.27 – 2.19 (m, 2H), 2.05 – 1.97 (m, 4H), 1.87 – 1.77 (m, 4H), 1.50 – 1.40 (m, 4H), 1.26 (s, 3H).

[00193] To a solution of **compound 13-8** (5.0 mg, 9.08 μmol) in THF (1.0 mL) was added 2M HCl solution (1.0 mL, 2.00 mmol) at rt and the reaction mixture was heated to 40 °C and stirred for 6 hours.

Then the mixture was cooled to rt and concentrated under reduced pressure to afford a residue. The residue was adjusted to pH = 8 with NaOH aqueous solution and purified by prep-HPLC (Column: 55-Boston Prime C18 150×30mm, 5μm, Mobile Phase: water(0.05%NH_3•H_2O+10mM NH_4HCO_3)-ACN, Mobile Phase B: acetonitrile Flow rate: 25 mL/min, gradient condition from 78% B to 100%) to give **compound 13** (0.37 mg, 0.746 μmol, 8% yield). LC-MS (ESI+): *m/z* = 496.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 – 7.32 (m, 1H), 6.91 (s, 2H), 5.33 – 5.02 (m, 1H), 2.99 – 2.91 (m, 1H), 2.90 – 2.80 (m, 1H), 2.68 – 2.60 (m, 1H), 2.55 – 2.50 (m, 3H), 2.35 (s, 3H), 2.25 – 2.15 (m, 1H), 2.02 – 1.88 (m, 4H), 1.86 – 1.70 (m, 5H), 1.70 – 1.55 (m, 3H), 1.32 (d, *J* = 6.4 Hz, 3H).

[00194] Example 7



Compound 14-1 was synthesized in a similar procedure to **compound 5-6** as a light yellow solid. LC-MS (ESI+): *m/z* = 346.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H), 2.90 - 2.80 (m, 1H), 2.71 - 2.61 (m, 1H), 2.61 - 2.50 (m, 2H), 2.47 - 2.28 (m, 2H), 2.15 - 1.95 (m, 3H), 1.94 - 1.76 (m, 3H), 1.74 - 1.60 (m, 2H).

Compound 14-2 was synthesized in a similar procedure to **compound 5-7** as a light yellow solid. LC-MS (ESI+): *m/z* = 382.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 2.94 – 2.83 (m, 1H), 2.78 – 2.61 (m, 2H), 2.61 – 2.49 (m, 1H), 2.48 – 2.30 (m, 2H), 2.23 – 1.95 (m, 4H), 1.95 – 1.70 (m, 4H).

Compound 14-3 was synthesized in a similar procedure to **compound 5-8** as a yellow solid. LC-MS (ESI+): *m/z* = 475.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 - 5.43 (m, 1H), 3.95 (s, 3H), 3.12 - 3.02 (m, 1H), 2.95 - 2.81 (m, 1H), 2.80 - 2.60 (m, 3H), 2.59 - 2.55 (m, 1H), 2.49 (s, 3H), 2.45 - 2.36 (m, 1H), 2.36 - 2.23 (m, 2H), 2.20 - 2.00 (m, 3H), 1.99 - 1.75 (m, 8H), 1.62 - 1.50 (m, 1H), 1.39 (d, *J* = 6.0 Hz, 3H).

To a solution of **compound 14-3** (1.0 g, 2.11 mmol, 1.00 eq) in DCM (20.0 mL) was added aluminum chloride (2.8 g, 21.05 mmol, 10.00 eq) at 0 ℃, the reaction mixture was stirred at room temperature for 18 hr. The reaction mixture was quenched with ice-water (30 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 10/1) to afford **compound 14-4** as a light yellow solid. LC-MS (ESI+): *m/z* = 461.4 $[M+H]^+$.

^{1}H NMR (400 MHz, CDCl3) δ 4.62 - 4.50 (m, 1H), 3.72 - 3.60 (m, 1H), 3.37 - 3.27 (m, 1H), 3.00 - 2.90 (m, 1H), 2.88 (s, 3H), 2.79 - 2.60 (m, 2H), 2.57 - 2.47 (m, 1H), 2.44 - 2.36 (m, 1H), 2.35 - 2.20 (m, 2H), 2.19 - 1.97 (m, 5H), 1.96 - 1.90 (m, 1H), 1.89 - 1.79 (m, 3H), 1.79 - 1.68 (m, 2H), 1.63 - 1.53 (m, 1H), 1.49 (d, *J* = 6.4 Hz, 3H).

To a solution of **compound 14-4** (820.0 mg, 1.78 mmol, 1.00 eq) in ethylene glycol (10.0 mL) was added TMSCl (966.0 mg, 8.89 mmol, 5.00 eq) at 0 ℃, then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with ice-water (30 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with water (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford crude **compound 14-5** as a light yellow solid. LC-MS (ESI): *m/z* = 502.9 $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 4.89 - 4.77 (m, 1H), 3.92 - 3.81 (m, 2H), 3.80 - 3.70 (m, 1H), 3.66 - 3.57 (m, 1H), 3.56 - 3.48 (m, 1H), 3.48 - 3.40 (m, 1H), 3.09 - 3.97 (m, 1H), 2.87 (s, 3H), 2.80 - 2.68 (m, 1H), 2.68 - 2.60 (m, 1H), 2.60 - 2.50 (m, 1H), 2.25 - 2.12 (m, 1H), 2.08 - 1.95 (m, 3H), 1.95 - 1.80 (m, 3H), 1.80 - 1.70 (m, 2H), 1.70- 1.56 (m, 6H), 1.36 (d, *J* = 6.0 Hz, 3H).

To a solution of **compound 14-5** (50.0 mg, 0.10 mmol, 1.00 eq) and NaOH (7.9 mg, 0.20 mmol, 2.00 eq) in acetonitrile (2.5 mL) and water (0.5 mL) was added difluoromethyl trifluoromethanesulfonate (39.6 mg, 0.20 mmol, 2.00 eq) dropwise at 0 °C, then the reaction mixture was stirred at 0 °C for 1 hr. The reaction mixture was quenched with NH_4Cl solution (aq, 5.0 mL) and extracted with EA (10.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by perp-TLC (SiO2, DCM/MeOH = 10/1) to afford **compound 14-6** as a light yellow solid. LC-MS (ESI+): *m/z* = 555.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (t, *J* = 70.4 Hz, 1H), 5.60 - 5.50 (m, 1H), 3.90 - 3.63 (m, 4H), 2.84 - 2.74 (m, 1H), 2.74 - 2.64 (m, 2H), 2.24 - 2.15 (m, 2H), 2.15 - 2.04 (m, 3H), 2.04 - 1.94 (m, 4H), 1.94 - 1.85 (m, 2H), 1.85 - 1.61 (m, 8H), 1.60 - 1.50 (m, 2H), 1.48 (d, *J* = 6.0 Hz, 3H).

Compound 14-7 was synthesized in a similar procedure to **compound 11-5** as a light yellow solid. LC-MS (ESI+): *m/z* = 700.3 $[M+H]^+$.

^{1}H NMR (400 MHz, methanol-*d4*) δ 8.72 (d, *J* =2.0 Hz, 1H), 7.04 (t, *J* =73.2 Hz, 1H), 7.00 (d, *J* =2.8 Hz, 1H), 5.58 - 5.50 (m, 1H), 4.63 - 4.53 (m, 1H), 4.01 - 3.89 (m, 4H), 3.89 - 3.76 (m, 3H), 3.75 - 3.68 (m, 1H), 3.67 - 3.57 (m, 1H), 3.30 - 3.20 (m, 1H), 3.15 - 3.05 (m, 1H), 2.94 - 2.75 (m, 2H), 2.69 (d, *J* =4.8 Hz, 3H), 2.40 - 2.27 (m, 2H), 2.24 - 2.05 (m, 4H), 2.00 - 1.80 (m, 6H), 1.75 - 1.50 (m, 6H), 1.47 (d, *J* =6.0 Hz, 3H).

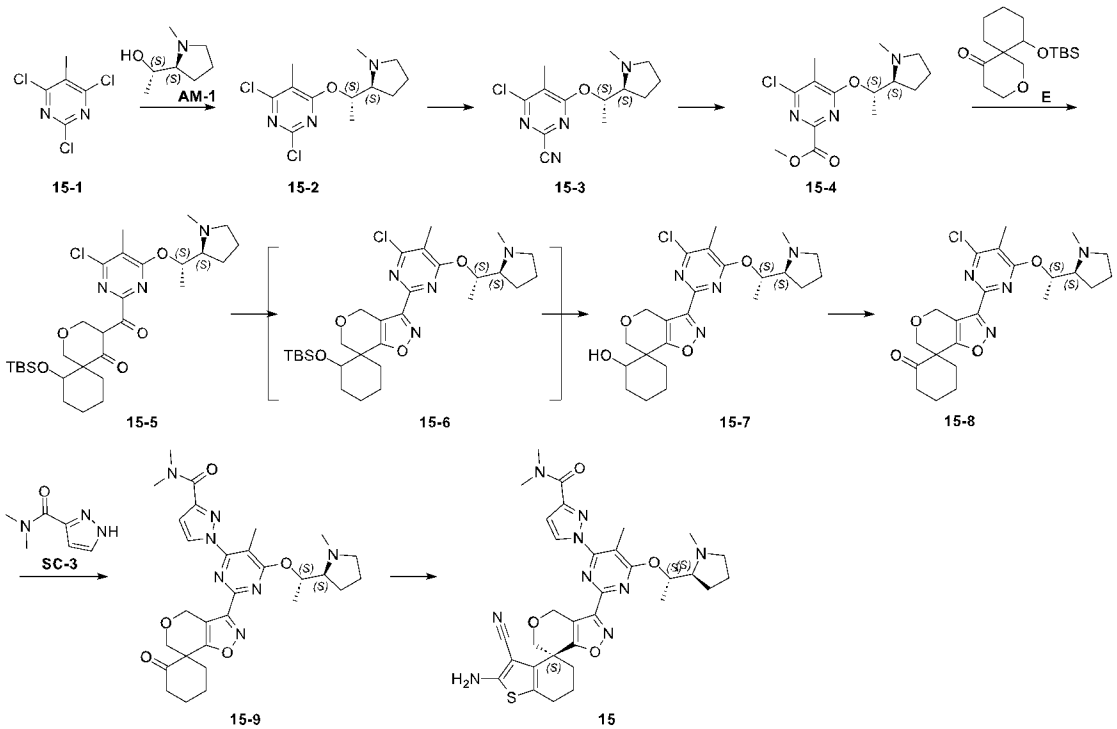
A solution of **compound 14-7** (54.0 mg, 0.08 mmol) in HCl/EtOH (0.5 mL, 10M) was stirred at room temperature for 1 h. The reaction mixture was directly concentrated in vacuum to give a residue. The residue was dissolved in MeOH (1.0 mL), basified with 3 drops of NH_3/MeOH (7M) and concentrated in vacuum to give a residue again. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 15/1) to afford **compound 14-8** as a light yellow solid. LC-MS (ESI+): *m/z* = 656.0 $[M+H]^+$.

^{1}H NMR (400 MHz, methanol-*d4*) δ 8.74 (d, *J* = 2.4 Hz, 1H), 7.05 (t, *J* = 73.2 Hz, 1H), 7.02 (d, *J* = 2.8 Hz, 1H), 5.60 - 5.50 (m, 1H), 4.67 - 4.57 (m, 1H), 4.09 - 3.89 (m, 2H), 3.88 - 3.78 (m, 1H), 3.77 - 3.67 (m, 1H), 3.40 - 3.30 (m, 1H), 3.00 - 2.85 (m, 2H), 2.83 (s, 3H), 2.78 - 2.70 (m, 1H), 2.55 - 2.42 (m, 2H), 2.42 - 2.18 (m, 5H), 2.18 - 1.80 (m, 10H), 1.74 - 1.62 (m, 2H), 1.50 (d, *J* = 6.0 Hz, 3H).

To a solution of **compound 14-8** (35.0 mg, 0.05 mmol, 1.00 eq) in ethanol (0.3 mL) was added malononitrile (7.1 mg, 0.11 mmol, 2.00 eq), ammonium acetate (8.2 mg, 0.11 mmol, 2.00 eq) and sulfur (3.4 mg, 0.11 mmol, 2.00 eq), then the reaction mixture was stirred at 80 ℃ for 2 hr. The reaction mixture was directly concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 15/1) and prep-HPLC (Column: Agilent C18, 19*250mm,10um; mobile phase A: 0.1% FA/H2O, B: ACN: flow rate:20mL/min: gradient:32-42% Retention time:7.5- 9.2 of 17 min) to afford **compound 14** FA salt. LC-MS (ESI+): *m/z* = 736.2 [M+H]$^+$.

^{1}H NMR (400 MHz, methanol-*d4*) δ 8.77 (d, *J* = 2.4 Hz, 1H), 8.50 (s, 1H), 7.06 (t, *J* = 73.6 Hz, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 5.62 - 5.52 (m, 1H), 4.67- 4.57 (m, 1H), 4.03 - 3.93 (m, 2H), 3.90 - 3.81 (m, 1H), 3.75 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 3.19 - 3.10 (m, 1H), 2.95 - 2.85 (m, 2H), 2.84 (s, 3H), 2.69 - 2.55 (m, 2H), 2.41 - 2.25 (m, 3H), 2.20 - 2.00 (m, 6H), 2.00 - 1.80 (m, 7H), 1.52 (d, *J* = 6.4 Hz, 3H).

[00195] Example 8



To a solution of **compound 15-1** (1.53 g, 7.74 mmol) and **AM-1** (1.00 g, 7.74 mmol) in THF (15 mL) was added NaHMDS (1.0 M in THF, 7.97 mL, 7.97 mmol) at -70 ℃, the reaction mixture was stirred at -70 ℃ for 10 min. The reaction mixture was warmed to 0 ℃, quenched with water (30 mL) and extracted with EA (30 mL x 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, PE/EA = 1/9) to afford **compound 15-2** as a yellow oil. LC-MS (ESI+): *m/z* = 289.9 [M+H]$^+$.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.34 - 5.25 (m, 1H), 3.12 - 3.05 (m, 1H), 2.65 - 2.56 (m, 1H), 2.45 (s, 3H), 2.35 - 2.25 (m, 1H), 2.19 (s, 3H), 1.93 - 1.84 (m, 1H), 1.81 - 1.66 (m, 3H), 1.34 - 1.29 (m, 3H).

To a solution of **compound 15-2** (1.50 g, 5.17 mmol) in acetonitrile (15 mL) and water (2 mL) was added NaCN (0.280 g, 5.71 mmol) and DABCO (0.696 g, 6.20 mmol) at 0 ℃, then the reaction mixture was stirred at rt for 4 h. The reaction mixture was quenched with water (40 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, PE/EA = 1/4) to afford **compound 15-3** as a brown oil. LC-MS (ESI+): *m/z* = 280.9 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 5.37 - 5.27 (m, 1H), 3.16 - 3.04 (m, 1H), 2.67 - 2.57 (m, 1H), 2.45 (s, 3H), 2.37 - 2.23 (m, 4H), 1.96 - 1.86 (m, 1H), 1.82 - 1.70 (m, 3H), 1.38 - 1.28 (m, 3H).

A solution of **compound 15-3** (1.20 g, 4.27 mmol) in 2 N HCl/MeOH (5.0 mL) was stirred at 50 ℃ for 3 h. The reaction mixture was cooled to room temperature and directly concentrated under reduced pressure to give a residue. The residue was diluted with DCM (30 mL), washed with saturated $NaHCO_3$ aq. (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude compound **compound 15-4** as a brown solid. The crude **compound 15-4** was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 313.9 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 5.51 - 5.42 (m, 1H), 3.99 (s, 3H), 3.17 - 3.00 (m, 1H), 2.72 - 2.60 (m, 1H), 2.48 (s, 3H), 2.35 - 2.22 (m, 4H), 1.92 - 1.82 (m, 1H), 1.82 - 1.67 (m, 3H), 1.40 - 1.31 (m, 3H).

Magnesium bromide diethyl etherate (15.80 g, 61.2 mmol, 1.50 eq) and **intermediate E** (18.26 g, 61.2 mmol, 1.50 eq) was added to a solution of **compound 15-4** (12.8 g, 40.8 mmol, 1.00 eq) in THF (100 ml) under Ar atmosphere. Then the resulting mixture was stirred at room temperature for 10 min before LiHMDS (102 ml, 102 mmol, 2.50 eq, 1M in THF) was added. The reaction mixture was stirred at 50 ℃ for 4 h. The reaction mixture was directly concentrated in vacuum, diluted with water (200 mL), adjusted to pH=6~7 with 1N HCl aq. and extracted with EA (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 40/1) to afford **compound 15-5** as a light yellow oil. LC-MS (ESI+): *m/z* = 580.0 $[M+H]^+$.

To a solution of **compound 15-5** (14.8 g, 25.5 mmol, 1.00 eq) in EtOH (100 mL) was added hydroxylamine hydrochloride (1.8 g, 25.5 mmol, 1.00 eq) and the reaction mixture was stirred at 70 ℃ for 16 h. The reaction mixture was cooled to rt and directly concentrated in vacuum to give a residue. The residue was diluted with saturated $NaHCO_3$ aq. (50 mL) and extracted with EA (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude **compound 15-6**, which was dissolved in a mixed solvent of EtOH (100 mL) and 10 M HCl/EtOH (10 mL) and stirred at 70 ℃ for 1 h. The reaction mixture was cooled to rt and directly concentrated in vacuum to give a residue. The residue was diluted with water (100 mL) and extracted with EA (200 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a another residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 40/1) to afford **compound 15-7** as a light yellow oil. LC-MS (ESI+): *m/z* = 463.0 $[M+H]^+$.

^1H NMR (400 MHz, CDCl3) δ 5.67 - 5.46 (m, 1H), 5.15 - 5.00 (m, 1H), 4.96 – 4.78 (m, 1H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.80 - 3.71 (m, 1H), 3.49 (d, *J* = 11.6 Hz, 1H), 3.05 - 2.90 (m, 1H), 2.83 – 2.42 (m, 4H), 2.29 (s, 3H), 2.27 - 2.17 (m, 1H), 2.20 - 1.55 (m, 12H), 1.45 (s, 3H).

To a solution of **compound 15-7** (10.0 g, 21.60 mmol, 1.00 eq) in DCM (200.0 ml) was added Dess-Martin periodinane (45.8 g, 108.00 mmol, 5.00 eq) at 0 °C, then the reaction mixture was stirred at 30 ℃ for 6 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq. (200 mL) and extracted with

DCM (200 mL x 2). The combined organic layers were washed with saturated $NaHCO_3$ aq. (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH = 25/1) to afford **compound 15-8** as a light yellow solid. LC-MS (ESI+): *m/z* = 460.9 $[M+H]^+$.

^1H NMR (400 MHz, CDCl3) δ 5.45 - 5.32 (m, 1H), 5.00 - 4.80 (m, 2H), 4.38 (dd, *J* = 11.6 Hz, 4.0 Hz, 1H), 3.60 (dd, *J* = 11.6 Hz, 4.0 Hz, 1H), 2.90 - 2.78 (m, 1H), 2.75 - 2.47 (m, 5H), 2.35 - 2.28 (m, 1H), 2.27 (s, 3H), 2.24 - 2.09 (m, 2H), 2.00 - 1.72 (m, 7H), 1.72 - 1.55 (m, 2H), 1.43 (d, *J* = 6.0 Hz, 3H).

To a solution of **compound 15-8** (200.0 mg, 0.43 mmol, 1.00 eq) in THF (5.0 ml) was added **SC-3** (91.0 mg, 0.65 mmol, 1.50 eq) and Cs_2CO_3 (424.0 mg, 1.30 mmol, 3.00 eq), then the reaction mixture was stirred at 50 ℃ for 2 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 15/1) to afford **compound 15-9** as a light yellow solid. LC-MS (ESI+): *m/z* = 564.2 $[M+H]^+$.

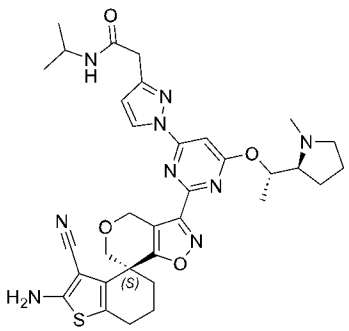
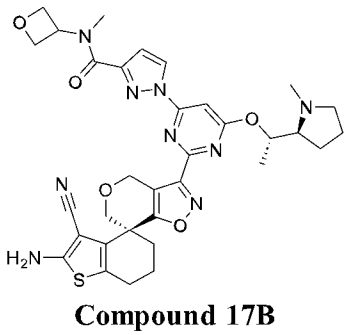
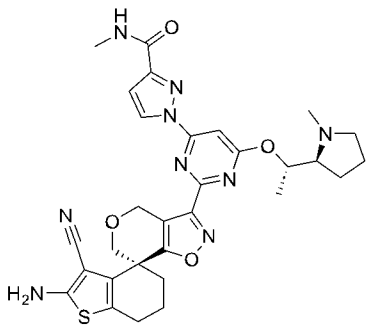
^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 6.94 - 6.89 (m, 1H), 5.72 -5.60 (m, 1H), 5.10 - 4.85 (m, 2H), 4.42 (dd, *J* = 11.6 Hz, 4.0 Hz, 1H), 3.65 (dd, *J* = 11.6 Hz, 4.0 Hz, 1H), 3.39 (d, *J* = 2.8 Hz, 3H), 3.16 (s, 3H), 2.96 - 2.81 (m, 1H), 2.76 - 2.65 (m, 1H), 2.61 - 2.56 (m, 1H), 2.55 (s, 3H), 2.40 - 2.26 (m, 2H), 2.25 - 2.10 (m, 3H), 2.10 - 1.60 (m, 10H), 1.53 - 1.42 (m, 3H).

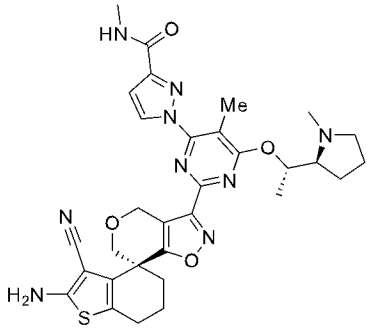
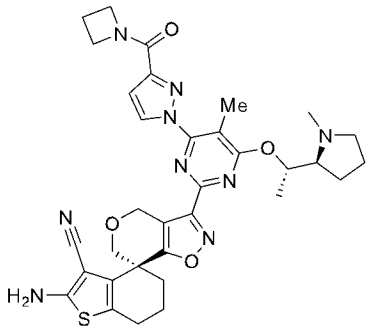
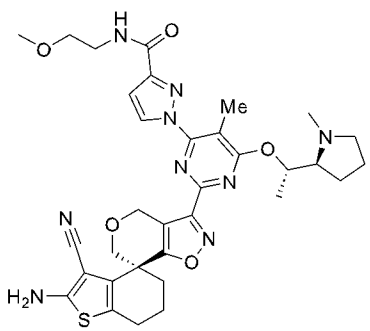
To a solution of **compound 15-9** (60.0 mg, 0.11 mmol, 1.00 eq) in ethanol (2.0 mL) was added ammonium acetate (16.4 mg, 0.21 mmol, 2.00 eq) and sulfur (6.8 mg, 0.21 mmol, 2.00 eq), then the reaction mixture was stirred at 60 °C for 20 min before a solution of malononitrile (14.1 mg, 0.21 mmol) in ethanol (0.25 mL) was added. The reaction mixture was stirred at 60 ℃ for another 2 hours. The reaction mixture was directly concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 15/1) and SFC (Column: Daicel AD, 250 mm * 30 mm * 10um, Mobile phase: 70% CO2, 30% IPA (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 140 ml/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time) to afford **compound 15B**. LC-MS (ESI+): *m/z* = 644.1 $[M+H]^+$.

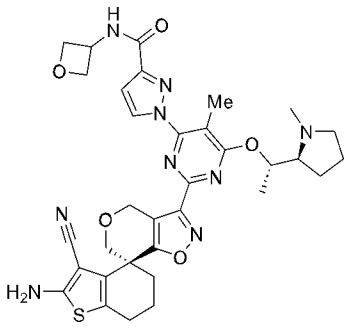
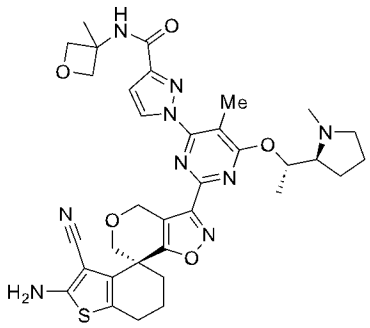
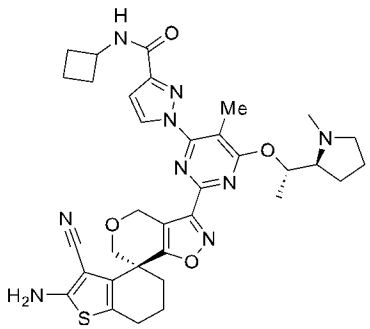
^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 2H), 6.89 (d, *J* = 2.4 Hz, 1H), 5.47 - 5.38 (m, 1H), 5.18 (d, *J* = 14.4 Hz, 1H), 4.87 (d, *J* = 14.4 Hz, 1H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.71 (d, *J* = 11.2 Hz, 1H), 3.29 (s, 3H), 3.03 (s, 3H), 3.03 - 2.95 (m, 1H), 2.72 - 2.64 (m, 1H), 2.63 - 2.53 (m, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 2.28 - 2.20 (m, 1H), 2.19 - 2.10 (m, 1H), 1.90 - 1.80 (m, 4H), 1.80 - 1.72 (m, 1H), 1.72 - 1.62 (m, 2H), 1.33 (d, *J* = 6.4 Hz, 3H).

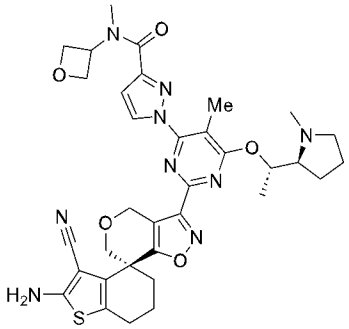
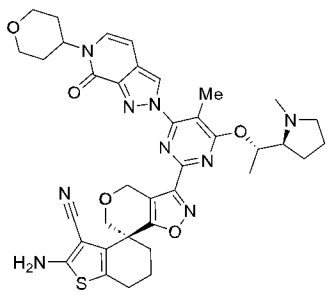
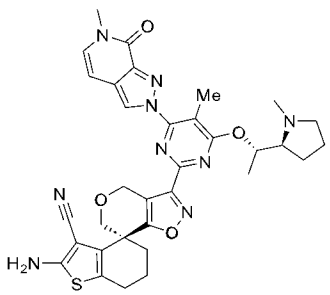
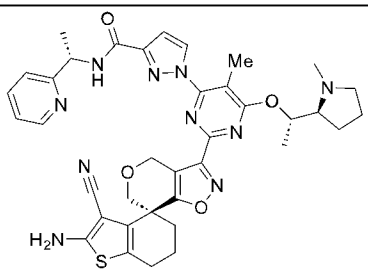
[00196] The following compounds in Table 10 were prepared using similar procedures as described in **Compound 15B**.

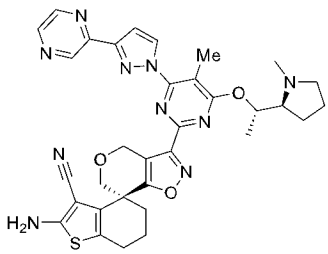
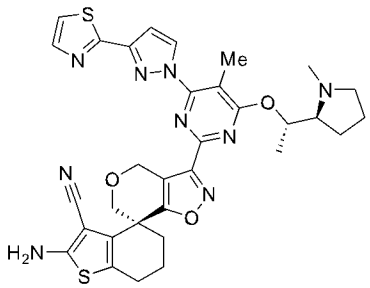
Table 10

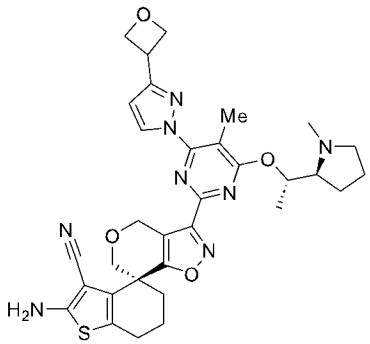
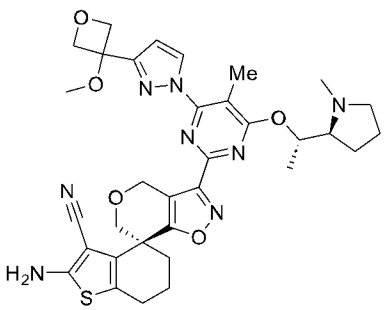
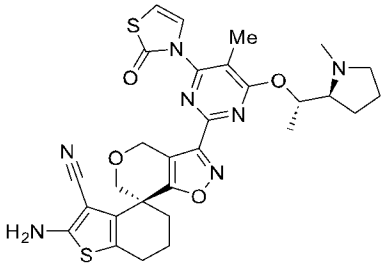
Structure	Spectrum	HPLC/SFC
 **Compound 16B**	LC-MS (ESI+): *m/z* = 658.7 $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-*d4*) δ 8.65 (d, *J* = 2.8 Hz, 1H), 7.33 (s, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 5.58 - 5.48 (m, 1H), 5.25 (d, *J* = 14.4 Hz, 1H), 4.99 (d, *J* = 14.4 Hz, 1H), 4.11 (d, *J* = 11.6 Hz, 1H), 4.03 - 3.93 (m, 1H), 3.83 (d, *J* = 11.6 Hz, 1H), 3.61 (s, 2H), 3.13 - 3.02 (m, 1H), 2.94 (s, 3H), 2.69 - 2.59 (m, 2H), 2.40 - 2.25 (m, 2H), 2.24 - 1.80 (m, 8H), 1.51 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 6H).	Column: Daicel AD, 250 mm * 30 mm, 10 um, eluting with 70% (v) CO2, 30% (v) IPA (+0.1% 7.0 mol/l ammonia in MeOH), Flow rate: 140 ml/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 17B**	LC-MS (ESI+): *m/z* = 672.3 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 - 8.60 (m, 1H), 7.27 - 7.10 (m, 1H), 6.95 - 6.84 (m, 1H), 5.95 - 5.45 (m, 2H), 5.30 - 5.20 (m, 1H), 5.10 - 5.01 (m, 1H), 4.98 - 4.78 (m, 4H), 4.76 - 4.66 (m, 2H), 4.10 - 4.01 (m, 1H), 3.95 - 3.85 (m, 1H), 3.62 - 3.30 (m, 3H), 3.25 - 3.05 (m, 1H), 2.80 - 2.59 (m, 3H), 2.55 (s, 3H), 2.44 - 2.30 (m, 1H), 2.29 - 2.16 (m, 1H), 2.09 - 1.98 (m, 2H), 1.98 - 1.86 (m, 2H), 1.86 - 1.74 (m, 3H), 1.42 (d, *J* = 6.0 Hz, 3H).	Column: DAICEL CHIRALPAK AD, 250 mm * 30 mm, 10 um, eluting with 40% (v) CO_2-*i*-PrOH (0.1% NH_3 in H_2O) at 150 mL/min, peak with later retention time, peak with later retention time
 **Compound 18B**	LC-MS (ESI+): *m/z* = 616.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.6 Hz, 1H), 7.29 (s, 1H), 7.01 (d, *J* = 2.6 Hz, 2H), 5.60 - 5.45 (m, 1H), 5.32 - 5.00 (m, 2H), 4.75 (s, 2H), 4.10 - 3.82 (m, 2H), 3.38 - 3.14 (m, 1H), 3.04 (d, *J* = 5.0 Hz, 3H), 2.93 - 2.77 (m, 1H), 2.76 - 2.51 (m, 5H), 2.50 - 2.37 (m, 1H), 2.32 - 2.20 (m, 1H), 2.13 - 1.80 (m, 7H), 1.44 (d, *J* = 6.2 Hz, 3H).	Column: DAICEL CHIRALPAK IG, 250 mm * 30 mm, 10 um, eluting with 60% (v) CO_2-EtOH (0.1% NH_3 in H_2O) at 80 mL/min, peak with later retention time.

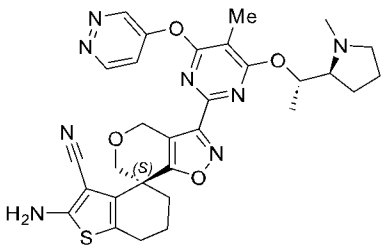
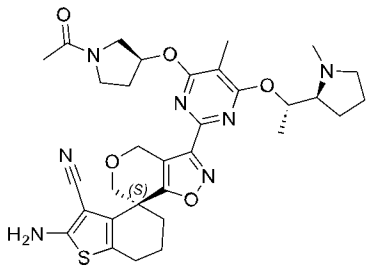
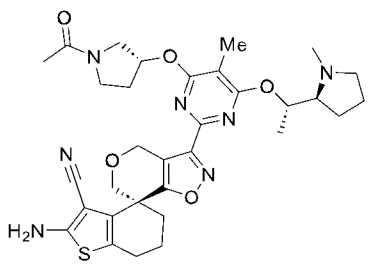
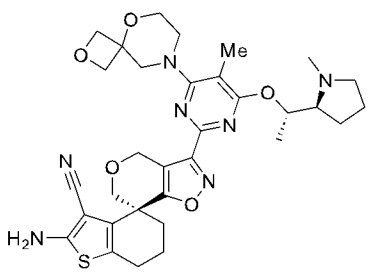
 **Compound 19B**	LC-MS (ESI+): *m/z* = 630.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 2.4 Hz, 1H), 8.35 - 8.27 (m, 1H), 7.05 (s, 2H), 6.96 (d, *J* = 2.8 Hz, 1H), 5.57 - 5.44 (m, 1H), 5.24 (d, *J* = 14.4 Hz, 1H), 4.81 (d, *J* = 14.4 Hz, 1H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.69 (d, *J* = 11.6 Hz, 1H), 3.04 - 2,93 (m, 1H), 2.80 (d, *J* = 4.8 Hz, 3H), 2.72 - 2.61 (m, 1H), 2.60 - 2.51 (m, 2H), 2.51 – 2.40 (m, 6H), 2.32 - 2.20 (m, 1H), 2.19 - 2. 05 (m, 2H), 2.06 - 1.76 (m, 6H), 1.51 - 1.40 (m, 3H).	Column: DAICEL CHIRALPAK IG, 250 * 30 mm, 10 um, Mobile phase: CO_2-EtOH (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 120 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 20B**	LC-MS (ESI+): *m/z* = 656.6 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.61 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 5.49 - 5.39 (m, 1H), 5.21 (d, *J* = 14.8 Hz, 1H), 4.83 (d, *J* = 14.8 Hz, 1H), 4.57 (t, *J* = 7.6 Hz, 2H), 4.14 - 4.03 (m, 3H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.03 - 2.93 (m, 1H), 2.68 - 2.62 (m, 1H), 2.62 - 2.52 (m, 2H), 2.50 (s, 3H), 2.47 (s, 3H), 2.39 - 2.25 (m, 3H), 2.18 - 2.00 (m, 2H), 1.96 - 1.76 (m, 6H), 1.48 - 1.28 (s, 3H).	Column: Daicel AD, 250 mm * 25 mm, 10 um, Mobile phase: CO_2-EtOH (+0.1% 7.0 mol/l ammonia in MeOH, Flow: 70 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 21B**	LC-MS (ESI+): *m/z* = 674.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-*d6)* δ 8.56 (d, *J* = 2.4 Hz, 1H), 8.30 (t, *J* = 5.2 Hz, 1H), 7.05 (s, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 5.50 - 5.37 (m, 1H), 5.18 (d, *J* = 14.0 Hz, 1H), 4.83 (d, *J* = 14.4 Hz, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 3.70 (d, *J* = 11.2 Hz, 1H), 3.51 - 3.38 (m, 4H), 3.27 (s, 3H), 3.05 - 2.95 (m, 1H), 2.73 - 2.63 (m, 1H), 2.63 - 2.51 (m, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.33 - 2.18 (m, 1H), 2.18 - 2.08 (m, 1H), 1.96 - 1.79 (m, 4H), 1.79 - 1.65 (m, 3H), 1.35 (s, 3H).	Column: DAICEL CHIRALPAK AD, 250 mm * 30mm, 10 um, Mobile phase: CO_2-ETOH (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 60 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time.

 **Compound 22B**	LC-MS (ESI+): *m/z* = 672.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, *J* = 6.4 Hz, 1H), 8.58 (s, 1H), 7.05 (s, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 5.53 - 5.42 (m, 1H), 5.27 - 5.17 (m, 1H), 5.10 - 5.00 (m, 1H), 4.82 (d, *J* = 14.4 Hz, 1H), 4.79 - 4.71 (m, 2H), 4.70 - 4.60 (m, 2H), 4.09 (d, *J* = 11.6 Hz, 1H), 3.68 (d, *J* = 11.6 Hz, 1H), 3.03 - 2.93 (m, 1H), 2.70 - 2.51 (m, 3H), 2.50 (s, 3H), 2.49 (s, 3H), 2.25 - 2.10 (m, 2H), 2.00 - 1.70 (m, 7H), 1.45 – 1.35 (m, 3H).	Column: Daicel AD, 250 mm * 30 mm, 10 um, Mobile phase: 70%CO_2-30% IPA (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 120 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time.
 **Compound 23B**	LC-MS (ESI+): *m/z* = 686.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.55 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 2H), 6.95 (d, *J* = 2.8 Hz, 1H), 5.45 - 5.35 (m, 1H), 5.16 (d, *J* = 14.8 Hz, 1H), 4.83 (d, *J* = 14.4 Hz, 1H), 4.77 – 4.64 (m, 2H), 4.36 (d, *J* = 6.4 Hz, 2H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.03 - 2.92 (m, 1H), 2.71 - 2.62 (m, 1H), 2.61 - 2.53 (m, 2H), 2.45 (s, 3H), 2.40 (s, 3H), 2.30 - 2.20 (m, 1H), 2.18 - 2.08 (m, 1H), 1.95 - 1.80 (m, 4H), 1.80 - 1.70 (m, 1H), 1.70 - 1.63 (m, 2H), 1.62 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 3H).	Column: Daicel AD, 250 mm * 25mm, 10 um, Mobile phase: 90% CO_2, 10% MeOH (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 140 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 24B**	LC-MS (ESI+): *m/z* = 670.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d6*) δ 8.54 (d, *J* = 2.8 Hz, 1H), 8.47 (d, *J*=8.0 Hz, 1H), 7.05 (s, 2H), 6.95 (d, *J* = 2.4 Hz, 1H), 5.48 - 5.36 (m, 1H), 5.17 (d, *J* =14.8 Hz, 1H), 4.83 (d, *J* =14.4 Hz, 1H), 4.50 - 4.39 (m, 1H), 4.08 (d, *J* =11.6 Hz, 1H), 3.69 (d, *J* =11.6 Hz, 1H), 3.10 - 2.93 (m, 1H), 2.75-2.65 (m, 1H), 2.64 - 2.52 (m, 2H), 2.46 (s, 3H), 2.45 (s, 3H), 2.25 - 2.07 (m, 6H), 1.90 - 1.60 (m, 9H), 1.34 (d, *J* =6.0 Hz, 3H).	Column: DAICEL CHIRALPAK AD, 250 mm * 30 mm, 10 μm, Mobile phase: CO_2, IPA (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 140mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time

 **Compound 25B**	LC-MS (ESI+): *m/z* = 686.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, *J* = 2.4 Hz, 1H), 7.05 (s, 2H), 6.94- 6.83 (m, 1H), 5.74 - 5.29 (m, 2H), 5.19 (d, *J* = 14.8 Hz, 1H), 4.87 (d, *J* = 14.8 Hz, 1H), 4.80 - 4.65 (m, 4H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.36 - 3.23 (m, 3H), 3.01 - 2.92 (m, 1H), 2.73 - 2.63 (m, 1H), 2.62 - 2.54 (m, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 2.28 - 2.18 (m, 1H), 2.17-2.10 (m, 1H), 1.91 - 1.80 (m, 4H), 1.80 - 1.70 (m, 1H), 1.70 - 1.58 (m, 2H), 1.34 (d, *J* = 6.0Hz, 3H).	Column: Daicel AD, 250 mm * 30 mm, 10 um, Mobile phase: 70% CO_2, 30% IPA (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 140 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 26B**	LC-MS (ESI+): *m/z* = 724.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 5.80 - 5.52 (m, 1H), 5.42 - 5.20 (m, 2H), 5.10 - 4.95 (m, 1H), 4.84 - 4.56 (m, 2H), 4.18 - 4.09 (m, 2H), 4.08 - 4.00 (m, 1H), 3.95 - 3.86 (m, 1H), 3.73 - 3.57 (m, 2H), 3.00 - 2.49 (m, 7H), 2.45 - 2.18 (m, 2H), 2.13 - 1.79 (m, 12H), 1.75 - 1.42 (m, 5H).	Column: DAICEL CHIRALPAK AD, 50 mm * 50 mm,10 um, Mobile Phase: CO_2-EtOH (0.1% NH_3•H_2O), Flow rate: 150 mL/min, gradient condition from 50% B to 50% B, peak with later retention time
 **Compound 27A**	LC-MS (ESI+): *m/z* = 149.7 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 7.2 Hz, 1H), 6.04 - 5.92 (m, 1H), 5.45 - 5.33 (m, 1H), 5.10 - 4.92 (m, 1H), 4.83 - 4.55 (m, 2H), 4.11 - 3.98 (m, 1H), 3.95 - 3.82 (m, 1H), 3.78 - 3.65 (m, 1H), 3.61 (s, 3H), 3.24 - 3.05 (m, 3H), 3.00 - 2.85 (m, 1H), 2.73 - 2.55 (m, 5H), 2.39 - 2.22 (m, 4H), 2.18 - 1.98 (m, 4H), 1.97 - 1.86 (m, 1H), 1.69 (d, *J* = 6.4 Hz, 3H).	Column: DAICEL CHIRALCEL OD, 250 mm * 30 mm,10 um, Mobile Phase: CO_2-EtOH (0.1% NH_3•H_2O), Flow rate: 80 mL/min, gradient condition from 60% B to 60% B, peak with earlier retention time
	LC-MS (ESI+): *m/z* = 721.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, *J* = 7.6 Hz, 1H), 8.58 (d, *J* = 2.8 Hz, 1H), 8.55 (d, *J* = 4.0 Hz, 1H), 7.84 – 7.74 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 6.8 Hz,	Column: Daicel AD, 250 mm * 30 mm* 10 um, Mobile phase: 60% CO2, 40% IPA (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 140

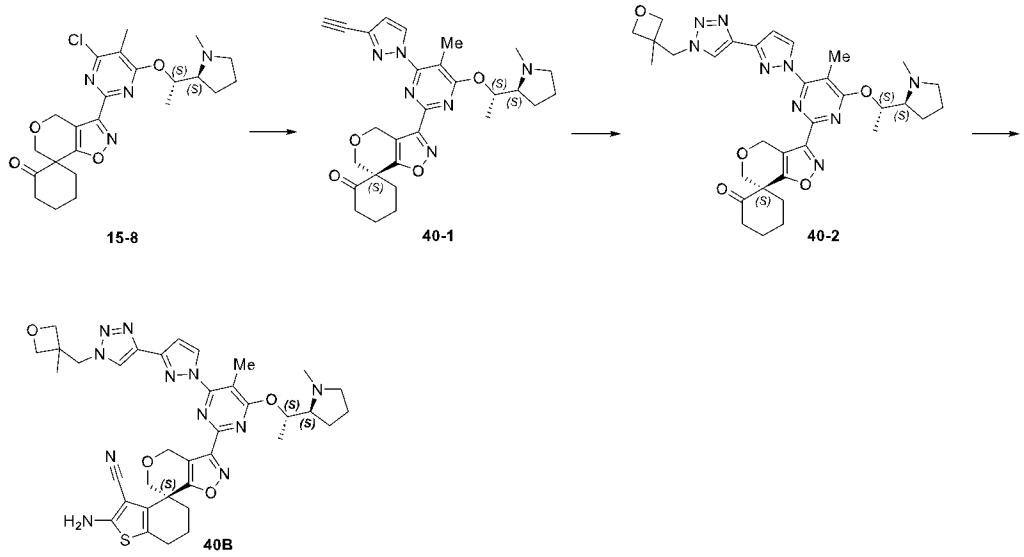
Compound 28B	5.2 Hz, 1H), 7.05 (s, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.50 – 5.40 (t, *J* = 6.4 Hz, 1H), 5.30 - 5.11 (m, 2H), 4.85 (d, *J* = 14.4 Hz, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.08 - 2.93 (m, 1H), 2.75 - 2.64 (m, 1H), 2.62 - 2.50 (m, 2H), 2.47 (s, 3H), 2.41 (s, 3H), 2.33 - 2.19 (m, 1H), 2.18 - 2.05 (m, 1H), 1.97 - 1.62 (m, 7H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H).	mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 29B**	LC-MS (ESI+): *m/z* = 651.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 – 9.35 (m, 1H), 8.68 – 8.62 (m, 1H), 8.61 (s, 1H), 8.57 – 8.50 (m, 1H), 7.20 – 7.12 (m, 1H), 5.57 – 5.47 (m, 1H), 5.30- 5.20 (m, 1H), 5.13 – 5.00 (m, 1H), 4.66 (s, 2H), 4.10 – 4.00 (m, 1H), 3.98 – 3.86 (m, 1H), 3.25 – 3.04 (m, 1H), 2.79 – 2.67 (m, 2H), 2.67 (s, 3H), 2.54 (s, 3H), 2.37 – 2.19 (m, 2H), 2.10 – 2.00 (m, 2H), 2.00 – 1.79 (m, 6H), 1.43 (d, *J* = 6.0 Hz, 3H).	Column: DAICEL CHIRALPAK AD, 250 mm * 30 mm,10 um, Mobile Phase: CO_2-EtOH (0.1% NH_3H_2O), Flow rate: 80 mL/min, gradient condition from 50% B to 50% B, peak with later retention time
 **Compound 30A**	LC-MS (ESI+): *m/z* = 656.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 3.2 Hz, 1H), 7.83 (d, *J* = 3.2 Hz, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 2H), 5.50 - 5.38 (m, 1H), 5.18 (d, *J* = 14.4 Hz, 1H), 4.87 (d, *J* = 14.4 Hz, 1H), 4.09 (d, *J* = 11.2 Hz, 1H), 3.71 (d, *J* = 11.6 Hz, 1H), 3.03 - 2.94 (m, 1H), 2.72 - 2.63 (m, 1H), 2.62 - 2.50 (m, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 2.32 - 2.17 (m, 1H), 2.16 - 2.06 (m, 1H), 1.92 - 1.65 (m, 7H), 1.33 (d, *J* = 6.4 Hz, 3H).	Column: Daicel IB, 250 mm * 30 mm, 10 um, 50% CO_2, Mobile phase: 50% IPA (+0.2% 7.0 mol/L ammonia in MeOH), Flow: 120 mL/min, Temp: RT, Back Pressure: 100 bar, peak with earlier retention time

 **Compound 31B**	LC-MS (ESI+): *m/z* = 629.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 2.4 Hz, 1H), 7.05 (s, 2H), 6.71 (d, *J* = 2.4 Hz, 1H), 5.47 - 5.36 (m, 1H), 5.15 (d, *J* = 14.4 Hz, 1H), 4.93 (dd, *J* = 8.4 Hz, 5.6 Hz, 2H), 4.85 (d, *J* = 14.4 Hz, 1H), 4.75 (dd, *J* = 6.8 Hz, 5.6 Hz, 2H), 4.45 - 4.33 (m, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 3.71 (d, *J* = 11.6 Hz, 1H), 3.03 - 2.92 (m, 1H), 2.74 - 2.52 (m, 3H), 2.46 (s, 3H), 2.39 (s, 3H), 2.28 - 2.17 (m, 1H), 2.17 - 2.09 (m, 1H), 1.93 - 1.62 (m, 7H), 1.32 (d, *J* = 6.0 Hz, 3H).	Column: SunFire Prep C18 OBD, 19*250 mm, 10um, Mobile phase A: 0.1% FA/H_2O, B: MeCN; flow rate: 20 mL/min; Gradient: 25-32%; Retention time: 10.0-11.4, 11.5-13.0 min of 18.0 min, peak with later retention time
 **Compound 32B**	LC-MS (ESI+): *m/z* = 658.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 2H), 6.66 (d, *J* = 2.8 Hz, 1H), 5.47 - 5.37 (m, 1H), 5.17 (d, *J* = 14.8 Hz, 1H), 4.93 - 4.79 (m, 3H), 4.80 - 4.71 (m, 2H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.13 (s, 3H), 3.04 - 2.93 (m, 1H), 2.74 - 2.63 (m, 1H), 2.63 - 2.52 (m, 2H), 2.46 (s, 3H), 2.39 (s, 3H), 2.30 - 2.18 (m, 1H), 2.17 - 2.07 (m, 1H), 1.96 - 1.80 (m, 4H), 1.80 - 1.63 (m, 3H), 1.32 (d, *J* = 6.4 Hz, 3H).	Column: SunFire Prep C18 OBD, 19*250 mm, 10 um, Mobile phase A: 0.1% FA/H_2O, B: MeCN, Flow rate: 20 mL/min, Gradient: 27-31%, Retention Time: 9.2-11.0, 11.2-12.3 min of 18 min, peak with later retention time
 **Compound 33B FA salt**	LC-MS (ESI+): *m/z* = 606.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (brs, 1H), 7.31 (d, *J* = 5.6 Hz, 1H), 7.04 (s, 2H), 6.75 (d, *J*=5.6 Hz, 1H), 5.42 - 5.33 (m, 1H), 5.10 (d, *J* = 14.8 Hz, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 3.68(d, *J* = 11.2 Hz, 1H), 3.03 - 2.92 (m, 1H), 2.72 - 2.62 (m, 1H), 2.61 - 2.52 (m, 2H), 2.39 (s, 3H), 2.28 - 2.20 (m, 1H), 2.17 - 2.07 (m, 1H), 2.04 (s, 3H), 1.93 - 1.72 (m, 4H), 1.72 - 1.60 (m, 3H), 1.32 (d, *J* = 6.0 Hz, 3H).	Column: SunFire C18, 19 mm * 250 mm,10 um, Mobile phase A: 0.1% FA/H_2O, B: MeCN, Flow rate: 20 mL/min: Gradient: 24-34%, Retention time:7.4 ~ 9 of 17 min), peak with later retention time

 **Compound 34A**	LC-MS (ESI+): *m/z* = 601.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 2H), 6.62 (dd, *J* = 8.4 Hz, 3.2 Hz, 1H), 5.47 - 5.35 (m, 1H), 5.14 (d, *J* = 14.8 Hz, 1H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.06 - 2.91 (m, 1H), 2.73 - 2.60 (m, 1H), 2.60 - 2.50 (m, 2H), 2.39 (s, 3H), 2.33 - 2.23 (m, 1H), 2.21 (s, 3H), 2.17 - 2.08 (m, 1H), 1.96 - 1.80 (m, 4H), 1.80 - 1.62 (m, 3H), 1.33 (d, *J* = 6.4 Hz, 3H).	Column: Daicel AD, 250 mm * 25 mm * 10 um, Mobile phase: 65% CO_2, 35% IPA (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 140 mL/min, Temp: RT, Back Pressure: 100 bar, peak with earlier retention time
 **Compound 35B**	LC-MS (ESI+): *m/z* = 634.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (s, 2H), 5.75 - 5.58 (m, 1H), 5.40 - 5.27 (m, 1H), 5.23 - 5.06 (m, 1H), 4.79 (d, *J* = 14.8 Hz, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 3.75 - 3.50 (m, 5H), 3.02 - 2.90 (m, 1H), 2.66 - 2.53 (m, 3H), 2.47 (s, 3H), 2.42 - 2.05 (m, 4H), 2.01 (s, 3H), 2.00 - 1.90 (m, 3H), 1.90 - 1.62 (m, 7H), 1.40 - 1.30 (m, 3H).	Column: IG, 250 * 30 mm, 10 mm, Mobile phase: 55% n-Hexane, 45% EtOH (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 60 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 36B**	LC-MS (ESI+): *m/z* = 634.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (s, 2H), 5.74 - 5.60 (m, 1H), 5.47 - 5.33 (m, 1H), 5.25 - 5.11 (m, 1H), 4.85 - 4.72 (m, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 3.91 - 3.54 (m, 5H), 3.00 - 2.90 (m, 1H), 2.70 - 2.50 (m, 3H), 2.48 (s, 3H), 2.40 - 2.05 (m, 4H), 2.01 (s, 3H), 1.96 (d, *J* = 24.0 Hz, 3H), 1.94 - 1.66 (m, 7H), 1.39 - 1.32 (m, 3H).	Column: IG, 250*30 mm, 10 mm, Mobile phase: 60% CO_2, 40% MeOH (+0.1% 7.0 mol/L ammonia in MeOH), Flow: 80 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 37B**	LC-MS (ESI+): *m/z* = 634.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) : 5.49 - 5.37 (m, 1H), 5.26 - 5.15 (m, 1H), 5.05 - 4.93 (m, 1H), 4.75 - 4.60 (m, 4H), 4.55 - 4.45 (m, 2H), 4.05 - 3.97 (m, 1H),3.93 - 3.85 (m, 1H), 3.85 - 3.74 (m, 2H), 3.66 - 3.55 (m, 2H), 3.35 - 3.24 (m, 2H), 3.24 - 3.12 (m, 1H), 2.82 - 2.57 (m, 3H), 2.54 (s,	Column: Daicel ChiralPak IG, 250 mm * 30 mm, 10 μm, Mobile Phase: CO_2-EtOH (0.1% NH_3H_2O), Flow rate: 80 mL/min, gradient condition from 60% B to 60% B, peak with later retention time

	3H), 2.41 - 2.31 (m, 1H), 2.30 - 2.20 (m, 1H), 2.13 (s, 3H), 2.10 - 1.74 (m, 7H), 1.41 - 1.33 (m, 3H).	

[00197] Example 9



To a solution of **compound 15-8** (30 mg, 0.065 mmol) in THF (1 mL) was added 3-ethynyl-1*H*-pyrazole (7.19 mg, 0.078 mmol) and Cs_2CO_3 (42.4 mg, 0.13 mmol). The reaction mixture was stirred at 50 ℃ for 12 hr. The reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (SiO2, DCM/MeOH = 9/1) to afford **compound 40-1** as a yellow oil. LC-MS (ESI+): *m/z* = 517.5 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.40 (m, 1H), 6.66 - 6.59 (m, 1H), 5.52 - 5.34 (m, 1H), 5.07 - 4.85 (m, 2H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.62 (d, *J* = 11.6 Hz, 1H), 3.20 (s, 1H), 3.16 - 3.04 (m, 1H), 2.95 - 2.84 (m, 1H), 2.72 - 2.11 (m, 12H), 2.03 - 1.65 (m, 7H), 1.43 - 1.33 (m, 3H).

Sodium azide (340 mg, 5.23 mmol) was added to a solution of tetrabutylammonium bromide (0.049 g, 0.15 mmol) in water (5 mL), then 3-(bromomethyl)-3-methyloxetane (0.35 mL, 3.0 mmol) was added to the mixture. The reaction mixture was stirred at 100 ℃ for 30 min. The reaction mixture was cooled to room temperature, adjusted to pH >10 with 1M NaOH aq. and stirred for 30 min. The resulting mixture was extracted with EA (5 mL*2). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was used directly to the next step without further purification.

DIPEA (0.014 mL, 0.077 mmol), above mentioned solution (2 mL) and copper (I) iodide (0.74 mg, 3.9 μmol) was added to a solution of **compound 40-1** (20 mg, 0.039 mmol) in DCM (5 mL). The reaction mixture was stirred at 40 ℃ for 1 h. The mixture was cooled to rt and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (SiO2, DCM/MeOH = 9/1) to afford **compound 40-2** as a yellow oil. LC-MS (ESI+): *m/z* = 644.5 $[M+H]^+$.

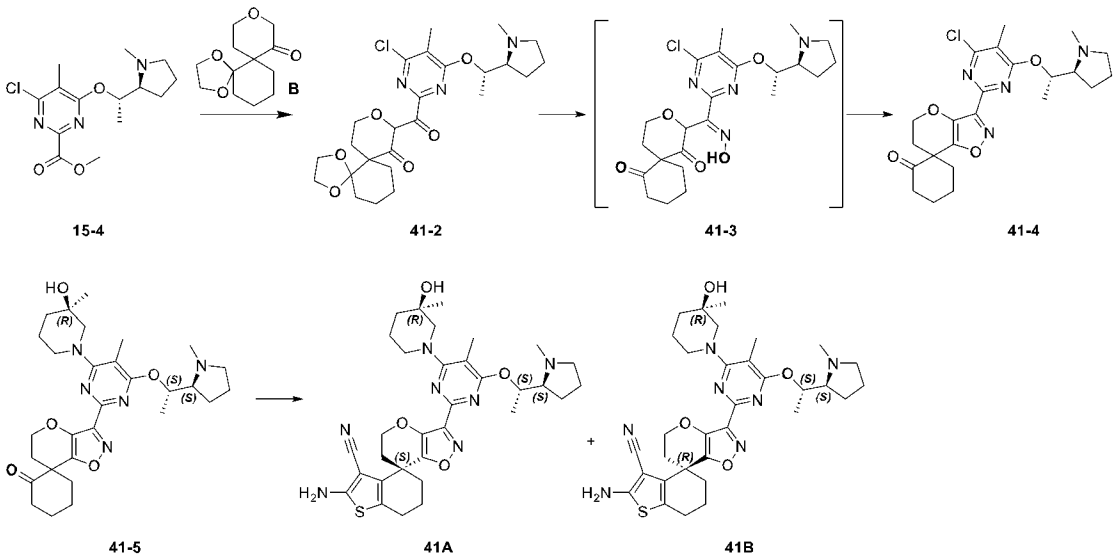
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 - 8.46 (m, 1H), 7.94 (s, 1H), 7.11 - 6.90 (m, 1H), 5.60 – 5.40 (m, 1H), 5.08 - 4.94 (m, 2H), 4.78 - 4.62 (m, 4H), 4.55 - 4.40 (m, 3H), 3.70 - 3.58 (m, 1H), 2.97 - 2.79 (m, 2H), 2.69 - 2.11 (m, 12H), 2.06 - 1.79 (m, 7H), 1.50 - 1.28 (m, 6H).

To a solution of **compound 40-2** (20.0 mg, 0.031 mmol) and ammonium acetate (4.79 mg, 0.062 mmol) in EtOH (1 ml) was added sulfur (10 mg, 0.312 mmol). The resulting mixture was stirred at 60 ℃ for 15

minutes, then malononitrile (4.1 mg, 0.062 mmol) was added at 60 ℃ and the reaction mixture was stirred at 60 ℃ for 2 hours. The reaction mixture was cooled to rt, quenched with saturated $NaHCO_3$ aq. (5 mL) and extracted with DCM (5.0 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Welch Xtimate C18 150 * 30 mm * 5 um, Mobile Phase: water (FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 20% B to 50% B) and SFC (Column: DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), Condition: CO_2-EtOH (0.1% NH_3H_2O), Begin B: 50%, Flow Rate: 150 ml/min, peak with later retention time) to afford **compound 40B**. LC-MS (ESI+): *m/z* = 724.4 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.4 Hz, 1H), 7.94 (s, 1H), 7.02 (d, *J* = 2.8 Hz, 1H), 5.05 -4.94 (m, *J* = 6.3 Hz, 1H), 5.22 (d, *J* = 14.8 Hz, 1H), 5.02 (d, *J* = 14.8 Hz, 1H), 4.78 – 4.70 (m, 4H), 4.67 (s, 2H), 4.47 (d, *J* = 6.4 Hz, 2H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.89 (d, *J* = 11.6 Hz, 1H), 3.16 - 3.07 (m, 1H), 2.75 - 2.59 (m, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 2.37 - 2.17 (m, 2H), 2.06 - 1.97 (m, 2H), 1.96 - 1.79 (m, 5H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.33 (s, 3H).

[00198] Example 10



To the mixture of **compound 15-4** (500 mg, 1.59 mmol), 3A MS (500 mg) and **intermediate B** (433 mg, 1.91 mmol) in acetonitrile (5 mL) was added magnesium bromide diethyl etherate (1.65 g, 6.37 mmol) and DIPEA (1.11 mL, 6.37 mmol) and the resulting mixture was stirred at 60 ℃ for 6 hours. After cooling to room temperature, the reaction mixture was adjusted to pH = 7 with 1N HCl aq. and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, DMC/MeOH = 9/1) to afford **compound 41-2** as a brown oil. LC-MS (ESI+): *m/z* = 508.3 $[M+H]^+$.

To a solution of **compound 41-2** (1.7 g, 2.01 mmol) in EtOH (15 mL) was added hydroxylamine hydrochloride (140 mg, 2.01 mmol) and the resulting mixture was stirred at 70 ℃ for 4 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a crude **compound 41-3**. The crude **compound 41-3** was directly used in the next step without further purification. LC-MS (ESI+): *m/z* = 479.2 $[M+H]^+$.

A solution of **compound 41-3** (1.80 g) in TFA (18 mL) was stirred at 80 ℃ for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a residue. The

residue was adjusted to pH = 7 with saturated $NaHCO_3$ aq. and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, DCM/MeOH = 9/1) to afford **compound 41-4** as a brown oil. LC-MS (ESI+): *m/z* = 461.2 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$): 5.57 - 5.44 (m, 1H), 4.42 - 4.33 (m, 1H), 4.22 - 4.10 (m, 1H), 3.22 - 3.07 (m, 1H), 2.95 - 2.85 (m, 1H), 2.79 - 2.64 (m, 1H), 2.59 - 2.38 (m, 7H), 2.38 - 2.30 (m, 1H), 2.25 - 2.17 (m, 2H), 1.96 - 1.76 (m, 8H), 1.70 - 1.60 (m, 2H), 1.40 - 1.33 (m, 3H).

To a solution of **compound 41-4** (150 mg, 0.325 mmol) in DMF (4 mL) was added (*R*)-3-methylpiperidin-3-ol hydrochloride (247 mg, 1.63 mmol) and DIEA (0.57 mL, 3.25 mmol). The reaction mixture was stirred at 100 ℃ for 16 h. The reaction mixture was cooled to room temperature, diluted with EA (10 mL) and washed with water (5 mL x 2) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO2, DCM/MeOH = 9/1) to afford **compound 41-5** as a yellow oil. LC-MS (ESI+): *m/z* = 540.3 $[M+H]^+$.

To a solution of **compound 41-5** (70.0 mg, 0.130 mmol) in ethanol (2 mL) was added ammonium acetate (20.0 mg, 0.259 mmol) and sulfur (8.30 mg, 0.259 mmol). The reaction mixture was stirred at 60 ℃ for 20 min, then a solution of malononitrile (17.1 mg, 0.259 mmol) in ethanol (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred at 60 ℃ for 8 h. The reaction mixture was cooled to room temperature, diluted with DCM (10 mL), washed with sat. $NaHCO_3$ aq. (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO2, DCM/MeOH = 9/1) and SFC (DAICEL CHIRALPAK AD (250 mm * 30 mm,10 um), eluting with 40% (v) CO_2 – *i*-PrOH (0.1% NH_3H_2O) at 150 mL/min) to afford **compound 41A** (peak with earlier retention time) and **compound 41B** (peak with later retention time).

Compound 41A

LC-MS (ESI+): *m/z* = 620.5 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 5.65 - 5.52 (m, 1H), 4.83 (s, 2H), 4.78 - 4.66 (m, 1H), 4.52 - 4.41 (m, 1H), 4.29 - 4.16 (m, 1H), 4.09 - 3.97 (m, 1H), 3.73 - 3.59 (m, 1H), 3.24 - 3.12 (m, 1H), 3.12 - 3.01 (m, 1H), 2.98 - 2.89 (m, 1H), 2.87 - 2.71 (m, 1H), 2.71 - 2.65 (m, 1H), 2.65 - 2.55 (m, 1H), 2.55 (s, 3H), 2.48 - 2.25 (m, 2H), 2.26 - 2.14 (m, 1H), 2.08 (s, 3H), 2.08 - 1.94 (m, 3H), 1.94 - 1.70 (m, 7H), 1.56 - 1.44 (m, 2H), 1.43 - 1.33 (m, 3H), 1.27 (s, 3H).

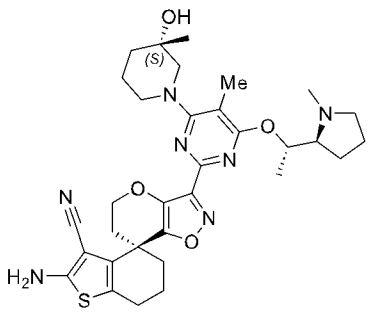
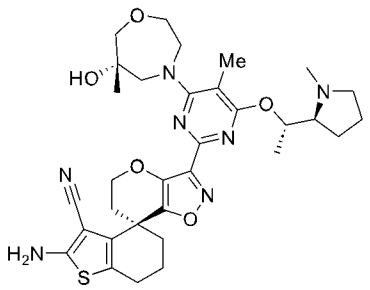
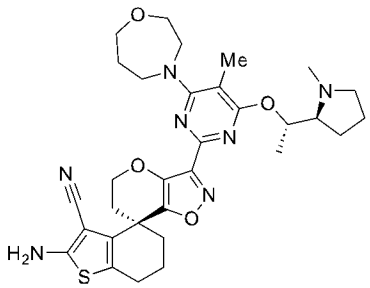
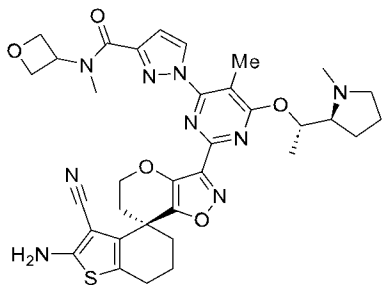
Compound 41B

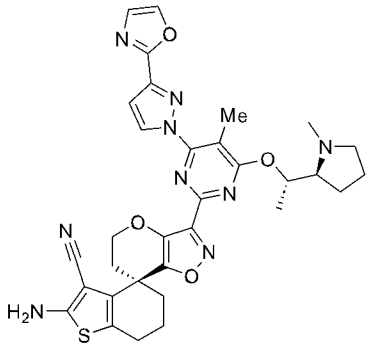
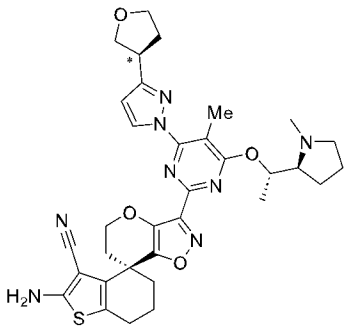
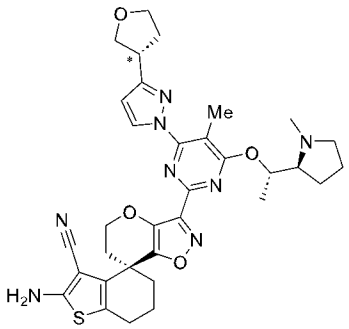
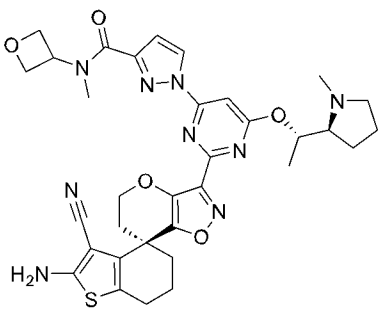
LC-MS (ESI+): *m/z* = 620.4 $[M+H]^+$.

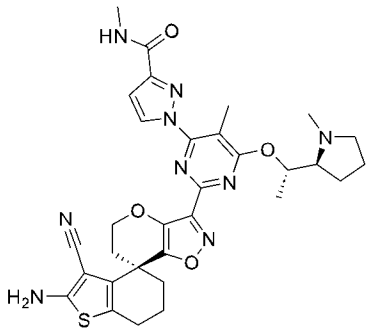
^1H NMR (400 MHz, $CDCl_3$) δ 5.64 - 5.50 (m, 1H), 5.01 - 4.86 (m, 1H), 4.81 (s, 2H), 4.51 - 4.40 (m, 1H), 4.29 - 4.13 (m, 2H), 3.77 - 3.65 (m, 1H), 3.31 - 3.21 (m, 1H), 3.17 - 3.05 (m, 1H), 3.00 - 2.83 (m, 2H), 2.74 - 2.54 (m, 5H), 2.53 - 2.40 (m, 2H), 2.22 - 2.11 (m, 1H), 2.06 (s, 3H), 2.03 - 1.93 (m, 3H), 1.93 - 1.70 (m, 7H), 1.53 - 1.44 (m, 2H), 1.44 - 1.35 (m, 3H), 1.27 (s, 3H).

[00199] The following compounds in Table 11 were prepared using similar procedures as described in **Compound 41B**.

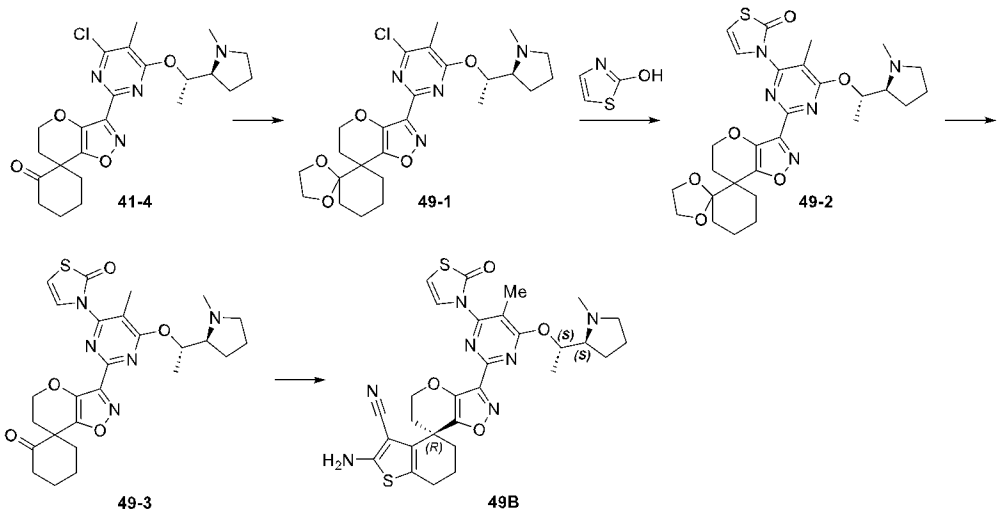
Table 11

Structure	Spectrum	HPLC/SFC
 **Compound 42B**	LC-MS (ESI+): *m/z* = 620.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 - 5.42 (m, 1H), 4.80 (s, 2H), 4.55 - 4.40 (m, 1H), 4.28 - 4.00 (m, 2H), 3.77 - 3.60 (m, 1H), 3.39 - 3.25 (m, 1H), 3.16 - 2.83 (m, 3H), 2.78 - 2.32 (m, 7H), 2.22 - 2.15 (m, 1H), 2. 07 (s, 3H), 2.02 - 1.70 (m, 11H), 1.57 - 1.34 (m, 5H), 1.27 (s, 3H).	Column: C18, 150 * 30 mm, Mobile Phase: water (FA), Mobile Phase B: acetonitrile Flow rate: 25 mL/min, gradient condition from 21% B to 51%), peak with later retention time
 **Compound 43B**	LC-MS(ESI+): *m/z* = 636.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 - 6.60 (m, 1H), 5.66 - 5.57 (m, 1H), 4.81 (s, 2H), 4.47 - 4.37 (m, 1H), 4.15 (t, *J* = 11.3 Hz, 1H), 4.08 - 3.91 (m, 2H), 3.90 - 3.82 (m, 1H), 3.67 (d, *J* = 12.3 Hz, 1H), 3.53 - 3.31 (m, 4H), 3.22 - 3.07 (m, 1H), 2.76 - 2.57 (m, 3H), 2.56 - 2.39 (m, 4H), 2.35 - 2.22 (m, 1H), 2.20 - 2.12 (m, 1H), 2.08 (s, 3H), 2.05 - 1.75 (m, 8H), 1.36 (d, *J* = 6.4 Hz, 3H), 1.33 (s, 3H).	Column: Daicel ChiralPak IG, 250 * 30 mm, 10 um, eluting with 60% - 60% (v) CO_2/EtOH (0.1% NH_3H_2O) at 80 mL/min, peak with later retention time
 **Compound 44A**	LC-MS (ESI+): *m/z* = 606.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) : 5.57 – 5.46 (m, 1H), 4.83 – 4.70 (m, 2H), 4.47 – 4.37 (m, 1H), 4.23 – 4.11 (m, 1H), 3.96 – 3.84 (m, 2H), 3.83 – 3.65 (m, 6H), 3.48 – 3.29 (m, 1H), 2.80 – 2.54 (m, 6H), 2.50 – 2.40 (m, 1H), 2.24 – 2.15 (m, 1H), 2.12 (s, 3H), 2.06 – 1.89 (m, 9H), 1.61 – 1.56 (m, 2H), 1.46 – 1.42 (m, 3H).	Column: DAICEL CHIRALCEL OX, 250 mm * 30 mm,10 μm, Mobile Phase: CO_2-MeOH (0.1% NH_3H_2O), Flow rate: 120 mL/min, gradient condition from 60% B to 60% B, peak with earlier retention time
 **Compound 45B**	LC-MS (ESI+): *m/z* = 686.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.62 (m, 1H), 6.90 (d, *J* = 15.3 Hz, 1H), 6.12 – 5.51 (m, 2H), 4.99 – 4.82 (m, 4H), 4.72 (s, 2H), 4.59 – 4.45 (m, 1H), 4.32 – 4.20 (m, 1H), 3.56 – 3.24 (m, 4H), 2.93 – 2.38 (m, 10H), 2.26 – 1.84 (m, 10H), 1.56 – 1.42 (m, 3H).	Column: DAICEL CHIRALPAK AD, 250 mm * 30 mm,10 um, eluting with 60%-60% (v) CO_2-EtOH (0.1% NH_3·H_2O) at 80 mL/min), peak with later retention time

 **Compound 46B**	LC-MS (ESI+): *m/z* = 640.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 - 8.70 (m, 1H), 7.81 - 7.72 (m, 1H), 7.34 - 7.26 (m, 1H), 7.08 - 6.98 (m, 1H), 5.89 - 5.77 (m, 1H), 4.79 - 4.70 (s, 2H), 4.57 - 4.46 (m, 1H), 4.33 - 4.20 (m, 1H), 3.07 - 2.95 (m, 1H), 2.87 - 2.55 (m, 7H), 2.50 - 2.40 (m, 1H), 2.27 - 1.86 (m, 10H), 1.77 - 1.65 (m, 2H), 1.55-1.45 (m, 3H).	Column: Phenomenex-Cellulose-2, 250 mm * 30 mm,10 um, Mobile phase: CO_2-EtOH (0.1% NH_3H_2O), eluting with B: 50%, Flow Rate: 70 ml/min, peak with later retention time
 **Compound 47B** *Single unknown configuration	LC-MS (ESI+): *m/z* = 643.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.8 Hz, 1H), 6.32 (d, *J* = 2.8 Hz, 1H), 5.90 - 5.76 (m, 1H), 4.70 (s, 2H), 4.55 - 4.48 (m, 1H), 4.31 - 4.21 (m, 1H), 4.19 - 4.15 (m, 1H), 4.06 - 4.00 (m, 1H), 3.97 - 3.93 (m, 1H), 3.91 - 3.87 (m, 1H), 3.62 - 3.54 (m, 1H), 3.10 - 3.07 (m, 1H), 2.76 - 2.60 (m, 3H), 2.53 (s, 3H), 2.50 - 2.32 (m, 3H), 2.27 – 1.75 (m, 13H), 1.82 - 1.72 (m, 3H).	Column: C18, 150*30 mm, Mobile Phase : water (NH_3H_2O + NH_4HCO_3)-MeCN, Mobile Phase B: MeCN, Flow rate: 25 mL/min, gradient condition from 70% B to 100% B, peak with later retention time
 **Compound 48B** *Single unknown configuration	LC-MS (ESI+): *m/z* = 643.4 $[M+H]^+$. ^1H NMR (400 MHz, CDCl3) δ 8.55 (d, *J* = 2.8 Hz, 1H), 6.32 (d, *J* = 2.8 Hz, 1H), 5.71 - 5.58 (m, 1H), 4.78 (s, 2H), 4.55 - 4.44 (m, 1H), 4.30 - 4.13 (m, 2H), 4.08 - 3.84 (m, 3H), 3.64 - 3.53 (m, 1H), 3.17 -3.05 (m, 1H), 2.78 - 2.57 (m, 3H), 2.57 - 2.43 (m, 7H), 2.42 - 2.13 (m, 4H), 2.11 - 1.94 (m, 3H), 1.94 -1.78 (m, 5H), 1.39 (d, *J* = 6.4 Hz, 3H).	Column: DAICEL CHIRALPAK IG, 250 mm * 30 mm,10 um, eluent: 60% to 60% (v/v) CO2-EtOH (0.1% NH3H2O), peak with later retention time
 **Compound 38B**	LC-MS (ESI+): *m/z* = 672.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 - 8.68 (m, 1H), 7.27 - 7.09 (m, 1H), 6.93 - 6.82 (m, 1H), 5.97 - 5. 45 (m, 2H), 4.98 - 4.80 (m, 4H), 4.78 - 4.65 (m, 2H), 4.56 - 4.45 (m, 1H), 4.31 - 4.18 (m, 1H), 3.57 - 3.31 (m, 3H), 3.22 - 3.09 (m, 1H), 2.86 - 2.72 (m, 1H), 2.72 - 2.59 (m, 2H), 2.56 (s, 3H), 2.52 - 2.42 (m, 1H), 2.41 - 2.30 (m, 1H), 2.27 - 2.17 (m, 1H), 2.12 - 2.05	Column: DAICEL CHIRALPAK AD, 250 mm * 30 mm, 10 um, eluting with 40% (v) CO_2-*i*-PrOH (0.1% NH_3H_2O) at 150 mL/min, peak with later retention time

	(m, 1H), 2.05 - 1.95 (m, 2H), 1.95 - 1.81 (m, 5H), 1.42 (d, *J* = 6.0 Hz, 3H).	
 **Compound 39B**	LC-MS (ESI+): *m/z* = 630.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.95 - 6.84 (m, 1H), 5.70 - 5.56 (m, 1H), 4.72 (s, 2H), 4.56 - 4.44 (m, 1H), 4.31 - 4.16 (m, 1H), 3.16 - 3.06 (m, 1H), 3.03 (d, *J* = 5.2 Hz, 3H), 2.79 - 2.55 (m, 3H), 2.54 - 2.43 (m, 7H), 2.37 - 2.14 (m, 2H), 2.14 - 1.95 (m, 3H), 1.94 - 1.71 (m, 5H), 1.40 (d, *J* = 6.4 Hz, 3H).	Column: DAICEL CHIRALPAK IG, 250 mm * 30 mm, 10 um, eluting with 60% (v) CO_2-EtOH (0.1% NH_3H_2O) at 80 mL/min, peak with later retention time

[00200] Example 11



To a mixture of **compound 41-4** (220 mg, 0.48 mmol) and 4A MS (200 mg) in ethane-1,2-diol (2 mL) was added TMSCl (153 μL, 1.19 mmol) and the resulting mixture was stirred at rt for 16 hours. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography (SiO2, DCM/MeOH = 9/1) **compound 49-1** as a brown oil. LC-MS (ESI+): *m/z* = 505.3 $[M+H]^+$.

To a solution of thiazol-2-ol (50.1 mg, 0.50 mmol) in THF (2 mL) was added sodium hydride (19.8 mg, 0.50 mmol) and the resulting mixture was stirred at rt for 0.5 hours. Then the mixture was added to the solution of **compound 49-1** (50.0 mg, 99.0 μmol) in THF (2 mL) and the reaction mixture was stirred at 80 ℃ for 16 hours. After cooling to room temperature, saturated NH_4Cl aq. (10 mL) was added, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: Welch Xtimate C18 150*30mm*5um, Mobile Phase: water(NH_4HCO_3)-ACN, Mobile Phase B: acetonitrile Flow rate: 25 mL/min, gradient condition from 68% B to 98%) and lyophilized to give **compound 49-2** (15.0 mg, 26.0 μmol, 27 % yield) as a white solid. LC-MS (ESI+): *m/z* = 570.3 $[M+H]^+$.

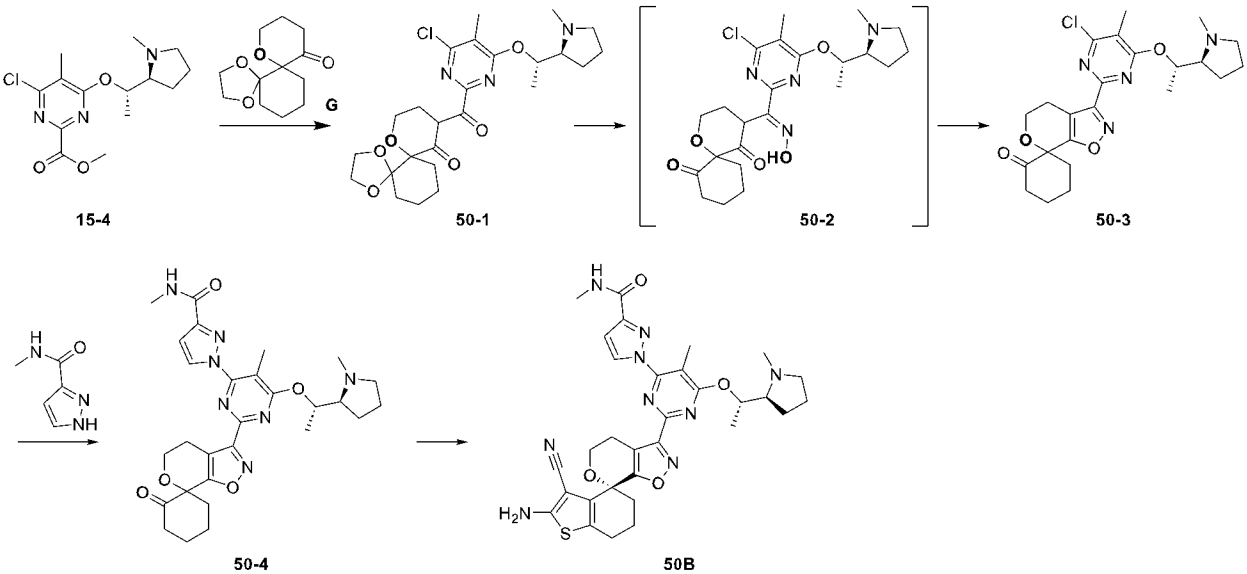
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 5.6 Hz, 1H), 6.29 (d, *J* = 5.6 Hz, 1H), 5.71 - 5.51 (m, 1H), 4.52 - 4.34 (m, 1H), 4.24 - 4.12 (m, 1H), 3.98 - 3.82 (m, 3H), 3.73 - 3.59 (m, 1H), 3.23 - 3.00 (m, 1H), 2.81 - 2.65 (m, 1H), 2.51 (s, 3H), 2.41 - 2.26 (m, 2H), 2.13 - 2.04 (m, 4H), 2.02 - 1.70 (m, 12H), 1.40 (d, *J* = 5.6 Hz, 3H).

A mixture of **compound 49-2** (110 mg, 193 μmol) in TFA (5 mL) was stirred at 80 ℃ for 2 hours. After cooling to room temperature, the reaction mixture was directly concentrated under reduced pressure to give a residue. The residue was adjusted to pH = 7~8 with saturated $NaHCO_3$ aq. and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford a crude **compound 49-3** (80 mg, 152 μmol, 79 % yield) as a brown oil. LC-MS (ESI+): *m/z* = 526.3 $[M+H]^+$.

To a solution of **compound 49-3** (60.0 mg, 114 μmol) and ammonium acetate (17.6 mg, 228 μmol) in EtOH (2 mL) was added sulfur (7.32 mg, 228 μmol) and the resulting mixture was stirred at 60 ℃ for 15 minutes. Malononitrile (15.1 mg, 228 μmol) was added at 60 ℃ and the reaction mixture was stirred at 60 ℃ for 2 hours. The reaction mixture was cooled to rt, quenched with saturated $NaHCO_3$ aq。(10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The crude was purified by prep-HPLC (Column: Welch Xtimate C18 150*30mm*5um, Mobile Phase A: water (10mM NH_4HCO_3)-ACN, Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 60% B to 90% B) and SFC (Column: DAICEL CHIRALPAK IG 250mm*30mm,10um, Mobile Phase: CO_2-*i*-PrOH (0.1% NH_3H_2O), Flow rate: 150 mL/min, gradient condition from 45% B to 45% B, peak with later retention time) to give **compound 49B**. LC-MS (ESI+): *m/z* = 606.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 5.6 Hz, 1H), 6.29 (d, *J* = 5.6 Hz, 1H), 5.75 - 5.60 (m, 1H), 4.73 (s, 2H), 4.50 - 4.41 (m, 1H), 4.27 – 4.12 (m, 1H), 2.83 - 2.54 (m, 5H), 2.48 - 2.40 (m, 1H), 2.24 - 2.12 (m, 4H), 2.11 - 1.71 (m, 11H), 1.53 - 1.46 (m, 3H).

[00201] Example 12



To a mixture of **compound 15-4** (5.0 g, 15.93 mmol, 1.00 eq) and **intermediate G** (5.4 g, 23.90 mmol, 1.50 eq) in MeCN (40 mL) was added DIEA (6.2 g, 47.80 mmol, 3.00 eq), the reaction mixture was stirred at room temperature for 5 min. Then magnesium bromide diethyl etherate (6.2 g, 23.90 mmol, 1.50 eq) was added to the reaction mixture and the mixture was stirred at 50 ℃ for 16 h under Ar

atmosphere. The reaction mixture was cooled to rt and directly concentrated in vacuum to give e residue. The residue was diluted with water (50 mL), adjusted to pH 6~7 with 1N HCl and extracted with DCM (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by chromatography column (SiO2, DCM/MeOH = 20/1) to afford **compound 50-1** as a yellow solid. LC-MS (ESI+): *m/z* = 508.3 $[M+H]^+$.

To a solution of **compound 50-1** (15.0 g, 29.50 mmol, 1.00 eq) in ethanol (150 mL) was added hydroxylamine hydrochloride (1.4 g, 20.67 mmol, 0.70 eq), the reaction was stirred at 70 ℃ for 16 h. The reaction mixture was cooled to rt and directly concentrated in vacuum to give a residue. The residue was diluted with water (150 mL) and extracted with EA (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude **compound 50-2** as a yellow oil which was directly used in the next step without further purification. LC-MS (ESI): *m/z* = 477.3 $[M-H]^-$.

The crude **compound 50-2** was dissolved in TFA (100 mL) and stirred at 80 ℃ for 2 h. The reaction mixture was cooled to rt and concentrated in vacuum to give a residue. The residue was diluted with water (30 mL), adjusted pH to 7~8 with sat. Na_2CO_3 aq. and extracted with EA (200 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by chromatography column (SiO2, DCM/MeOH = 20/1) and liquid chromatography (C8, H_2O/MeCN = 8/2) to afford **compound 50-3** as a yellow solid. LC-MS (ESI): *m/z* = 461.3 $[M-H]^-$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 - 5.32 (m, 1H), 4.22 - 4.13 (m, 1H), 3.81 - 3.70 (m, 1H), 3.13 - 3.02 (m, 1H), 3.01 - 2.90 (m, 2H), 2.84 - 2.73 (m, 1H), 2.68 - 2.56 (m, 2H), 2.50 - 2.40 (m, 3H), 2.38 - 2.27 (m, 2H), 2.27 (s, 3H), 2.18 - 2.08 (m, 1H), 2.06 - 1.82 (m, 5H), 1.80 - 1.68 (m, 3H), 1.39 - 1.29 (m, 3H).

To a solution of **compound 50-3** (180.0 mg, 0.39 mmol, 1.00 eq) in THF (3.0 mL) was added N-methyl-1H-pyrazole-3-carboxamide (73.3 mg, 0.59 mmol, 1.50 eq) and Cs_2CO_3 (254.0 mg, 0.78 mmol, 2.00 eq), then the reaction mixture was stirred at 70 ℃ for 16 h. The reaction mixture was cooled to room temperature, diluted with DCM (20 mL) and filtered. The filtrate was concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO2, DCM/MeOH = 12/1) to afford **compound 50-4** as a white solid. LC-MS (ESI+): *m/z* = 550.3 $[M+H]^+$.

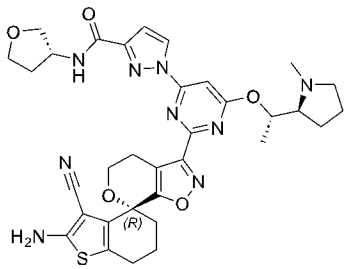
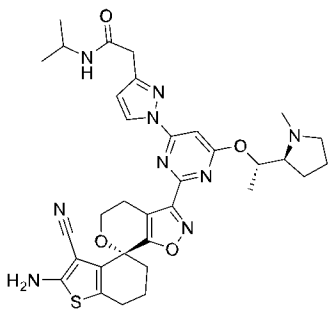
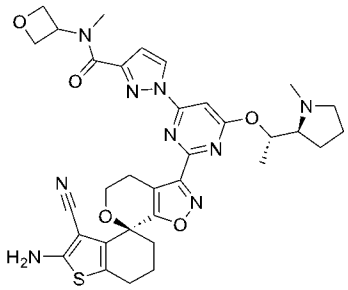
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.90 - 6.80 (m, 1H), 5.56 - 5.42 (m, 1H), 4.25 - 4.15 (m, 1H), 3.82 - 3.72 (m, 1H), 3.12 - 3.03 (m, 1H), 3.03 (d, *J* = 4.8 Hz, 3H), 3.02 - 2.94 (m, 1H), 2.93 - 2.79 (m, 1H), 2.70 - 2.57 (m, 2H), 2.53 (s, 3H), 2.48 (s, 3H), 2.38 - 2.28 (m, 2H), 2.24 - 2.15 (m, 1H), 2.08 - 1.84 (m, 6H), 1.84 - 1.72 (m, 3H), 1.38 (d, *J* = 6.4 Hz, 3H).

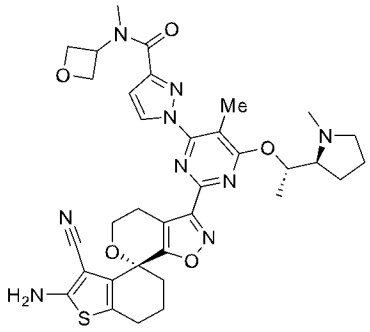
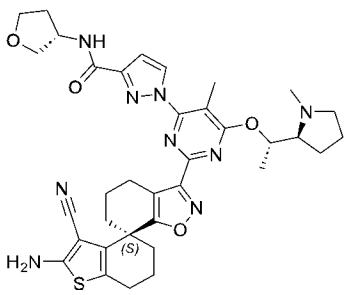
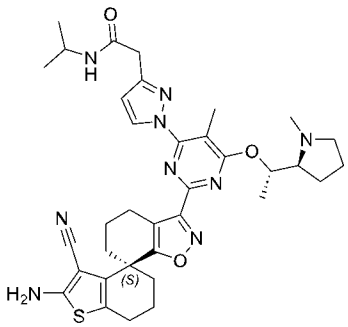
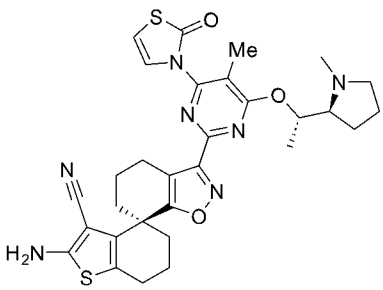
To a solution of **compound 50-4** (120.0 mg, 0.218 mmol, 1.0 eq) in EtOH (2.0 mL) was added ammonium acetate (33.7 mg, 0.44 mmol, 2.00 eq) and sulfur (14.0 mg, 0.44 mmol, 2.0 eq), then the reaction mixture was stirred at 60 ℃ for 20 min. A solution of malononitrile (28.8 mg, 0.44 mmol, 2.00 eq) in EtOH (0.2 mL) was added to the reaction mixture and the resulting mixture was stirred at 60 ℃ for another 3 hr. The reaction mixture was cooled to rt and directly concentrated in vacuum to give a residue. The residue was purified pre-TLC (SiO2, DCM/MeOH = 12/1) and SFC (Daicel IG 250mm*30mm*10um, Mobile phase: CO_2, 60% EtOH 40% ACN (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 120mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time) to afford **compound 50B**. LC-MS (ESI+): *m/z* = 630.0 $[M+H]^+$.

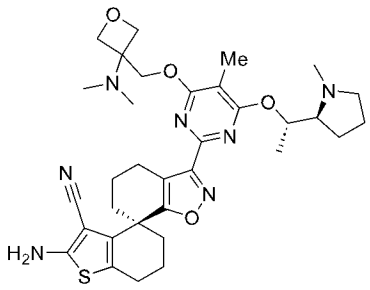
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 4.8 Hz, 1H), 7.02 - 6.90 (m, 3H), 5.52 - 5.41 (m, 1H), 4.16 - 4.07 (m, 1H), 3.97 - 3.87 (m, 1H), 3.16 - 2.95 (m, 3H), 2.81 (d, J = 4.4 Hz, 3H), 2.72 - 2.63 (m, 1H), 2.63 - 2.60 (m, 2H), 2.52 (s, 3H), 2.50 (s, 3H), 2.35 - 2.20 (m, 2H), 2.14 - 2.00 (m, 3H), 1.99 - 1.80 (m, 4H), 1.46 (s, 3H).

[00202] The following compounds in Table 12 were prepared using similar procedures as described in **Compound 50B**.

Table 12

Structure	Spectrum	HPLC/SFC
 **Compound 51B**	LC-MS (ESI+): m/z = 672.9 $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-$d4$) δ 8.83 (d, J = 2.4 Hz, 1H), 7.50 (s, 1H), 6.98 (d, J = 2.8 Hz, 1H), 5.50 - 5.40 (m, 1H), 4.67 - 4.57 (m, 1H), 4.24 - 4.13 (m, 1H), 4.06 - 3.91 (m, 3H), 3.87 - 3.80 (m, 1H), 3.79 - 3.71 (m, 1H), 3.20 - 3.10 (m, 1H), 2.85 - 2.75 (m, 1H), 2.72 - 2.59 (m, 2H), 2.56 (s, 3H), 2.49 - 2.39 (m, 1H), 2.38 - 2.26 (m, 2H), 2.22 - 2.07 (m, 2H), 2.07 - 1.95 (m, 5H), 1.89 - 1.74 (m, 3H), 1.42 (d, J = 6.0 Hz, 3H).	Column: Daicel IG, 250 mm * 30 mm, 10 um, Mobile phase: 55% CO2, 45% MeOH/MeCN = 1/1 (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 140 mL/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 52A**	LC-MS (ESI+): m/z = 658.6 $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-$d4$) δ 8.71 (s, 1H), 7.24 (s, 1H), 6.53 (s, 1H), 5.47 - 5.36 (m, 1H), 4.23 - 4.13 (m, 1H), 4.09 - 3.90 (m, 2H), 3.67 - 3.48 (m, 2H), 3.27 - 3.15 (m, 3H), 2.67 - 2.45 (m, 5H), 2.36 - 2.25 (m, 1H), 2.21 - 2.08 (m, 2H), 2.08 - 1.97 (m, 4H), 1.92 - 1.72 (m, 3H), 1.41 (d, J = 4.4 Hz, 3H), 1.17 (d, J = 6.4 Hz, 6H).	Column: REGIS (S,S) WHELK-O1, 250 mm * 25 mm, 10 um, Mobile phase: 55% CO2, 45% MeOH (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 140 ml/min, Temp: RT, Back Pressure: 100 bar, peak with earlier retention time
 **Compound 53B**	LC-MS (ESI+): m/z = 672.3 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.26 - 7.15 (m, 1H), 6.96 - 6.84 (m, 1H), 5.98 - 5.43 (m, 2H), 5.02 - 4.79 (m, 4H), 4.76 - 4.59 (m, 2H), 4.33 - 4.18 (m, 1H), 4.04 - 3.90 (m, 1H), 3.57 - 3.06 (m, 6H), 2.77 - 2.35 (m, 6H), 2.31 - 2.16 (m, 2H), 2.16 - 2.04 (m, 2H), 2.04 - 1.72 (m, 5H), 1.44 (d, J = 5.6 Hz, 3H).	Column: DAICEL CHIRALPAK AD, 250 mm * 30 mm,10 um, eluting with 35% (v) CO2-EtOH (0.1% NH3H2O) at 150 mL/min), peak with later retention time

 **Compound 54B**	LC-MS (ESI+): *m/z* = 686.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 6.97 (s, 2H), 6.90 (d, *J* = 19.6 Hz, 1H), 5.75 - 5.30 (m, 2H), 4.80 - 4.67 (m, 4H), 4.17 - 4.07 (m, 1H), 3.99 - 3.86 (m, 1H), 3.33 - 3.17 (m, 3H), 3.09 - 2.96 (m, 3H), 2.75 - 2.53 (m, 3H), 2.53-2.42 (m, 6H), 2.35 - 2.20 (m, 2H), 2.06 - 1.70 (m, 7H), 1.54 - 1.29 (m, 3H).	Column: Daicel AD, 250 mm * 30 mm, 10 um, 75% CO2, 25% EtOH, Flow: 120 ml/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time
 **Compound 55B**	LC-MS (ESI+): *m/z* = 684.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d6)* δ 8.52 (d, *J* = 2.4 Hz, 1H), 8.37 (d, *J* = 6.8 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.96 (s, 2H), 5.50 - 5.40 (m, 1H), 4.52 - 4.43 (m, 1H), 3.91 - 3.82 (m, 2H), 3.76 - 3.66 (m, 1H), 3.64 - 3.57 (m, 1H), 3.15 - 3.07 (m, 1H), 3.07 - 2.98 (m, 1H), 2.75 - 2.62 (m, 2H), 2.61 - 2.52 (m, 2H), 2.47 - 2.36 (m, 6H), 2.25 - 2.12 (m, 2H), 2.11 - 1.94 (m, 5H), 1.94 - 1.85 (m, 5H), 1.85 - 1.65 (m, 3H), 1.34 (d, *J* = 6.4 Hz, 3H).	Column: Daicel AD, 250 mm * 30 mm, 10 um, 70% CO2, 30% EtOH, Flow: 100 ml/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time.
 **Compound 56B**	LC-MS (ESI+): *m/z* = 670.7 $[M+H]^+$. ^1H NMR (400 MHz, methanol-*d4*) δ 8.51 (s, 1H), 6.51 (s, 1H), 5.60 - 5.50 (m, 1H), 4.02 - 3.90 (m, 1H), 3.65 (s, 2H), 3.26 - 3.17 (m, 2H), 3.05 - 2.95 (m, 1H), 2.87 - 2.76 (m, 1H), 2.63 (s, 3H), 2.63 - 2.50 (m, 2H), 2.55 (s, 3H), 2.25 - 1.98 (m, 6H), 1.98 - 1.75 (m, 7H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.20 - 1.10 (m, 6H).	Column: SunFire Prep C18 OBD, 19 mm * 250 mm, 10 um, Mobile phase: 0.1% FA in water, 7.8 min, peak with later retention time
 **Compound 57B**	LC-MS (ESI+): *m/z* = 604.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol-*d4*) δ 7.21 (d, *J* = 5.2 Hz, 1H), 6.59 (d, *J* = 5.6 Hz, 1H), 5.60 - 5.48 (m, 1H), 3.21 - 3.12 (m, 2H), 3.03 - 2.89 (m, 1H), 2.85 - 2.71 (m, 1H), 2.65 - 2.50 (m, 2H), 2.61 (s, 3H), 2.24 - 2.16 (m, 1H), 2.15 (s, 3H), 2.14 - 1.75 (m, 12H), 1.42 (d, *J* = 6.4 Hz, 3H).	Column: SunFire Prep C18 OBD, 19 mm * 250 mm, 10 um, Mobile phase: 0.1% FA in water, 9.60 min, 10.47 min, peak with later retention time

 **Compound 58B**	LC-MS (ESI+): *m/z* = 634.3 $[M+H]^+$. ^1H NMR (400 MHz, methanol-*d4*) δ 5.48 - 5.37 (m, 1H), 4.90 (s, 2H), 4.65 - 4.53 (m, 4H), 3.29 - 3.09 (m, 2H), 2.89 - 2.78 (m, 2H), 2.69 - 2.55 (m, 2H), 2.54 (s, 3H), 2.51 - 2.40 (m, 1H), 2.36 (s, 6H), 2.16 - 2.10 (m, 2H), 2.09 (s, 3H), 2.08 - 1.85 (m, 7H), 1.85 - 1.72 (m, 3H), 1.36 (d, *J* = 6.4 Hz, 3H).	Column: Daicel AD, 250 mm * 25 mm, 10 um, 70% CO_2, 30% IPA (+0.1% 7.0 mol/l ammonia in MeOH), Flow: 140 ml/min, Temp: RT, Back Pressure: 100 bar, peak with later retention time

[00203] Example A: KRAS-GDP/BODIPY-GTP exchange assay

[00204] The following procedure was used to test the compounds described herein: The ability of the compounds to affect nucleotide exchange on Ras was assessed using TR-FRTE. Compounds are dispensed onto assay plates (384 low binding plate, corning4514) using an Access Labcyte Workstation with the Labcyte Echo 55x from a DMSO solution. For the chosen highest assay concentration of 100 µM (this can be changed upon request), 100 nL of compound solution are transferred from a 10 mM DMSO compound stock solution. Compounds are tested in duplicates. A series of 10 concentrations is transferred for each compound at which each concentrationis 3x fold lower than the previous one. DMSO is added such that every well has a total of 100 nL compound solution. Forthe assay 20µL containing KRAS G12D protein (15 nM final assay concentration), SOS1 (250 nM final assay concentration), BODIPY-GTP (0.2 µM final assay concentration), His-Tbmixed in assay buffer (PPI buffer,PE) are added to the 100 nl of compounds. Plates are kept at room temperature. After 180 minutes incubation time the TR-FRET signal is measured in a BMGHTS Multilabel Reader. Each plate contains negative controls (diluted DMSO instead of test compound; described mix with KRAS G12D protein) and positive controls (diluted DMSO instead of test compound; described mix without KRAS G12D). Negative and positive control values are used for normalization.. Low IC50 values in this assay setting are indicative of strong inhibition of protein-protein interaction between SOS1 and KRAS.

Table 13

Reagent	Vendor	Work con.
KRAS G12D_GDP	ICE	15 nM
KRAS G12C_GDP	ICE	15 nM
KRAS WT_GDP	ICE	15 nM
KRAS G12V_GDP	ICE	10 nM
BODIPY-GTP	Invitrogen	200 nM
KRAS G13D_GDP	ICE	10 nM
KRAS G13C_GDP	ICE	10 nM
BODIPY-GTP	Invitrogen	150 nM

[00205] The data from Example A is shown in **Table 14**.

Table 14

Compound ID	**KRAS G12C IC 50 (nM)**	**KRAS G12D IC 50 (nM)**	**KRAS G12V IC 50 (nM)**	**KRAS WT IC 50 (nM)**
1A	A	A	A	A
2A	A	A	A	A
3A	A	A	A	A

Compound ID	KRAS G12C IC 50 (nM)	KRAS G12D IC 50 (nM)	KRAS G12V IC 50 (nM)	KRAS WT IC 50 (nM)
4A	A	A	A	A
5A		A	A	A
6A		A	A	A
7A		A	A	A
8A		A	A	A
9A		A	A	A
10A		A	A	A
11A		A	A	A
12A		A	A	A
13			A	A

A = IC_{50} > 0 nM and ≤ 200 nM;

B = IC_{50} > 200 nM and ≤ 500 nM;

C = IC_{50} > 500 nM;

NT = not tested.

[00206] Example B: KRAS_GDP nucleotide exchange HTRF assay

[00207] The inhibition of KRAS WT enzyme activity was tested by the HTRF method. In the KRAS WT_GDP exchange experiment, KRAS WT-GDP (Biotin marker) was converted to KRAS WT-GTP (GTP marker BODIPY) under the action of SOS1. When donor SA-Tb binds to KRAS WT-GTP, a FRET signal is generated to detect the exchange of KRAS WT-GDP with GTP. KRAS WT-GDP is inactive and becomes active when GDP is replaced by GTP under the action of SOS1. Prepare KRAS WT-GDP (ICE, Cat # E2207T-H15HA), SOS1 (ICE, Cat # E2204T-H10G), GDP (Sigma, Cat # G7127), and BODIPY-GTP (Invitrogen, Cat # G12411) solutions in reaction buffer (25 mM HEPES, pH 7.4, 120 mM NaCl, 5 mM MgCl2,1 mM DTT (fresh), 0.01% Tween 20, 0.1% BSA). The final concentrations of KRAS WT-GDP, GDP, SOS1, and BODIPY-GTP in the reaction mixture were 0.5 nM, 5 nM, 500 nM, and 200 nM, respectively. The initial concentration of the positive reference MRTX1133 was 1 μM, 3 times diluted, 10 dose. The 100% DMSO-diluted compound was transferred 0.1 μL to a 384-well plate with Echo655. Add 5 μL of 2× KRAS WT_GDP-GDP mixed solution into 384 reaction plates, centrifuge at 1000 rpm for 1 min, and incubate at 25°C for 15 min. A mixture of 5 μL 2× BODIPY-GTP, SOS1, and SA-Tb (Cisbio, Cat#610SATLB) was transferred to 384 reaction plates, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 180 min. Finally, the HTRF signal (665/620) is read by BMG. The KRAS G12V_GDP exchange experiment and KRAS G12D_GDP exchange experiment were also conducted following the same steps described previously, except that KRAS G12V-GDP (ICE, Cat # E2207T-H17HA) was utilized in KRAS G12V_GDP exchange experiment and KRAS G12D-GDP (ICE, Cat # E2203T-H48HA) was utilized in KRAS G12D_GDP exchange experiment. IC50 values and nonlinear regression curve fitting were obtained using GraphPad Prism software.

[00208] The data from Example B is shown in **Table 15**.

Table 15

Compound ID	KRAS G12D IC 50 (nM)	KRAS G12V IC 50 (nM)	KRAS WT IC 50 (nM)
1A		0.15	0.49
8A		0.31	0.51
11A		0.18	0.54

Compound ID	KRAS G12D IC 50 (nM)	KRAS G12V IC 50 (nM)	KRAS WT IC 50 (nM)
14		18.2	
15B	3.28	0.32	0.34
16B		0.30	0.54
17B		0.16	0.51
18B	0.56	0.16	0.43
19B	1.93	0.21	0.30
20B	1.99	0.29	0.47
21B	1.73	0.22	0.21
22B	1.12	0.17	0.38
23B	2.60	0.26	0.28
24B	0.78	0.26	0.30
25B	2.55	0.42	0.35
26B	1.74	0.20	0.41
27A			0.44
28B	0.82	0.17	0.21
29B			0.87
30A		0.57	1.52
31B		0.25	0.69
32B			2.03
33B	1.35	0.53	0.36
34A			1.92
35B		12.61	
36B			2.53
37B			3.30
38B		0.30	0.65
39B	2.73	0.15	0.38
40B	0.72	0.21	
41A		5.33	
41B	0.07	0.11	0.13
42B		2.13	
43B	0.08	0.11	0.17
44A			1.19
45B		0.45	0.53
46B			1.57
47B		0.45	1.67
48B			0.73
49B	2.14	0.38	0.61
50B	10.82	0.45	0.80
51B		0.28	1.45
52A		0.29	0.91
53B		0.15	0.66
54B		0.78	1.29

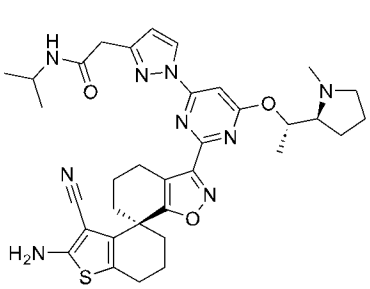
Compound ID	KRAS G12D IC 50 (nM)	KRAS G12V IC 50 (nM)	KRAS WT IC 50 (nM)
55B		0.25	0.69
56B			0.33
57B		0.49	1.21
58B		1.64	

Compounds in this disclosure showed excellent activities against wild type and different KRAS mutations.

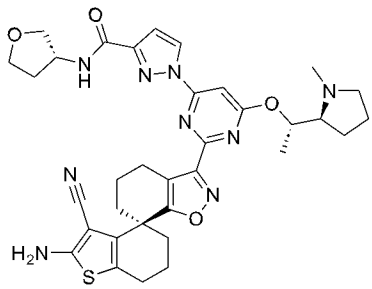
[00209] Example C: Kinetic Solubility assay

The objective of this study was to determine the kinetic solubility of in 50 mM phosphate buffer solution (pH 7.4) at room temperature for 24 hours with shake plate method.

Test Compound and Control Compounds



sample 1
WO2023/099624 A1
example 182



sample 2
WO2023/099624 A1
example 192

Compound **sample 1** and Compound **sample 2** were prepared according to the synthetic route reported in patent WO2023099624. Amiodarone hydrochloride, carbamazepine and chloramphenicol were used as control compounds in these assays. Test compound and control compounds (amiodarone hydrochloride, carbamazepine and chloramphenicol) were dissolved in DMSO. The stock solutions were kept stored at -80 °C freezer until used. The detailed information of control compounds is shown in the following table.

Compound	Application	Source	CAS	FW
Amiodarone hydrochloride	Control compound	Sigma	19774-82-4	681.77
Carbamazepine	Control compound	Accela	298-46-4	236.27
Chloramphenicol	Control compound	Bidepharm	56-75-7	323.13

Chemicals and Reagents

The chemicals and reagents are listed in the following table.

Name	Source	Lot Number
NaH_2PO_4	Sigma	SLCK2210
Na_2HPO_4	Sigma	BCCH4864

Equipment and Materials

UPLC	(Waters, ACQUITY, America)
Plate Sealer	(G5585A, Agilent, America)
pH meter	(S220, Mettler, Switzerland)
Centrifuge	(5810Ri, Eppendorf, Germany)
Filter plates	(Merck, Germany)
Pure water meter	(Milli-Q, Merck, Germany)

Compact Digital Microplate Shaker (Thermo Fisher Scientific, America)

Preparation of Preparation of 50 mM Phosphate Buffer (PB) with the pH 7.4

The preparation of 50 mM Na2HPO4: Dissolved 3.549 g of Na2HPO4 with 500 mL of water, and the pH measured was about 9.4. The preparation of 50 mM NaH2PO4: Dissolved 3.000 g of NaH2PO4 with 500 mL of water, and the pH measured was about 4.5. The preparation of 50 mM PB (pH 7.4): 15 mL of 50 mM Na2HPO4 was added into a 50 mL tube, and then adjusted pH to 7.4 ± 0.05 with 50 mM NaH2PO4.

Assay Procedure

10 μL of DMSO stock solution of test and control compounds was added into each well of a 96-well plate, respectively. Added 490 μL of medium into the well of the 96-well plate, respectively. Vortexed the solubility samples for at least 2 minutes. Shook the 96-well plate on a shaker at room temperature at the speed of 800 rpm for 24 hours. Centrifuged at 25℃ for 10 minutes (eg. 4000 rpm). Transferred the supernatant into a filter plate, and then collected the filtrates into a new 96-well plate by centrifuging for at least 5 minutes. The concentrations of the filtrates were quantified by LC-UV system. Materials: MultiScreen® Solvinert (PTFE Filter Media with polyolefin copolymer device) from Millipore_Merck.

Analytical Assay

For the test compounds and the control compounds (amiodarone hydrochloride, carbamazepine and chloramphenicol), the concentrations of filtrates were determined by LC-UV method.
The calibration curve of test compound and control compounds was prepared as follows:

Solution ID	Concentration (μM)	Source Solution ID	Source Volume (μL)	Dilution Volume (μL)	Total Volume (μL)	Diluent
Solution 1	200	10 mM DMSO stock	15.0	735	750	DMSO

Serial Number	Final Solution ID	Dilution Factor	Final Conc. (μM)	Source Solution ID	Source Volume (μL)	Solvent Volume (μL)	Total Volume (μL)	Diluent
1	C1	1	200	Solution 1	500	0.00	500	DMSO
2	C2	2	100	C1	250	250	500	
3	C3	4	25.0	C2	250	750	1000	
4	C4	2	12.5	C3	250	250	500	
5	C5	4	3.13	C4	250	750	1000	
6	C6	2	1.56	C5	250	250	500	

Compound ID	Kinetic Solubility (μg/ml)	Compound ID	Kinetic Solubility (μg/ml)
sample 1	11.8	8A	79.6
sample 2	18.5	16B	71.3
11A	71.2	51B	78.5

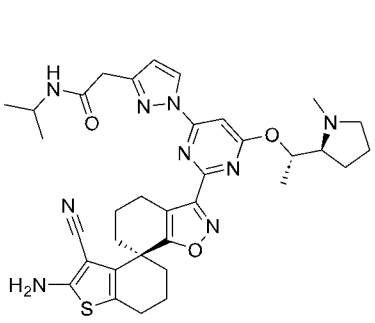
Compounds in this disclosure showed better kinetic solubility.

[00210] Example D: Liver Microsomes Stability Assay

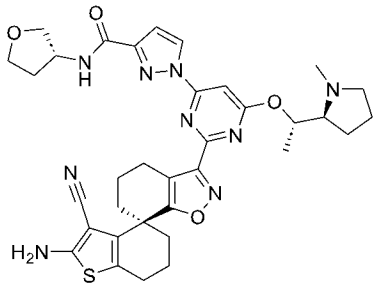
Materials

Animal or human liver microsomes were purchased from IPHASE or Corning and stored in a freezer (lower than -60℃) before use. β-nicotinamide adenine dinucleotide phosphate reduced form, tetrasodium salt. Control compounds: Testosterone, diclofenac and propafenone.

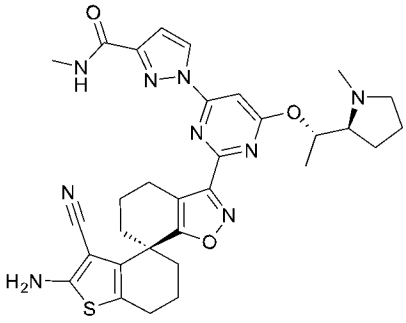
Preparation of Working Solution



sample 1
WO2023/099624 A1
example 182



sample 2
WO2023/099624 A1
example 192



sample 3
WO2023/099624 A1
example 20

Compound **samples 1-3** were prepared according to the synthetic route reported in patent WO2023099624. Stock Solution: 10 mM test compound in DMSO. Working solution: 100 μM test or control compounds in 100% acetonitrile (Concentration of organic solvent: 1% (v/v) DMSO and 99% (v/v) acetonitrile)

Assay Procedure

A total of two sample plates with 96-well format were prepared for incubation, labeled as 'Incubation' T60 and 'Incubation' NCF60. Empty 'Incubation' T60 and NCF60 plates were pre-warmed for 10 min minutes. Liver microsomes were diluted to 0.56 mg/mL in 100 mM phosphate buffer. Microsome working solutions (0.56 mg/mL) were transferred (445 uL) into pre-warmed 'Incubation' T60 and NCF60 plates, followed by incubation for 10 min at 37℃ with constant shaking. Liver microsomes (54 μL) were transferred to a Blank60 plate, followed by the addition of 6 μL NAPDH cofactor and 180 μL stop solution (acetonitrile containing internal standards) into each well. An aliquot (5 μL) of compound working solution (100 μM) was added into the 'incubation' plates (T60 and NCF60) containing microsomes and mixed 3 times thoroughly. For the 'Incubation' NCF60 plate, 50 uL of buffer was added and mixed 3 times thoroughly. The plates were incubated at 37℃ for 60 min while shaking. samples were mixed once and 60 μL was transferred from the NCF60 incubation plate to the stop plate containing stop solution after the 60-min incubation. Stop solution (180 μL) and NAPDH cofactor (6 μL) were added to 'Quenching' plate T0. Plates were chilled to prevent evaporation. For the 'Incubation' T60 plate: mixed 3 times thoroughly, and immediately removed 54 μL mixture for the 0-min time point to stop plate ('Quenching' plate T0). NAPDH cofactor (44 μL) was added to the 'Incubation' T60 plate. The plate was incubated at 37℃ for 60 min while shaking. At 5, 15, 30, 45, and 60 min, 180 μL stop solution was added to the 'Quenching' plates, samples were mixed once, and 60 μL was serially transferred from 'Incubation' T60 plate per time point. Consequently, for the wells containing the test or control compounds, the final concentration was 1 μM for test compounds, testosterone, diclofenac and propafenone, 0.5 mg/mL for animal or human liver microsomes, 0.01% (v/v) for DMSO and 0.99% (v/v) for acetonitrile. All sampling plates were shaken for 10 min, then centrifuged at 3220 ×g for 20 minutes at 4℃. Supernatant (80 μL) was transferred into 240 μL pure water, and mixed by plate shaker for 10 min. Each bioanalysis plate was sealed and shaken for 10 minutes prior to LC-MS/MS analysis.

Bioanalytical Analysis

Concentrations of test conpounds and positive controls, testosterone, diclofenac and propafenone in the samples were determined by using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Data Calculation

In the determination of the in vitro elimination constant, k_e, of test compound and control compounds, the peak area ratios (PAR) of analyte/internal standard were used to calculate the percentage of remaining (%Remaining) with the following equation:

$$\%\text{Remaining} = \frac{\text{PAR of analyte to internal standard at each timepoint}}{\text{PAR of analyte to internal standard at T} = 0} \times 100$$

$$C_t = C_0 \bullet e^{-k_e \bullet t}$$

$$\text{when } C_t = \frac{1}{2} C_0 ,$$

$$T_{1/2} = \frac{Ln2}{k_e} = \frac{0.693}{k_e}$$

$CL_{int(mic)}$ = 0.693 / $T_{1/2}$ / mg microsome protein per mL

$CL_{int(liver)}$ = $CL_{int(mic)}$ × mg microsomal protein/g liver weight × g liver weight/kg body weight

According to the well-stirred model, hepatic intrinsic clearance and hepatic clearance can be calculated by the following formula.

$CL_{(liver)}$ = ($CL_{int(liver)}$ × f_u × Q_h)/ ($CL_{int(liver)}$ × f_u + Q_h)

The default value of f_u (the fraction unbound in blood) is assumed as 1.

The parameters in equations are listed in following table.

Species	Liver Weight (g/kg Body Weight) [1-2]	Hepatic Blood Flow (Q_h) (mL/min/kg) [1-2]	Microsomal Protein (mg/g liver weight)
Mouse	88	90.0	
Rat	40	55.2	
Dog	32	30.9	45
Monkey	30	43.6	
Human	20	20.7	

When the %Remaining value at the maximal incubation time, which was 60 min in this study, was higher than 75%, it is considered to be within the acceptable experimental variation, i.e., CV =25%. Therefore, a corresponding $T_{1/2}$ value of >145 min is reported. Consequently, the corresponding $CL_{int(mic)}$value is reported as <9.6 μL/min/mg protein.

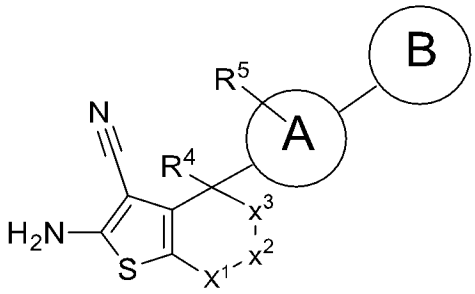
Compound ID	rMMS CLliver (mL/min/kg)	Compound ID	rMMS CLliver (mL/min/kg)
sample 1	27.3	52A	19.3
sample 2	29.1	11A	14.1
sample 3	28.0	39B	14.9
		19B	<13.2

Compounds in this disclosure showed better liver microsomes stability.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (I);

wherein:

X^1 is $C(R^{1a})(R^{1b})$, O, S, or $N(R^{1c})$;

X^2 is $C(R^{2a})(R^{2b})$, O, S, or $N(R^{2c})$;

X^3 is $C(R^{3a})(R^{3b})$, O, S, or $N(R^{3c})$;

R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, R^{2c}, R^{3a}, R^{3b}, and R^{3c} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$; and optionally,

one of R^{1a}, R^{1b}, and R^{1c} and one of R^{2a}, R^{2b}, and R^{2c} together with the atoms they are attached to form a 3-7 membered ring; or one of R^{2a}, R^{2b}, and R^{2c} and one of R^{3a}, R^{3b}, and R^{3c} together with the atoms they are attached to form a 3-7 membered ring; or one of R^{1a}, R^{1b}, and R^{1c} and one of R^{3a}, R^{3b}, and R^{3c} form a bond, a C_{1-4}alkylene, or C_{1-3}heterolkylene; and optionally,

R^{1a} and R^{1b} together with the carbon atom they are attached to form a optionally substituted C_{3-6}cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl; and/or R^{2a} and R^{2b} together with the carbon atom they are attached to form a optionally substituted C_{3-6}cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl; and/or R^{3a} and R^{3b} together with the carbon atom they are attached to form a optionally substituted C_{3-6}cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl; wherein each of the C_{3-6}cycloalkyl is optionally substituted with one, two or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-}$

$_9$heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$;

R^4 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$; or R^4 together with one of R^{1a}, R^{1b}, and R^{1c}, or R^4 together with one of R^{2a}, R^{2b}, and R^{2c}, or R^4 together with one of R^{3a}, R^{3b}, and R^{3c} form a group selected from -CH_2CH_2-, -$CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2$- optionally substituted by one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})$;

R^5 is absent or is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -$S(=O)(=NH)(R^{13})$, -$S(=O)(=NR^{13})R^{13}$, -$CH_2C(O)N(R^{10})(R^{11})$, -$CH_2N(R^{12})C(O)R^{13}$, -$CH_2S(O)_2R^{13}$, -$CH_2S(O)_2N(R^{10})(R^{11})$, -$Si(C_{1-6}alkyl)_3$, and -$P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -CH_2-C_{1-9}heteroaryl, -OR^{10}, -SR^{10}, -SF_5, -$N(R^{10})(R^{11})$, -$C(O)OR^{10}$, -$OC(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)OR^{13}$, -$N(R^{12})S(O)_2R^{13}$, -$C(O)R^{13}$, -$S(O)R^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{10})(R^{11})$, -$C(O)C(O)N(R^{10})(R^{11})$, -$N(R^{12})C(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{10})(R^{11})$-, -$N{=}S(=O)(R^{13})_2$, -$S(=O)(=NH)N(R^{10})(R^{11})$, -

$S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

or R^4 and R^5 together with the atoms they are attached to form a C_{5-7}cycloalkyl or a 5-7 membered heterocyclyl optionally substituted with 1-3 R^{4a}, wherein each R^{4a} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$; or

Ring A is a 5-8 membered ring optionally substituted with 1-3 R^A;

Ring B is a 5-8 membered ring optionally substituted with 1-4 R^B;

or one of R^B and R^5 together with the atoms they are attached to form a 5-8 membered ring optionally substituted with 1-4 R^C;

each R^A is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^B is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C_{1-9}$heteroaryl-C_{1-9}heteroaryl, $-OR^{B10}$, $-SR^{B10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, -

$CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$, wherein the C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, or $-CH_2-C_{1-9}$heteroaryl is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, oxo, C_{1-6}alkyl, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$,C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy;

each R^C is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^{B10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-C_{1-3}$alkylene-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-C_{1-3}$alkylene-C_{1-9}heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-C_{1-3}$alkylene-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{2-9}heterocycloalkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-C_{1-3}$alkylene-C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, $-C(O)R^{13}$, oxo, C_{1-6}alkyl, C_{1-6}heteroalkyl, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, $-P(O)(R^{10})$, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein each of the C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl is optionally substituted with one, two, or three groups selected from halogen, -CN,

hydroxy, oxo, -N(R^{10})(R^{11}), -C(O)OR^{10}, -C(O)N(R^{10})(R^{11}), -N(R^{12})C(O)R^{13},C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy;

each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -CH_2-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and -CH_2-C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, -CH_2-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -CH_2-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and -CH_2-C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy;

each R^{11} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{10} and R^{11}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy;

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; and

each R^{13} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl.

2. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Ring A is a 5-8 membered heteroaryl ring optionally substituted with 1, 2, or 3 R^A.

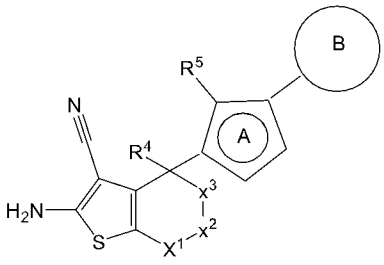
3. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Ring A is a 5-8 membered heteroaryl ring substituted with 1, 2, or 3 R^A.

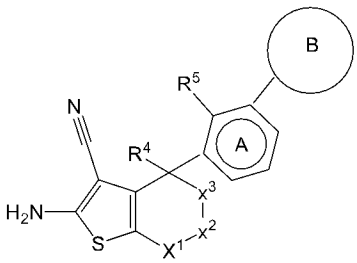
4. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Ring A is selected from furan, pyrrole, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrazole, imidazole, thiadiazole, triazole, pyridine, pyridazine, pyrimidine, pyrazine, azepine, diazepine, and triazepine.

5. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, having the structure of:

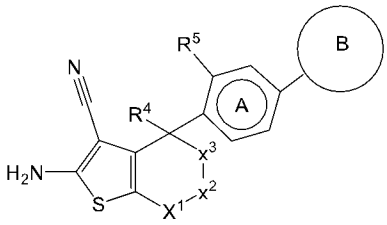


A-1



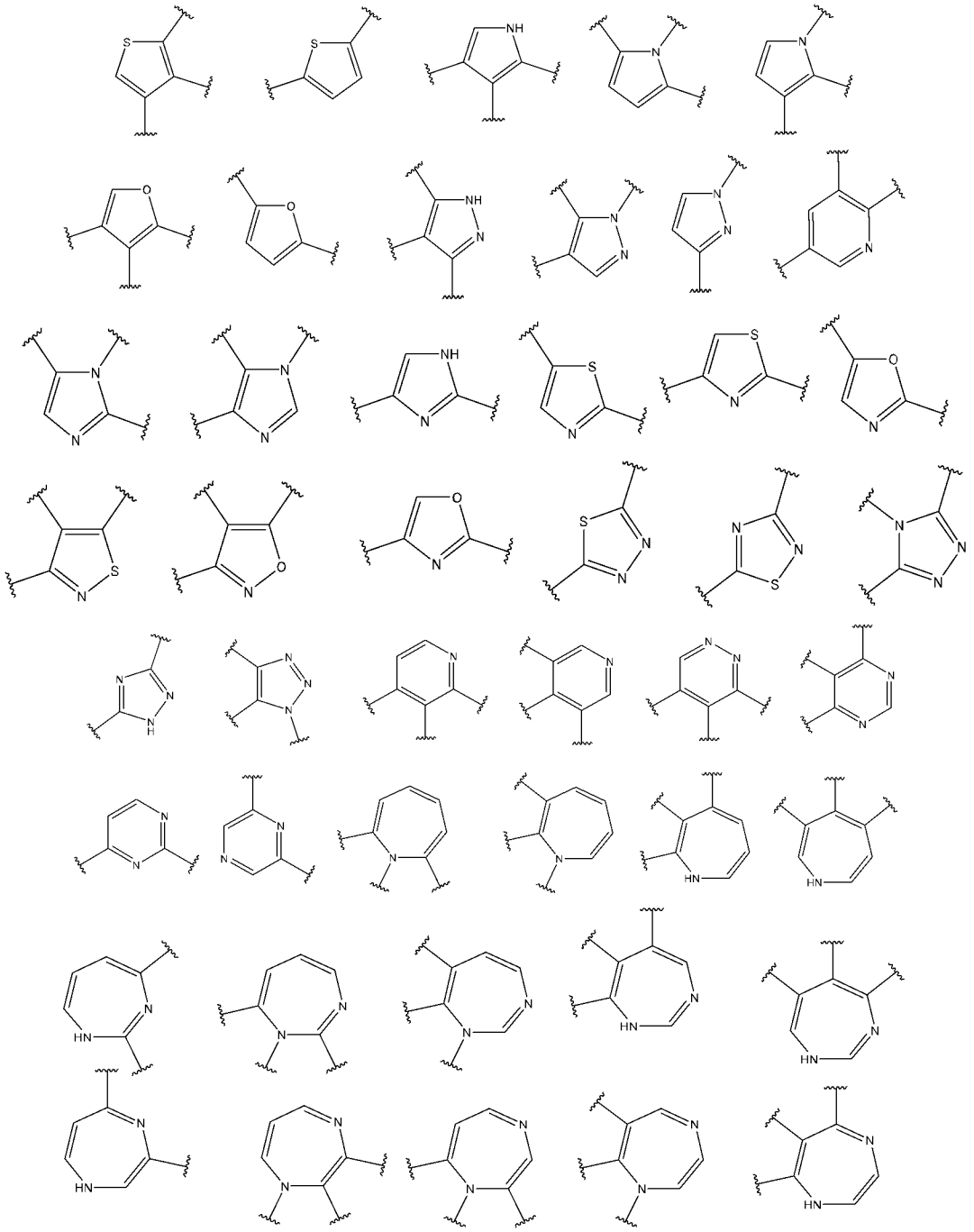
A-2

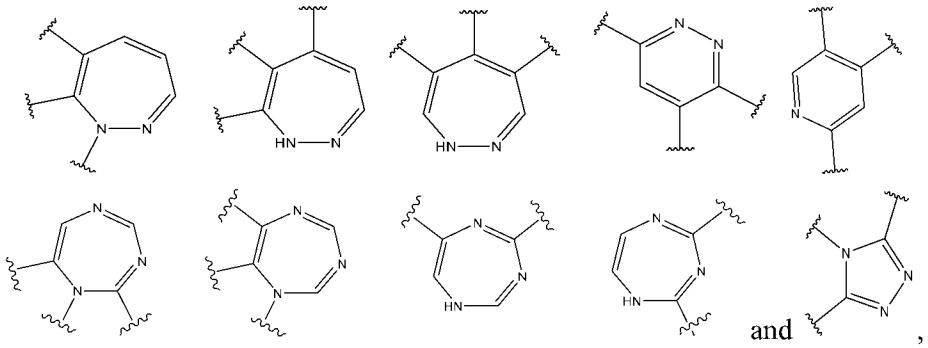
or



A-3

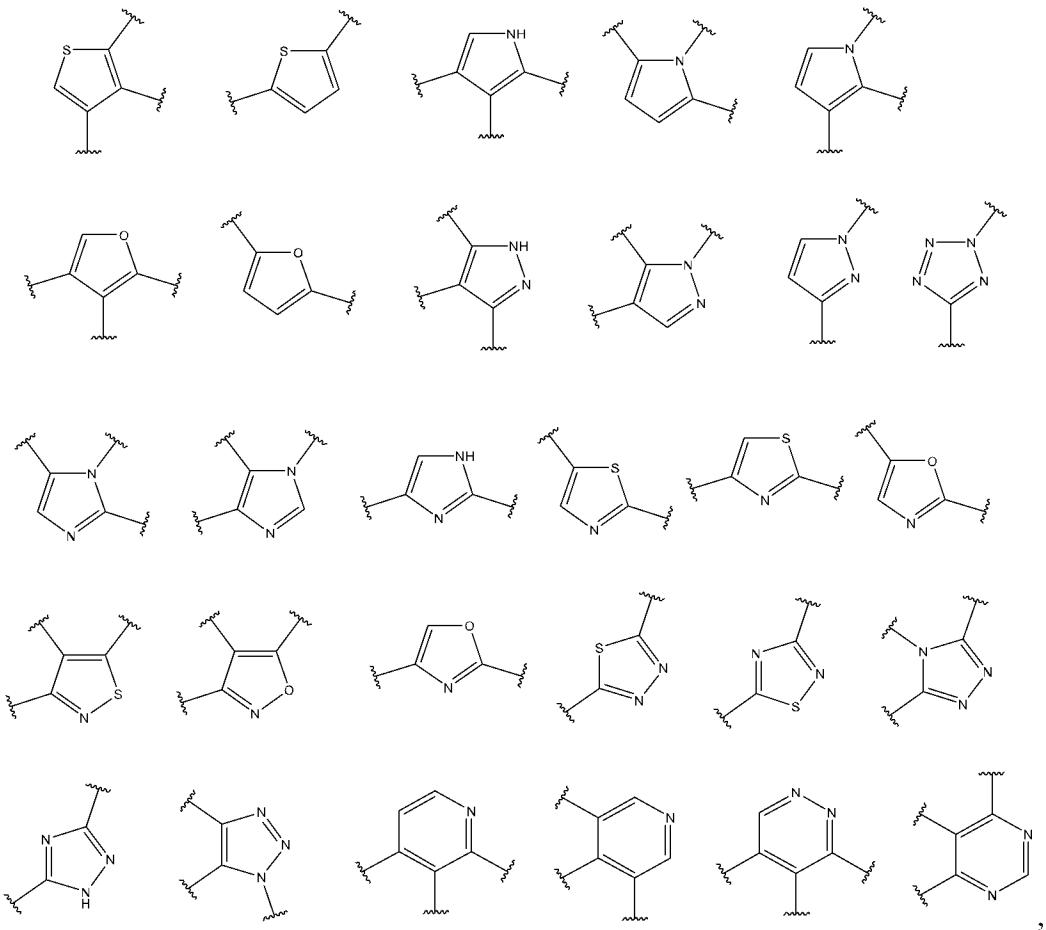
6. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is selected from:




and ,

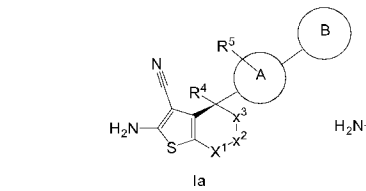
wherein each hydrogen on a ring atom is independently and optionally replaced by a R^A group.

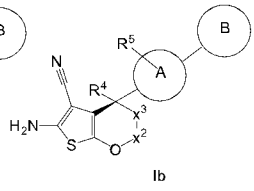
7. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is selected from:


, and

wherein each hydrogen on a ring atom is independently and optionally replaced by a R^A group.

8. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, having a structure of:


Ia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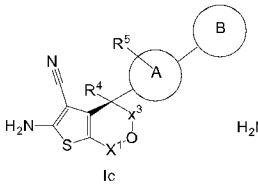
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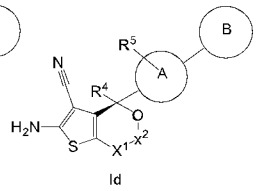
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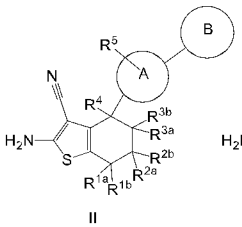
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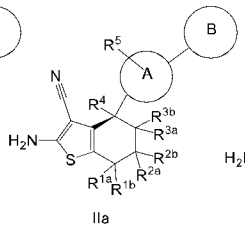
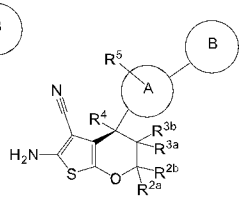

IIa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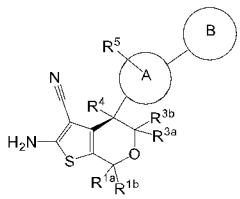
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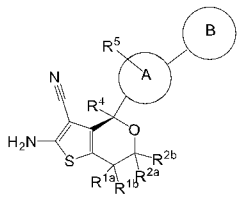
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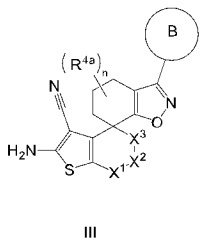
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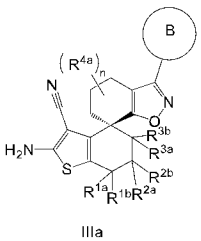
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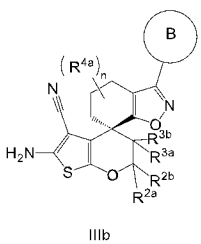
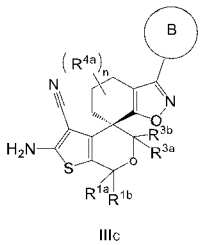

IIIb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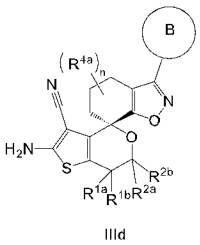
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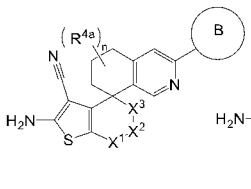
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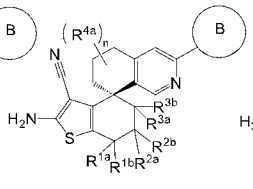
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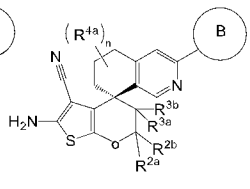
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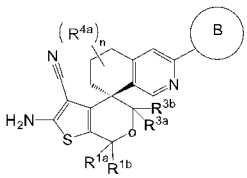
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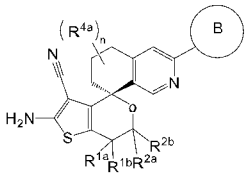
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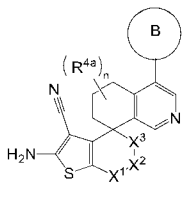
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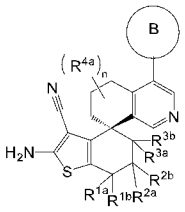
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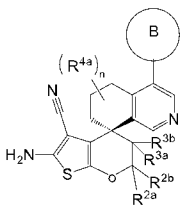
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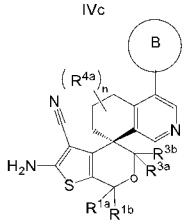
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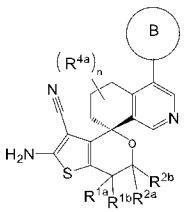
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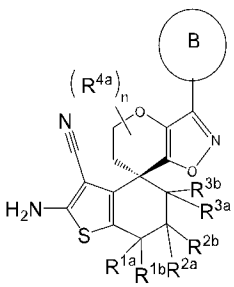
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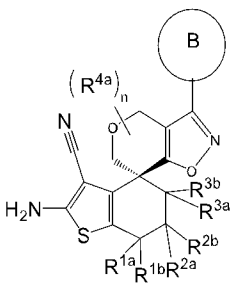
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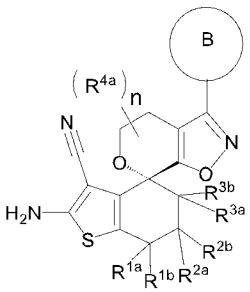
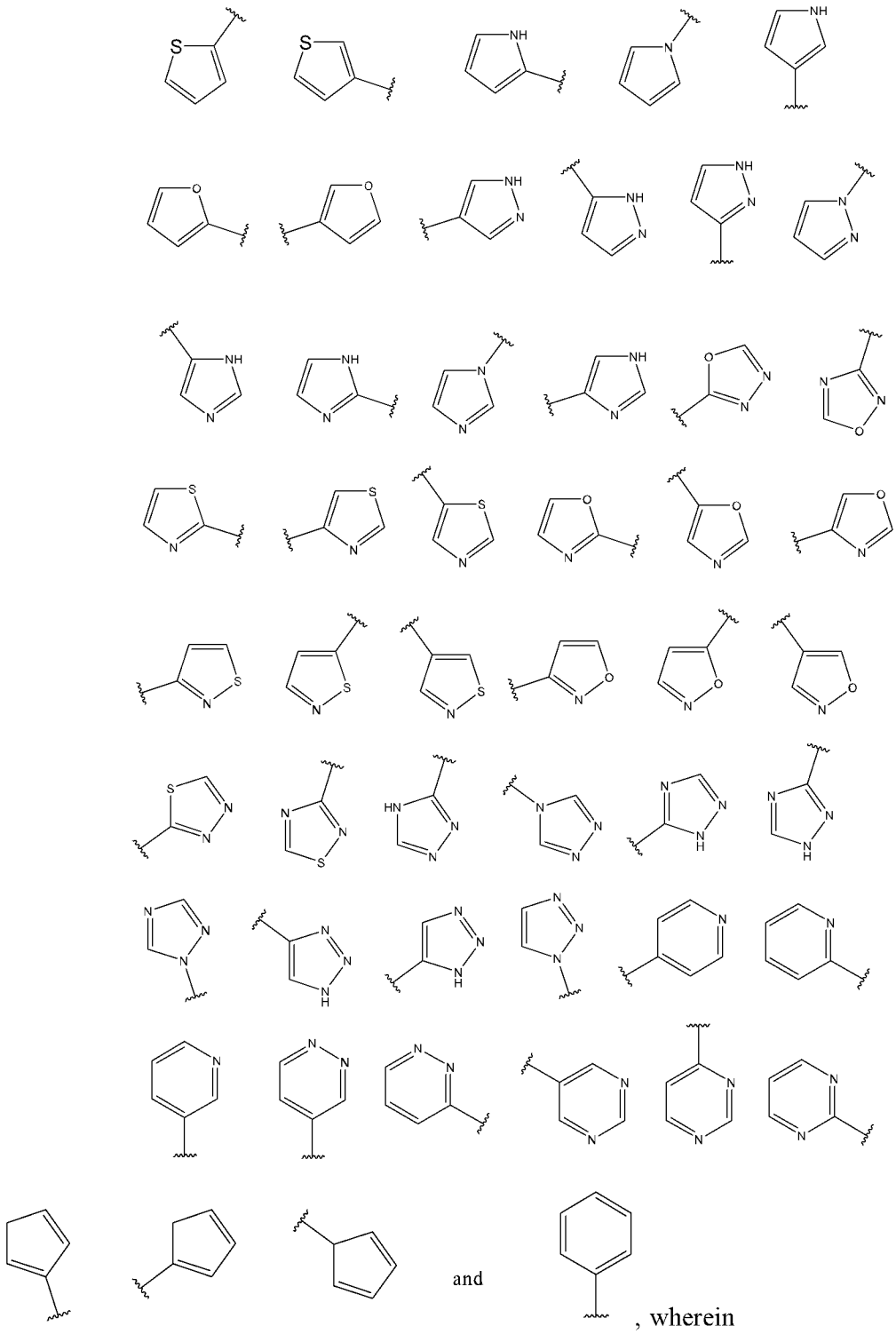

Vg

, , or , wherein: each n is independently 0, 1, 2, or 3.

9. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Ring B is a 5-8 membered ring substituted with 1-3 R^B.

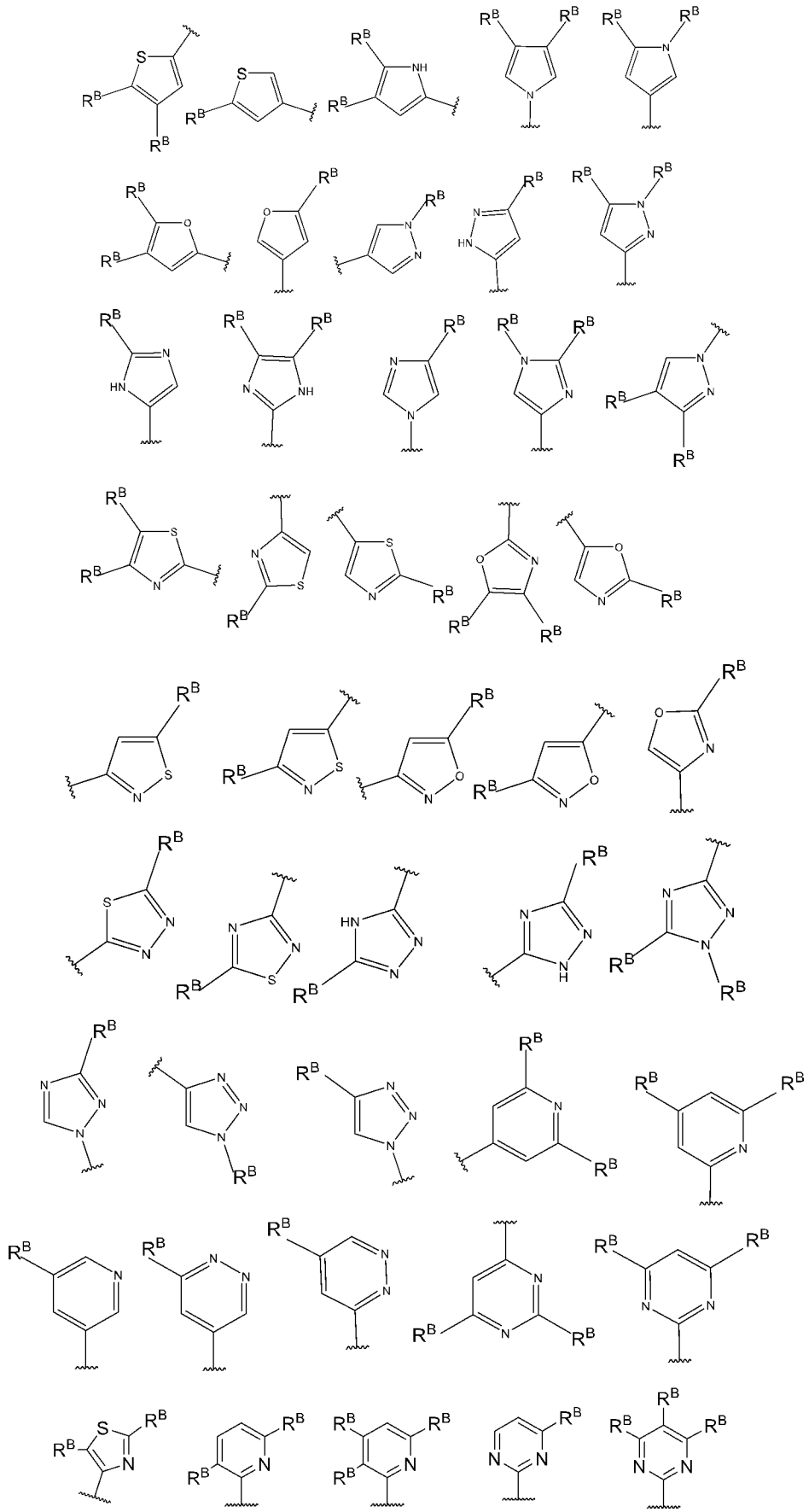
10. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein: Ring B is selected from:

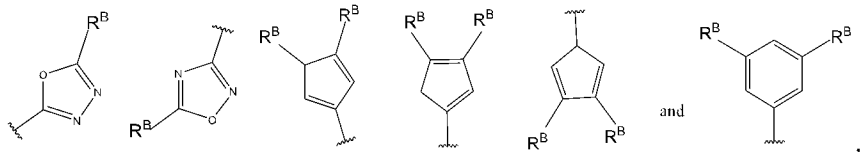


and , wherein

each hydrogen on a ring atom is independently and optionally replaced by a R^B group.

11. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring B is selected from:





12. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{B10}$, $-SR^{B10}$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2N(R^{10})(R^{11})$-, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$.

13. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{B10}$ (for example, $-OR^{10}$), $-SR^{B10}$ (for example $-SR^{10}$), $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-S(O)_2N(R^{10})(R^{11})$-, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})_2$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, C_{1-9}heteroaryl, $-CH_2-C_{1-9}$heteroaryl,

each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2-C_{3-6}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-CH_2-C_{6-10}$aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2-C_{1-9}$heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy; and

each R^{11} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{10} and R^{11}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl.

14. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})(R^{11})$.

15. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{B10}$, $-SR^{B10}$, $-N(R^{10})(R^{11})$.

16. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{2-9}heterocycloalkyl, and $-OR^{10}$.

17. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B'}$, wherein $R^{B'}$ is selected from optionally substituted C_{2-9}heterocycloalkyl, and $-OR^{B10}$.

18. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

at least one R^B is $R^{B''}$, wherein $R^{B''}$ is C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from $-N(R^{10})(R^{11})$, $-C(O)OR^{10}$, $-OC(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)N(R^{10})(R^{11})$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$-, $-N=S(=O)(R^{13})_2$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-S(=O)(=NH)(R^{13})$, $-S(=O)(=NR^{13})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, $-CH_2S(O)_2N(R^{10})(R^{11})$, $-Si(C_{1-6}alkyl)_3$, and $-P(O)(R^{10})$;

each R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2$-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, $-CH_2$-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2$-C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, $-CH_2$-C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, $-CH_2$-C_{6-10}aryl, C_{6-10}aryl, C_{1-9}heteroaryl, and $-CH_2$-C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy;

each R^{11} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{10} and R^{11}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl which is optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy.

19. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

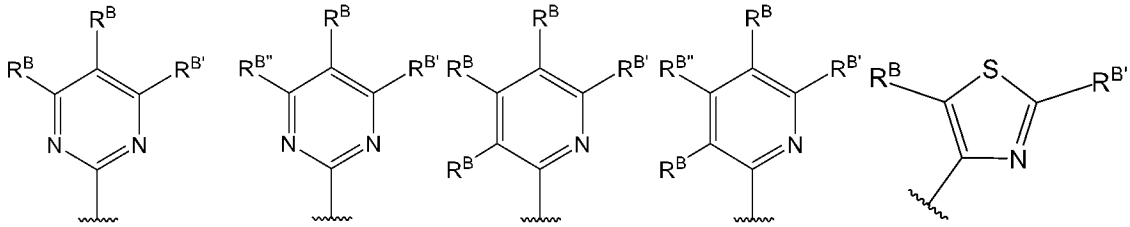
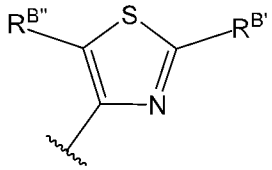
at least one R^B is $R^{B''}$, wherein $R^{B''}$ is optionally substituted C_{1-9}heteroaryl.

20. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

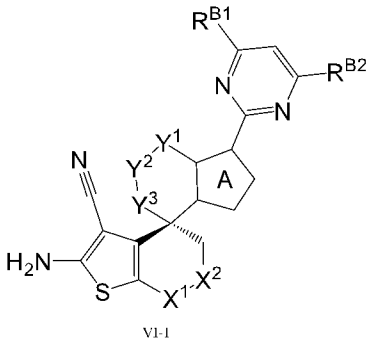
at least one R^B is $R^{B''}$, wherein $R^{B''}$ is optionally substituted thiazolyl.

21. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein at least one R^B is $R^{B'}$ and at least one R^B is $R^{B''}$.

22. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring B is selected from:


and

.

23. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, having a structure of: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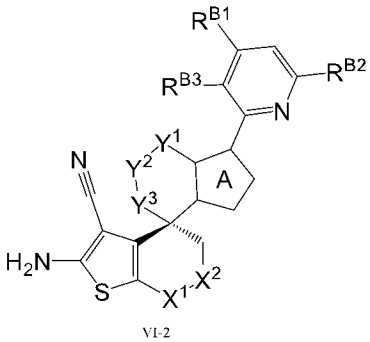
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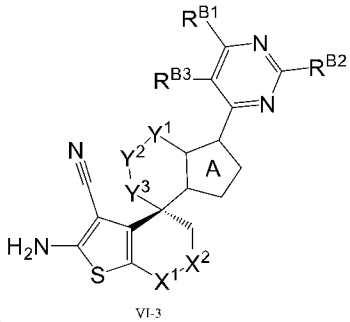
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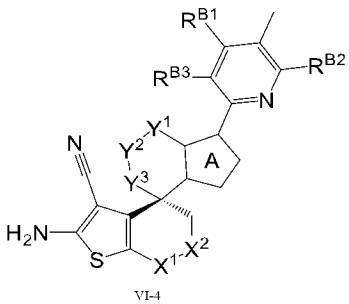
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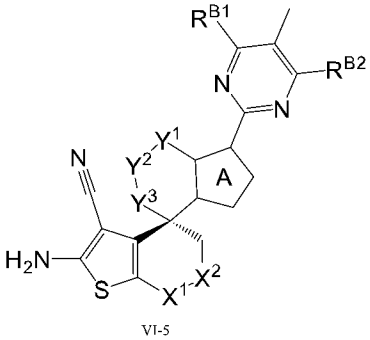
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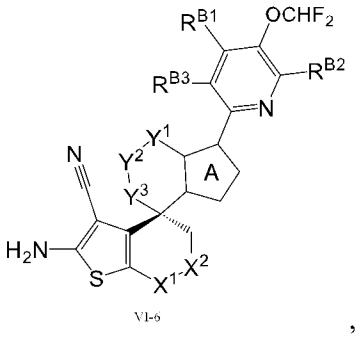
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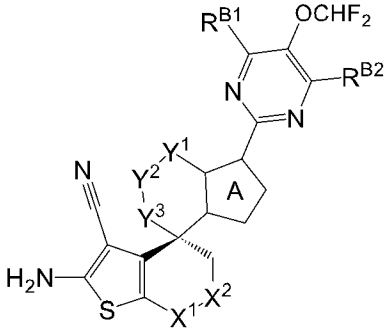
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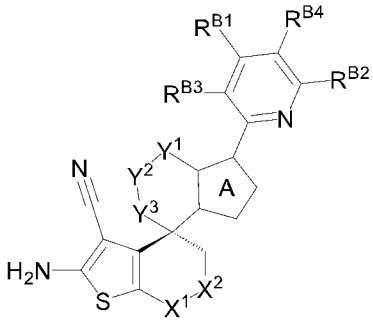
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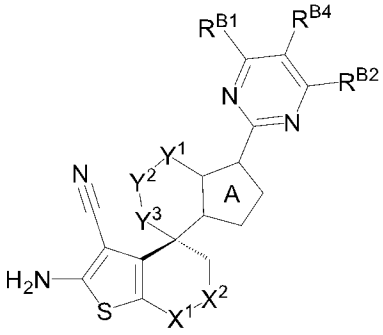
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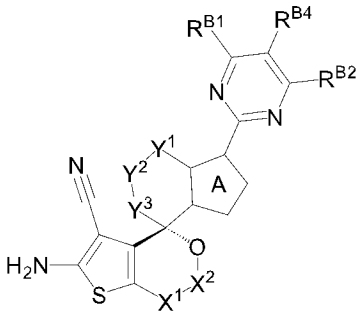
VI-10

R^{B1}, R^{B2}, R^{B3}, and R^{B4} are independently selected from R^B;

X^1 is $C(R^{1a})(R^{1b})$, O, S, or $N(R^{1c})$;

X^2 is $C(R^{2a})(R^{2b})$, O, S, or $N(R^{2c})$;

Y^1 is $C(R^{1Ya})(R^{1Yb})$, O, S, or $N(R^{1Yc})$;

Y^2 is $C(R^{2Ya})(R^{2Yb})$, O, S, or $N(R^{2Yc})$;

Y^3 is $C(R^{3Ya})(R^{3Yb})$, O, S, or $N(R^{3Yc})$;

R^{1Ya}, R^{2Ya} and R^{3Ya} are independently selected from R^{1a};

R^{1Yb}, R^{2Yb} and R^{3Ya} are independently selected from R^{1b};

R^{1Yc}, R^{2Yc} and R^{3Yc} are independently selected from R^{1c};

provided that at least one of the following conditions are satisfied in Formula (VI-1), (VI-2), (VI-3), (VI-4), (VI-5), (VI-6), or (VI-7) : (i) X^1 is not $C(R^{1a})(R^{1b})$; (ii) X^2 is not $C(R^{2a})(R^{2b})$; (iii) Y^1 is not $C(R^{1Ya})(R^{1Yb})$; (iv) Y^2 is not $C(R^{2Ya})(R^{2Yb})$; or (v) Y^3 is not $C(R^{3Ya})(R^{3Yb})$;

provided that in Formula (VI-8) or (VI-9), when X^1 is $C(R^{1a})(R^{1b})$, X^2 is $C(R^{2a})(R^{2b})$, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$ and Y^3 is $C(R^{3Ya})(R^{3Yb})$, then R^{B4} is not hydrogen, halogen and OMe;

provided that in Formula (VI-10), X^1 is $C(R^{1a})(R^{1b})$, X^2 is $C(R^{2a})(R^{2b})$, Y^1 is $C(R^{1Ya})(R^{1Yb})$, Y^2 is $C(R^{2Ya})(R^{2Yb})$ and Y^3 is $C(R^{3Ya})(R^{3Yb})$.

24. The compound of claim 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 is $C(R^{1a})(R^{1b})$, X^2 is $C(R^{2a})(R^{2b})$, and one of Y^1,Y^2 and Y^3 is O.

25. The compound of claim 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 is CH_2, X^2 is CH_2, Ring A is isoxazole, one of Y^1, Y^2 and Y^3 is O.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^4 is selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups selected from halogen, oxo, -CN, -OH, -SH, $-SF_5$, and $-NH_2$.

27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^5 is absent.

28. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^5 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OH, -SH, $-SF_5$, and $-NH_2$.

29. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^4 and R^5 together with the atoms they are attached to form a C5-7cycloalkyl or a 5-7 membered heterocyclyl optionally substituted with 1-3 R^{4a}, wherein each R^{4a} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OH, -SH, $-SF_5$, and $-NH_2$.

30. The compound of any of preceding claims, or a pharmaceutically acceptable salt or stereoisomer thereof, which is selected from the compounds of Table 1 or Table 2 or a pharmaceutically acceptable salt or stereoisomer thereof.

31. A pharmaceutical composition comprising a compound of any one of claims 1-30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

32. A method of treating a cancer, the method comprising administering an effective amount of a compound of any one of claims 1-30, or a pharmaceutically acceptable salt or stereoisomer thereof, to the subject in need thereof.

33. The method of claim 32, wherein the cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, cholangiocarcinoma, appendiceal cancer, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukaemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, oesophageal cancer, chronic lymphocytic leukaemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, renal cancer and sarcoma.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/098986

A. CLASSIFICATION OF SUBJECT MATTER

C07D498/20(2006.01)i; A61K31/506(2006.01)i; A61P35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D,A61K,A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

VCN,CNTXT,ENTXTC,CNKI,CAPLUS(STN),REGISTRY(STN): KRAS,RAS,PD-L1 expression, inhibitor,cancer,pancreatic, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 117946135 A (SHANGHAI PAILONG BIOTECHNOLOGY CO., LTD.) 30 April 2024 (2024-04-30) claims 1-11, paragraphs [0004]-[0027],examples	8-25,29-33
X	WO 2023099608 A1 (BOEHRINGER INGELHEIM INT., et al.) 08 June 2023 (2023-06-08) Table 20, pages 3-17 in the description,examples	8-25,29-33
X	WO 2023099612 A1 (BOEHRINGER INGELHEIM INT., et al.) 08 June 2023 (2023-06-08) Tables 15-23,pages 3-18 in the description,examples	8-25,29-33
X	WO 2023099623 A1 (BOEHRINGER INGELHEIM INT., et al.) 08 June 2023 (2023-06-08) Tables 19-21,23 and 25-30,pages 3-21 in the description,examples	8-25,29-33
X	WO 2023099624 A1 (BOEHRINGER INGELHEIM INT.,et al.) 08 June 2023 (2023-06-08) Tables 54-77,pages 3-38 in the description,examples	8-25,29-33
X	KIM,Dongsung et al. "Pan-KRAS inhibitor disables oncogenic signalling and tumour growth." *Nature*, Vol. 619, 31 May 2023 (2023-05-31), 160-166 left column on page 165,compound BI-2493	8-17,29-33

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 September 2024	**11 September 2024**
Name and mailing address of the ISA/CN **CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	Authorized officer **WANG,Chao** Telephone No. **(+86) 010-53962337**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/098986

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **32-33**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 32-33 are directed to methods for the treatment of the human body by therapy, and thus relate to the subject matter for which an international search is not required. The search report has been established and based on the subject matter of the use in the manufacture of medicament for treating the corresponding diseases.

2. ☑ Claims Nos.: **1-7,8-25(part),26-28,29-33(part)**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of formulas claimed in the present application covers a large number of known compounds, making search efforts difficult to fully enumerate the prior art. And the formulas or compounds claimed in claims 1-30 encompass a very large number of possible embodiments, while the description discloses and provides support for only a relatively small proportion of those embodiments. Claims 1-33 are not fully supported by description. The search has been carried out on the base of the formulas (III)-(Vg) in claim 8 and the compounds in claims 9-25, 29-33 falling within scope of preceding the formulas (III)-(Vg).

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/098986

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	117946135	A	30 April 2024	None			
WO	2023099608	A1	08 June 2023	TW	202337432	A	01 October 2023
WO	2023099612	A1	08 June 2023	TW	202340209	A	16 October 2023
WO	2023099623	A1	08 June 2023	TW	202340208	A	16 October 2023
WO	2023099624	A1	08 June 2023	AU	2022402390	A1	30 May 2024
				CO	2024007014	A2	29 July 2024
				TW	202337431	A	01 October 2023
				CA	3240980	A1	08 June 2023
				US	2024174690	A1	30 May 2024
				US	12060367	B2	13 August 2024
				IL	312905	A	01 July 2024