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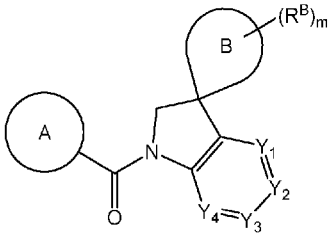
(54) Title: SPIRO INDOLINE INHIBITORS OF KIF18A



(I),

(57) Abstract: The present disclosure relates generally to inhibitors of KIF18A, compositions thereof, and methods of using said compounds and compositions thereof. More specifically, the present disclosure relates to indoline inhibitors of KIF18A and methods of their use for treating disease mediated by KIF18A, such as cancer.

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SPIRO INDOLINE INHIBITORS OF KIF18A

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Provisional Patent Application No. 63/237,275, filed August 26, 2021; U.S. Provisional Patent Application No. 63/306,452, filed February 3, 2022; and U.S. Provisional Patent Application No. 63/344,435, filed May 20, 2022, the disclosures of each of which are hereby incorporated herein by reference in their entirety.

FIELD

[0002] The present disclosure relates generally to inhibitors of KIF18A, compositions thereof, and methods of using said compounds and compositions thereof. More specifically, the present disclosure relates to indoline inhibitors of KIF18A and methods of their use for treating disease mediated by KIF18A, such as cancer.

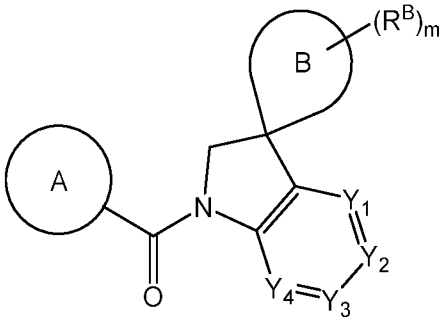
BACKGROUND

[0003] KIF18A is a kinesin involved in assisting the kinetochore-microtubule (kt-MT) attachment and chromosomal alignment during cell mitosis. Its cargo domain binds directly to protein phosphatase 1 (PP1) and carries it to the plus end of MT where PP1 dephosphorylates Hec1, a kinetochore complex component, further enhancing kt-MT attachment throughout metaphase and anaphase. Its MT-binding motor domain has ATPase activity that powers the KIF18A translocation along MT lattice, enhanced by its C-terminal MT-binding site, and caps and depolymerizes growing microtubule at the plus end, thus dampening MT dynamics. This modulation of MT dynamics by KIF18A often occurs at the following (or trailing) sister chromatid, thereby providing a counterbalancing tension to the leading sister chromatid movement catalyzed by another kinesin Kif2C/MCAK. Loss of KIF18A function causes defective kt-MT attachments and loss of tension within the spindle in cells of high chromosome instability (CIN), leading to hyper stable, longer and multipolar spindles, mitotic arrest, centrosome fragmentation and spindle assembly checkpoint activation or cell death. KIF18A is identified from DEPMAP RNAi data re-analysis as one of the top candidates essential for CIN-high cells. Reported synthetic lethality screens also singled out KIF18A as a potential anticancer target whose knockdown preferentially renders

CIN-high (but not CIN-low), aneuploid and whole-genome doubled cells vulnerable to death. Cellular toxicity assay in isogenic cell lines confirmed the enhanced sensitivity of CIN-high cells to KIF18A inhibitors. Ongoing in vivo mouse models using KIF18A inhibitor or knockdown demonstrated effect of inhibited tumor growth. Thus, there is a need for new compounds for use in treating diseases mediated by KIF18A.

BRIEF SUMMARY

[0004] The present disclosure provides compounds of Formula (I), compositions thereof, and methods of using said compounds and compositions thereof for the treatment of diseases or conditions associated with KIF18a. In one aspect, provided is a compound of Formula (I):

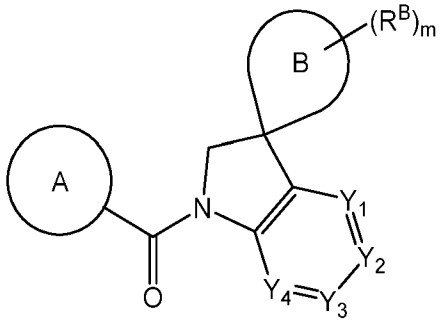


(I),

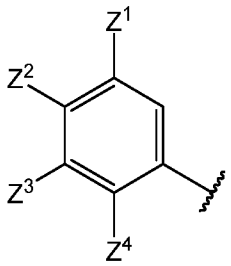
or a pharmaceutically acceptable salt thereof, wherein: ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo; R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon; each R^B

group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; m is 0, 1, 2, 3, or 4; Y^1 is N or CR^{C1}; Y^2 is N or CR^{C2}; Y^3 is N or CR^{C3}; Y^4 is N or CR^{C4}; wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N; R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

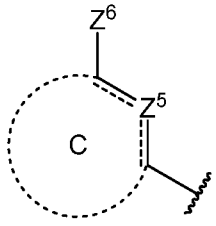
[0005] In another aspect, provided is a compound of Formula (II):



(II),

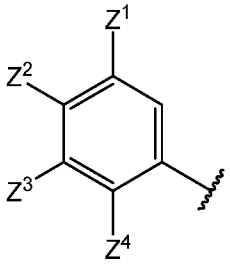


or a pharmaceutically acceptable salt thereof, wherein: ring A is (i) , wherein Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C{=}NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl, provided that (1) when Z^4 is hydrogen, then at least one of Z^1 and Z^3 is R^D; and (2) when Z^4

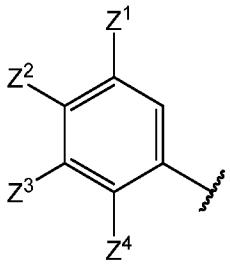
is R^D, then Z^1 is R^D, or (ii) 

, wherein  is a single bond or a double bond, Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl, Z^6 is $-NR^{a26}C(O)NR^{a27}R^{a28}$, $-NR^{a29}C(O)OR^{a30}$, $-N=S(O)R^{a31}R^{a32}$, $-S(O)R^{a33}$, $-S(O)(NR^{a34})R^{a35}$, $-S(O)_2NR^{a36}R^{a37}$, $-S(O)_2R^{a38}$, $-SR^{a39}$, 3- to 10-membered heterocycloalkyl , $-C(O)R^{a40}$ or $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo, and ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl; R^{a4}-R^{a40} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon; each R^B group is independently halo or C_{1-6} alkyl optionally substituted with one or more halo; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together to form a $=CR^{1a3}R^{1a4}$ group, wherein R^{1a3} and R^{1a4} are each independently hydrogen or C_{1-6} alkyl; m is 0, 1, 2, 3, or 4; Y^1 is N or CR^{C1}; Y^2 is N or CR^{C2}; Y^3 is N or CR^{C3}; Y^4 is N or CR^{C4}; wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N; R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, $-O-S(O)_2R^{c19}$, or C_{1-6} alkyl substituted

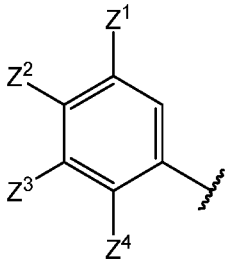
with one or more substituents independently selected from the group consisting of halo and -OH, and R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -O(C_{1-6} alkyl), - NHC(O)(C_{1-6} alkyl), and -OH; provided that (1) when ring B is



unsubstituted cyclopentyl, then ring A is , wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) substituted with one or more halo, (2) when ring



B is unsubstituted cyclohexyl and ring A is , then at least one of R^{C1}-R^{C4} is R^F, and (3) when ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4



R^B, then ring A is , wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) optionally substituted with one or more halo.

[0006] In another aspect, provided is pharmaceutical composition comprising a compound of Formula (I), Formula (I-1), Formula (Ia1), Formula (Ia2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0007] In another aspect, provided herein is a method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound or a pharmaceutical composition as described herein.

[0008] In another aspect, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically

effective amount of a compound or a pharmaceutical composition as described herein. In some embodiments, the disease or condition is mediated by KIF18A. In some embodiments, the disease or condition is cancer. In some embodiments, the disease or condition is a cellular proliferation disorder.

DESCRIPTION OF FIGURES

[0009] **Figures 1A-1E** show graphs of tumor volume of vehicle- and compound-treated mice plotted as a function of time after start of treatment.

[0010] **Figure 1A** shows Compound **22** (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of HCC15 implanted SCID Beige mice.

[0011] **Figure 1B** shows Compound **22** (10 mg/kg QD, 30 mg/kg QD, 60 mg/kg QD) treatment of OVCAR-3 implanted Balb/C nude mice.

[0012] **Figure 1C** shows Compound **134** (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of HCC15 implanted SCID Beige mice.

[0013] **Figure 1D** shows Compound **134** (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of OVCAR-3 implanted Balb/C nude mice.

[0014] **Figure 1E** shows Compound **134** (30 mg/kg BID, 30 mg/kg QD, 60 mg/kg QD) treatment of OVCAR-3 implanted Balb/C nude mice.

DETAILED DESCRIPTION

[0015] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

[0016] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0017] Throughout this application, unless the context indicates otherwise, references to a compound of Formula (I), Formula (I-1), Formula (Ia1), Formula (Ia2), Formula (I-2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II)include all subgroups defined herein, such as Formula (I-1), (Ia1), or (Ia2), including all substructures, subgenera, preferences, embodiments, examples and particular compounds defined and/or described herein. In some embodiments, references to a compound of Formula (I), Formula (I-1), Formula (Ia1), Formula (Ia2), Formula (I-2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), and subgroups thereof, such as Formula (I-1), (Ia1), or (Ia2), include ionic forms, polymorphs, pseudopolymorphs, amorphous forms, solvates, co-crystals, chelates, isomers, tautomers, oxides (e.g., N-oxides, S-oxides), esters, prodrugs, isotopes and/or protected forms thereof. In some embodiments, references to a compound of Formula (I), Formula (I-1), Formula (Ia1), Formula (Ia2), Formula (I-2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), and subgroups thereof, such as Formula (I-1), (Ia1), or (Ia2), include polymorphs, solvates, co-crystals, isomers, tautomers and/or oxides thereof. In some embodiments, references to a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), and subgroups thereof, such as Formula (I-1), (Ia1), or (Ia2), include polymorphs, solvates, and/or co-crystals thereof. In some embodiments, references to a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), and subgroups thereof, such as Formula (I-1), (Ia1), or (Ia2), include isomers, tautomers and/or oxides thereof. In some embodiments, references to a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), and subgroups thereof, such as Formula (I-1), (Ia1), or (Ia2), include solvates thereof.

[0018] "Alkyl" encompasses straight and branched carbon chains having the indicated number of carbon atoms, for example, from 1 to 20 carbon atoms, or 1 to 8 carbon atoms, or 1 to 6 carbon atoms, or 1 to 3 carbon atoms. For example, $C_{1\text{-}6}$ alkyl encompasses both straight and branched chain alkyl of from 1 to 6 carbon atoms. When an alkyl residue having a specific number of carbons is named, all branched and straight chain versions having that number of carbons are intended to be encompassed; thus, for example, "propyl" includes n-

propyl and isopropyl; and "butyl" includes n-butyl, sec-butyl, isobutyl and t-butyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

[0019] When a range of values is given (e.g., C_{1-6} alkyl), each value within the range as well as all intervening ranges are included. For example, "C_{1-6} alkyl" includes C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{2-6}, C_{3-6}, C_{4-6}, C_{5-6}, C_{1-5}, C_{2-5}, C_{3-5}, C_{4-5}, C_{1-4}, C_{2-4}, C_{3-4}, C_{1-3}, C_{2-3}, and C_{1-2} alkyl.

[0020] "Alkenyl" refers to an unsaturated branched or straight-chain alkyl group having the indicated number of carbon atoms (e.g., 2 to 8, or 2 to 6 carbon atoms) and at least one carbon-carbon double bond. The group may be in either the cis or trans configuration (Z or E configuration) about the double bond(s). Alkenyl groups include, but are not limited to, ethenyl, propenyl (e.g., prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl), and butenyl (e.g., but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl).

[0021] "Alkynyl" refers to an unsaturated branched or straight-chain alkyl group having the indicated number of carbon atoms (e.g., 2 to 8 or 2 to 6 carbon atoms) and at least one carbon-carbon triple bond. Alkynyl groups include, but are not limited to, ethynyl, propynyl (e.g., prop-1-yn-1-yl, prop-2-yn-1-yl) and butynyl (e.g., but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl).

[0022] "Cycloalkyl" indicates a non-aromatic, fully saturated carbocyclic ring having the indicated number of carbon atoms, for example, 3 to 10, or 3 to 8, or 3 to 6 ring carbon atoms. Cycloalkyl groups may be monocyclic or polycyclic (e.g., bicyclic, tricyclic). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, as well as bridged and caged ring groups (e.g., norbornane, bicyclo[2.2.2]octane). In addition, one ring of a polycyclic cycloalkyl group may be aromatic, provided the polycyclic cycloalkyl group is bound to the parent structure via a non-aromatic carbon. For example, a 1,2,3,4-tetrahydronaphthalen-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is a cycloalkyl group, while 1,2,3,4-tetrahydronaphthalen-5-yl (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a cycloalkyl group. Examples of polycyclic cycloalkyl groups consisting of a cycloalkyl group fused to an aromatic ring are described below.

[0023] "Cycloalkenyl" indicates a non-aromatic carbocyclic ring, containing the indicated number of carbon atoms (e.g., 3 to 10, or 3 to 8, or 3 to 6 ring carbon atoms) and at least one carbon-carbon double bond. Cycloalkenyl groups may be monocyclic or polycyclic (e.g., bicyclic, tricyclic). Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl, as well as bridged and caged ring groups (e.g., bicyclo[2.2.2]octene). In addition, one ring of a polycyclic cycloalkenyl group may be aromatic, provided the polycyclic alkenyl group is bound to the parent structure via a non-aromatic carbon atom. For example, inden-1-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is considered a cycloalkenyl group, while inden-4-yl (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a cycloalkenyl group. Examples of polycyclic cycloalkenyl groups consisting of a cycloalkenyl group fused to an aromatic ring are described below.

[0024] "Aryl" indicates an aromatic carbocyclic ring having the indicated number of carbon atoms, for example, 6 to 12 or 6 to 10 carbon atoms. Aryl groups may be monocyclic or polycyclic (e.g., bicyclic, tricyclic). In some instances, both rings of a polycyclic aryl group are aromatic (e.g., naphthyl). In other instances, polycyclic aryl groups may include a non-aromatic ring fused to an aromatic ring, provided the polycyclic aryl group is bound to the parent structure via an atom in the aromatic ring. Thus, a 1,2,3,4-tetrahydronaphthalen-5-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydronaphthalen-1-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered an aryl group. Similarly, a 1,2,3,4-tetrahydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is not considered an aryl group. However, the term "aryl" does not encompass or overlap with "heteroaryl," as defined herein, regardless of the point of attachment (e.g., both quinolin-5-yl and quinolin-2-yl are heteroaryl groups). In some instances, aryl is phenyl or naphthyl. In certain instances, aryl is phenyl. Additional examples of aryl groups comprising an aromatic carbon ring fused to a non-aromatic ring are described below.

[0025] "Heteroaryl" indicates an aromatic ring containing the indicated number of atoms (e.g., 5 to 12, or 5 to 10 membered heteroaryl) made up of one or more heteroatoms (e.g., 1, 2, 3 or 4 heteroatoms) selected from N, O and S and with the remaining ring atoms being carbon. Heteroaryl groups do not contain adjacent S and O atoms. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 1. Unless otherwise indicated, heteroaryl groups may be bound to the parent structure by a carbon or nitrogen atom, as valency permits. For example, "pyridyl" includes 2-pyridyl, 3-pyridyl and 4-pyridyl groups, and "pyrrolyl" includes 1-pyrrolyl, 2-pyrrolyl and 3-pyrrolyl groups.

[0026] In some instances, a heteroaryl group is monocyclic. Examples include pyrrole, pyrazole, imidazole, triazole (e.g., 1,2,3-triazole, 1,2,4-triazole, 1,2,4-triazole), tetrazole, furan, isoxazole, oxazole, oxadiazole (e.g., 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole), thiophene, isothiazole, thiazole, thiadiazole (e.g., 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole), pyridine, pyridazine, pyrimidine, pyrazine, triazine (e.g., 1,2,4-triazine, 1,3,5-triazine) and tetrazine.

[0027] In some instances, both rings of a polycyclic heteroaryl group are aromatic. Examples include indole, isoindole, indazole, benzoimidazole, benzotriazole, benzofuran, benzoxazole, benzoisoxazole, benzoxadiazole, benzothiophene, benzothiazole, benzoisothiazole, benzothiadiazole, 1H-pyrrolo[2,3-b]pyridine, 1H-pyrazolo[3,4-b]pyridine, 3H-imidazo[4,5-b]pyridine, 3H-[1,2,3]triazolo[4,5-b]pyridine, 1H-pyrrolo[3,2-b]pyridine, 1H-pyrazolo[4,3-b]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-[1,2,3]triazolo[4,5-b]pyridine, 1H-pyrrolo[2,3-c]pyridine, 1H-pyrazolo[3,4-c]pyridine, 3H-imidazo[4,5-c]pyridine, 3H-[1,2,3]triazolo[4,5-c]pyridine, 1H-pyrrolo[3,2-c]pyridine, 1H-pyrazolo[4,3-c]pyridine, 1H-imidazo[4,5-c]pyridine, 1H-[1,2,3]triazolo[4,5-c]pyridine, furo[2,3-b]pyridine, oxazolo[5,4-b]pyridine, isoxazolo[5,4-b]pyridine, [1,2,3]oxadiazolo[5,4-b]pyridine, furo[3,2-b]pyridine, oxazolo[4,5-b]pyridine, isoxazolo[4,5-b]pyridine, [1,2,3]oxadiazolo[4,5-b]pyridine, furo[2,3-c]pyridine, oxazolo[5,4-c]pyridine, isoxazolo[5,4-c]pyridine, [1,2,3]oxadiazolo[5,4-c]pyridine, furo[3,2-c]pyridine, oxazolo[4,5-c]pyridine, isoxazolo[4,5-c]pyridine, [1,2,3]oxadiazolo[4,5-c]pyridine, thieno[2,3-b]pyridine, thiazolo[5,4-b]pyridine, isothiazolo[5,4-b]pyridine, [1,2,3]thiadiazolo[5,4-b]pyridine, thieno[3,2-b]pyridine, thiazolo[4,5-b]pyridine, isothiazolo[4,5-b]pyridine, [1,2,3]thiadiazolo[4,5-b]pyridine,

thieno[2,3-c]pyridine, thiazolo[5,4-c]pyridine, isothiazolo[5,4-c]pyridine, [1,2,3]thiadiazolo[5,4-c]pyridine, thieno[3,2-c]pyridine, thiazolo[4,5-c]pyridine, isothiazolo[4,5-c]pyridine, [1,2,3]thiadiazolo[4,5-c]pyridine, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, naphthyridine (e.g., 1,8-naphthyridine, 1,7-naphthyridine, 1,6-naphthyridine, 1,5-naphthyridine, 2,7-naphthyridine, 2,6-naphthyridine), imidazo[1,2-a]pyridine, 1H-pyrazolo[3,4-d]thiazole, 1H-pyrazolo[4,3-d]thiazole and imidazo[2,1-b]thiazole.

[0028] In other instances, polycyclic heteroaryl groups may include a non-aromatic ring (e.g., cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl) fused to a heteroaryl ring, provided the polycyclic heteroaryl group is bound to the parent structure via an atom in the aromatic ring. For example, a 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered a heteroaryl group, while 4,5,6,7-tetrahydrobenzo[d]thiazol-5-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered a heteroaryl group. Examples of polycyclic heteroaryl groups consisting of a heteroaryl ring fused to a non-aromatic ring are described below.

[0029] "Heterocycloalkyl" indicates a non-aromatic, fully saturated ring having the indicated number of atoms (e.g., 3 to 10, or 3 to 7, membered heterocycloalkyl) made up of one or more heteroatoms (e.g., 1, 2, 3 or 4 heteroatoms) selected from N, O and S and with the remaining ring atoms being carbon. Heterocycloalkyl groups may be monocyclic or polycyclic (e.g., bicyclic, tricyclic). Examples of heterocycloalkyl groups include oxiranyl, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl. Examples include thiomorpholine S-oxide and thiomorpholine S,S-dioxide. In addition, one ring of a polycyclic heterocycloalkyl group may be aromatic (e.g., aryl or heteroaryl), provided the polycyclic heterocycloalkyl group is bound to the parent structure via a non-aromatic carbon or nitrogen atom. For example, a 1,2,3,4-tetrahydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is considered a heterocycloalkyl group, while 1,2,3,4-tetrahydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a heterocycloalkyl group. Examples of polycyclic heterocycloalkyl groups consisting of a heterocycloalkyl group fused to an aromatic ring are described below.

[0030] "Heterocycloalkenyl" indicates a non-aromatic ring having the indicated number of atoms (e.g., 3 to 10, or 3 to 7, membered heterocycloalkyl) made up of one or more heteroatoms (e.g., 1, 2, 3 or 4 heteroatoms) selected from N, O and S and with the remaining ring atoms being carbon, and at least one double bond derived by the removal of one molecule of hydrogen from adjacent carbon atoms, adjacent nitrogen atoms, or adjacent carbon and nitrogen atoms of the corresponding heterocycloalkyl. Heterocycloalkenyl groups may be monocyclic or polycyclic (e.g., bicyclic, tricyclic). Examples of heterocycloalkenyl groups include dihydrofuranyl (e.g., 2,3-dihydrofuranyl, 2,5-dihydrofuranyl), dihydrothiophenyl (e.g., 2,3-dihydrothiophenyl, 2,5-dihydrothiophenyl), dihydropyrrolyl (e.g., 2,3-dihydro-1H-pyrrolyl, 2,5-dihydro-1H-pyrrolyl), dihydroimidazolyl (e.g., 2,3-dihydro-1H-imidazolyl, 4,5-dihydro-1H-imidazolyl), pyranyl, dihydropyranyl (e.g., 3,4-dihydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl), tetrahydropyridinyl (e.g., 1,2,3,4-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl) and dihydropyridine (e.g., 1,2-dihydropyridine, 1,4-dihydropyridine). In addition, one ring of a polycyclic heterocycloalkenyl group may be aromatic (e.g., aryl or heteroaryl), provided the polycyclic heterocycloalkenyl group is bound to the parent structure via a non-aromatic carbon or nitrogen atom. For example, a 1,2-dihydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is considered a heterocycloalkenyl group, while 1,2-dihydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a heterocycloalkenyl group. Examples of polycyclic heterocycloalkenyl groups consisting of a heterocycloalkenyl group fused to an aromatic ring are described below.

[0031] Examples of polycyclic rings consisting of an aromatic ring (e.g., aryl or heteroaryl) fused to a non-aromatic ring (e.g., cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl) include indenyl, 2,3-dihydro-1H-indenyl, 1,2,3,4-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, tetrahydroquinolinyl, 2,3-dihydrobenzo[1,4]dioxinyl, indolinyl, isoindolinyl, 2,3-dihydro-1H-indazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, 1,3-dihydrobenzo[c]isoxazolyl, 2,3-dihydrobenzo[d]isoxazolyl, 2,3-dihydrobenzo[d]oxazolyl, 2,3-dihydrobenzo[b]thiophenyl, 1,3-dihydrobenzo[c]thiophenyl, 1,3-dihydrobenzo[c]isothiazolyl, 2,3-dihydrobenzo[d]isothiazolyl, 2,3-dihydrobenzo[d]thiazolyl, 5,6-dihydro-4H-cyclopenta[d]thiazolyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, 5,6-dihydro-4H-pyrrolo[3,4-d]thiazolyl, 4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridinyl, indolin-2-one, indolin-3-one, isoindolin-1-one, 1,2-dihydroindazol-3-one, 1H-benzo[d]imidazol-2(3H)-one, benzofuran-2(3H)-one, benzofuran-3(2H)-one, isobenzofuran-1(3H)-one, benzo[c]isoxazol-3(1H)-one, benzo[d]isoxazol-3(2H)-one, benzo[d]oxazol-2(3H)-one, benzo[b]thiophen-2(3H)-one, benzo[b]thiophen-3(2H)-one, benzo[c]thiophen-1(3H)-one, benzo[c]isothiazol-3(1H)-one, benzo[d]isothiazol-3(2H)-one, benzo[d]thiazol-2(3H)-one, 4,5-dihydropyrrolo[3,4-d]thiazol-6-one, 1,2-dihydropyrazolo[3,4-d]thiazol-3-one, quinolin-4(3H)-one, quinazolin-4(3H)-one, quinazoline-2,4(1H,3H)-dione, quinoxalin-2(1H)-one, quinoxaline-2,3(1H,4H)-dione, cinnolin-4(3H)-one, pyridin-2(1H)-one, pyrimidin-2(1H)-one, pyrimidin-4(3H)-one, pyridazin-3(2H)-one, 1H-pyrrolo[3,2-b]pyridin-2(3H)-one, 1H-pyrrolo[3,2-c]pyridin-2(3H)-one, 1H-pyrrolo[2,3-c]pyridin-2(3H)-one, 1H-pyrrolo[2,3-b]pyridin-2(3H)-one, 1,2-dihydropyrazolo[3,4-d]thiazol-3-one and 4,5-dihydropyrrolo[3,4-d]thiazol-6-one. As discussed herein, whether each ring is considered an aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl group is determined by the atom through which the moiety is bound to the parent structure.

[0032] "Halogen" or "halo" refers to fluoro, chloro, bromo or iodo.

[0033] "Haloalkyl" refers to alkyl substituted with one or more halogen. A haloalkyl group may have a halogen substituent at any valence-permitted location on the alkyl and may have any number of halogen substituents ranging from one to the maximum valence-permitted number. Particular haloalkyl groups have 1, 2, or 3 halogen substituents. Examples of haloalkyl groups include, but are not limited to, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2CH_2Cl$, $-CH_2CHCl_2$, $-CH_2CCl_3$.

[0034] Unless otherwise indicated, compounds disclosed and/or described herein include all possible enantiomers, diastereomers, meso isomers and other stereoisomeric forms, including racemic mixtures, optically pure forms and intermediate mixtures thereof. Enantiomers, diastereomers, meso isomers and other stereoisomeric forms can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Unless specified otherwise, when the compounds disclosed and/or described herein contain olefinic double bonds or other centers of geometric asymmetry, it is intended that the compounds include both E and Z isomers. When the compounds described herein contain moieties capable of tautomerization, and unless specified otherwise, it is intended that the compounds include all possible tautomers.

[0035] "Protecting group" has the meaning conventionally associated with it in organic synthesis, i.e., a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site, and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T.H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999). For example, a "hydroxy protected form" contains at least one hydroxy group protected with a hydroxy protecting group. Likewise, amines and other reactive groups may similarly be protected.

[0036] The term "pharmaceutically acceptable salt" refers to a salt of any of the compounds herein which are known to be non-toxic and are commonly used in the pharmaceutical literature. In some embodiments, the pharmaceutically acceptable salt of a compound retains the biological effectiveness of the compounds described herein and are not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts can be found in Berge et al., Pharmaceutical Salts, *J. Pharmaceutical Sciences*, January 1977, 66(1), 1-19. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethylsulfonic acid, p-toluenesulfonic acid, stearic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines; cyclic amines; and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is selected from ammonium, potassium, sodium, calcium, and magnesium salts.

[0037] If the compound described herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the compound is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds (see, e.g., Berge et al., Pharmaceutical Salts, *J. Pharmaceutical Sciences*, January 1977, 66(1), 1-19). Those skilled in the art will recognize various synthetic methodologies that may be used to prepare pharmaceutically acceptable addition salts.

[0038] A "solvate" is formed by the interaction of a solvent and a compound. Suitable solvents include, for example, water and alcohols (e.g., ethanol). Solvates include hydrates having any ratio of compound to water, such as monohydrates, dihydrates and hemi-hydrates.

[0039] The term "substituted" means that the specified group or moiety bears one or more substituents including, but not limited to, substituents such as alkoxy, acyl, acyloxy, alkoxycarbonyl, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, aryl, heteroaryl, aryloxy, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, alkyl, alkenyl, alkynyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo and the like. The term "unsubstituted" means that the specified group bears no substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. When a group or moiety bears more than one substituent, it is understood that the substituents may be the same or different from one another. In some embodiments, a substituted group or moiety bears from one to five substituents. In some embodiments, a substituted group or moiety bears one substituent. In some embodiments, a substituted group or moiety bears two substituents. In some embodiments, a substituted group or moiety bears three substituents. In some embodiments, a substituted group or moiety bears four substituents. In some embodiments, a substituted group or moiety bears five substituents.

[0040] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined herein. 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, synthetically non-feasible, and/or inherently unstable. It will also be understood that where a group or moiety is optionally substituted, the disclosure includes both embodiments in which the group or moiety is substituted and embodiments in which the group or moiety is unsubstituted.

[0041] The compounds disclosed and/or described herein can be enriched isotopic forms, e.g., enriched in the content of ^{2}H, ^{3}H, ^{11}C, ^{13}C and/or ^{14}C. In one embodiment, the compound contains at least one deuterium atom. Such deuterated forms can be made, for example, by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. Such deuterated compounds may improve the efficacy and increase the duration of action of compounds disclosed and/or described herein. Deuterium substituted compounds can be synthesized using various methods, such as those described in: Dean, D., Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development, *Curr. Pharm. Des.*, 2000; 6(10); Kabalka, G. et al., The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, *Tetrahedron*, 1989, 45(21), 6601-21; and Evans, E., Synthesis of radiolabeled compounds, *J. Radioanal. Chem.*, 1981, 64(1-2), 9-32.

[0042] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in pharmaceutical compositions is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0043] The terms "patient," "individual," and "subject" refer to an animal, such as a mammal, bird, or fish. In some embodiments, the patient or subject is a mammal. Mammals include, for example, mice, rats, dogs, cats, pigs, sheep, horses, cows and humans. In some embodiments, the patient, individual, or subject is a human, for example a human that has been or will be the object of treatment, observation or experiment. The compounds, compositions and methods described herein can be useful in both human therapy and veterinary applications.

[0044] The term "therapeutically effective amount" or "effective amount" refers to that amount of a compound disclosed and/or described herein that is sufficient to affect treatment, as defined herein, when administered to a patient in need of such treatment. A therapeutically effective amount of a compound may be an amount sufficient to treat a disease responsive to modulation (e.g., inhibition) of KIF18a. The therapeutically effective amount will vary depending upon, for example, the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the particular compound, the dosing regimen to be followed, timing of administration, the manner of administration, all of which can readily be determined by one of ordinary skill in the art. The therapeutically effective amount may be ascertained experimentally, for example by assaying blood concentration of the chemical entity, or theoretically, by calculating bioavailability.

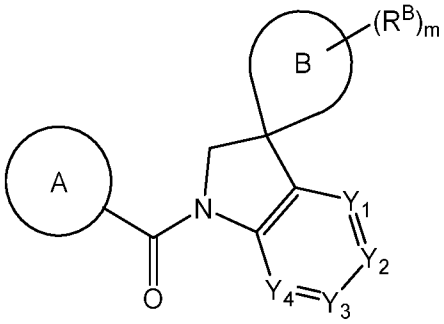
[0045] "Treatment" (and related terms, such as "treat," "treated," "treating") includes one or more of: inhibiting a disease or disorder; slowing or arresting the development of clinical symptoms of a disease or disorder; and/or relieving a disease or disorder (i.e., causing relief from or regression of clinical symptoms). The term covers both complete and partial reduction of the condition or disorder, and complete or partial reduction of clinical symptoms of a disease or disorder. Thus, compounds described and/or disclosed herein may prevent an existing disease or disorder from worsening, assist in the management of the disease or disorder, or reduce or eliminate the disease or disorder.

[0046] It is understood that embodiments described herein as "comprising" include "consisting of" and "consisting essentially of" embodiments.

Compounds

[0047] Compounds and salts thereof (such as pharmaceutically acceptable salts) are detailed herein, including in the Brief Summary and in the appended claims. Also provided are the use of all of the compounds described herein, including any and all stereoisomers, including geometric isomers (cis/trans), E/Z isomers, enantiomers, diastereomers, and mixtures thereof in any ratio including racemic mixtures, salts and solvates of the compounds described herein, as well as methods of making such compounds. Any compound described herein may also be referred to as a drug.

[0048] In one aspect, provided are compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

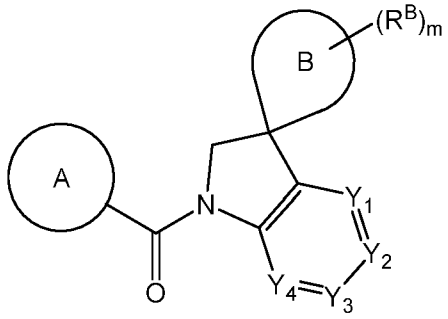
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0049] In one aspect, provided are compounds of Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

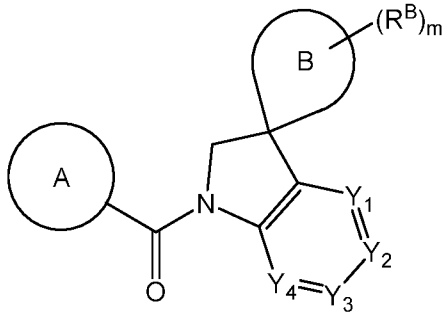
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0050] In another aspect, provided herein is a compound of Formula (I-2)



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, -

$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

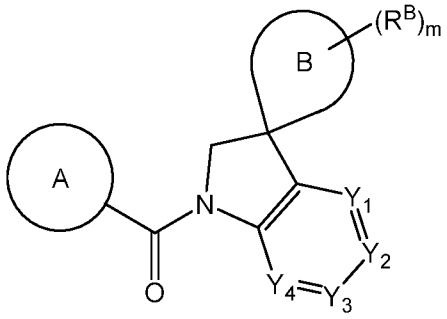
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0051] In another aspect, provided herein is a compound of Formula (I-3):



(I-3),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C_{3-7} cycloalkyl;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0052] In some embodiments of Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3), or a pharmaceutically acceptable salt thereof, ring A is substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more halo. In some embodiments, ring A is substituted with $-SR^{a21}$, $-C(O)R^{a22}$, or C_{1-6} alkyl substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more halo. In some embodiments, R^{a21} and R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl.

[0053] In some embodiments of Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3), , or a pharmaceutically acceptable salt thereof, one or more R^B groups are independently C_{1-6} alkyl substituted with one, two, three, four, five, or more halo. In some embodiments, an R^B group is C_{1-6} alkyl substituted with one, two, three, four, five, or more halo.

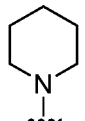
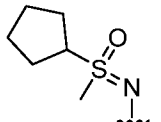
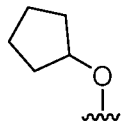
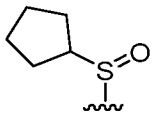
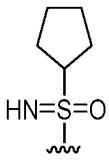
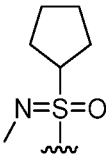
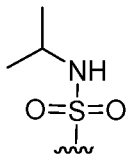
[0054] In some embodiments of Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3), , or a pharmaceutically acceptable salt thereof, R^{C2} is $-NR^{c14}C(O)OR^{c15}$, wherein R^{c14} and R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

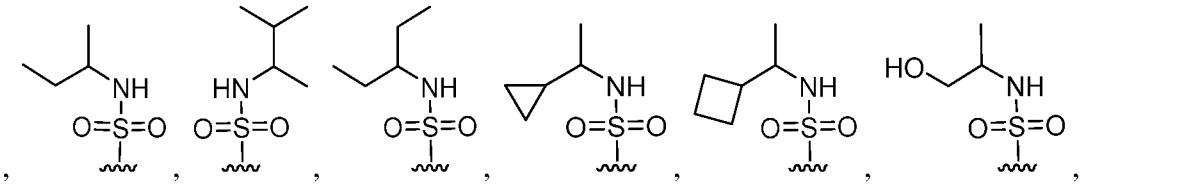
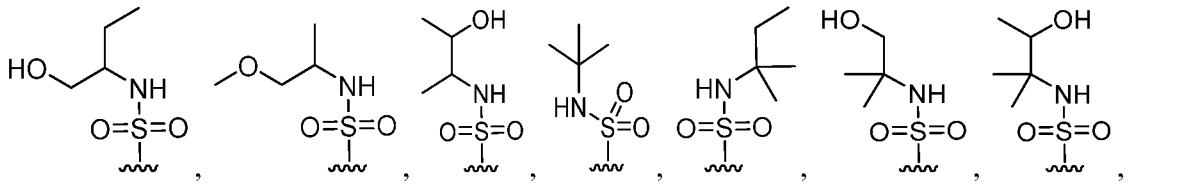
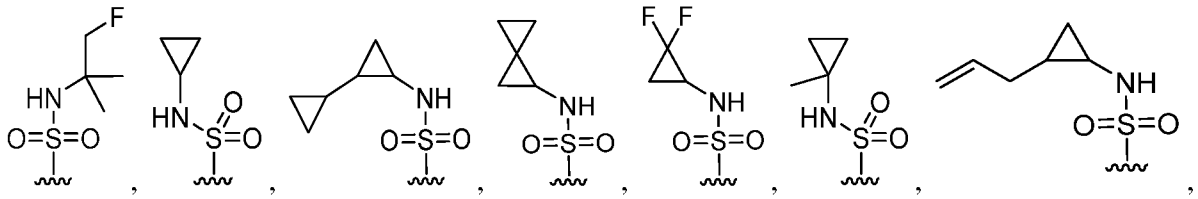
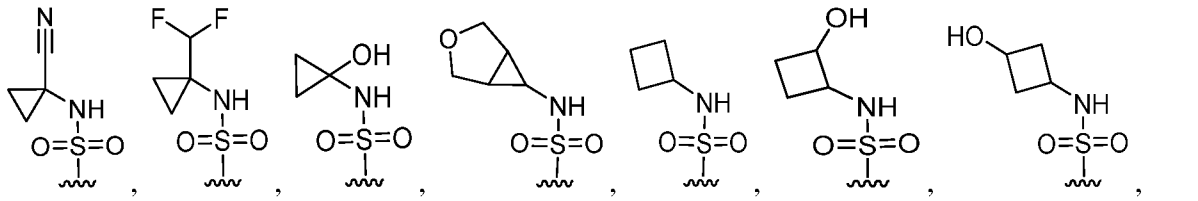
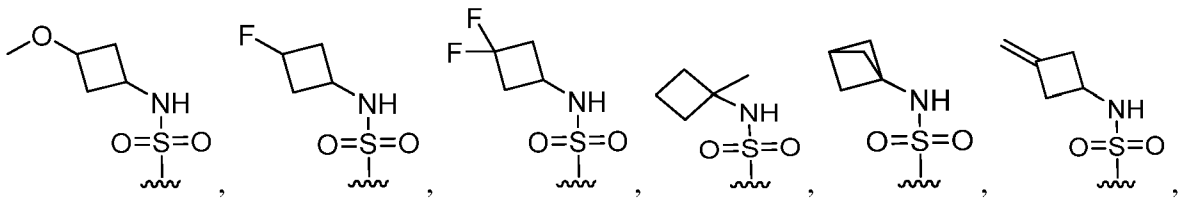
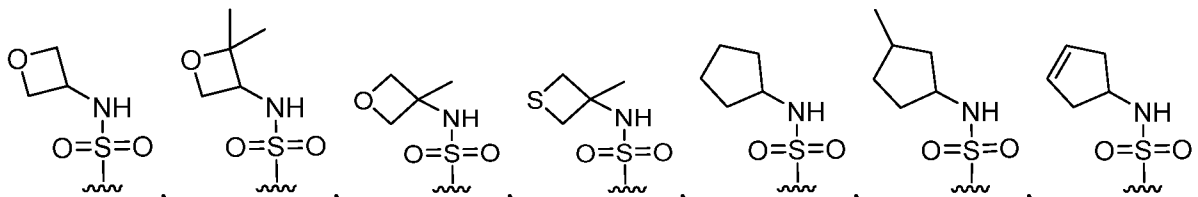
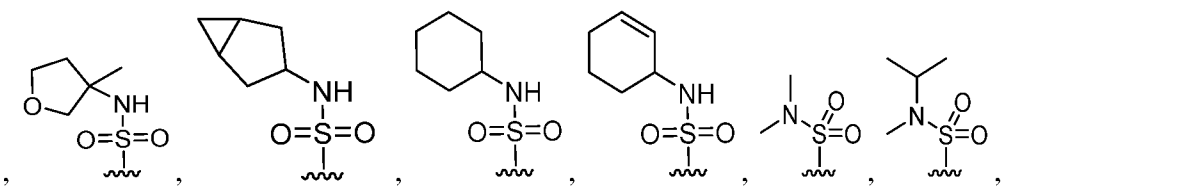
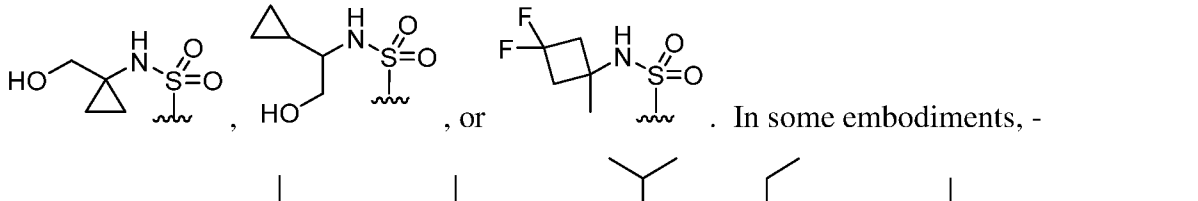
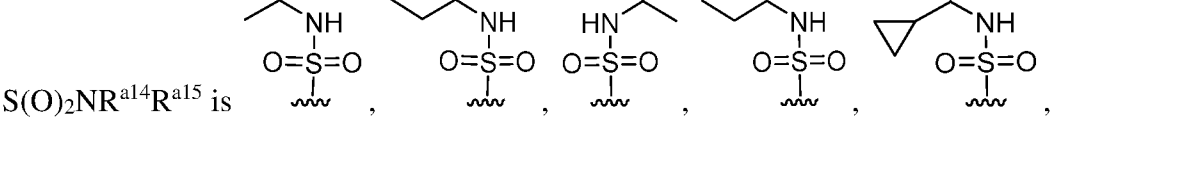
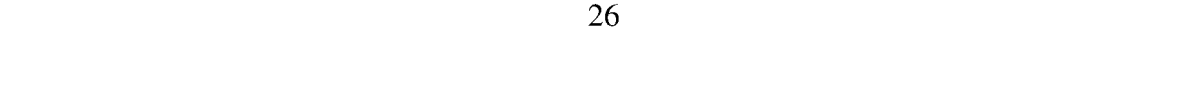
[0055] In some embodiments, cycloalkyl or heterocycloalkyl groups include spiro groups. In some embodiments, cycloalkyl or heterocycloalkyl groups include fused groups.

[0056] In some embodiments of Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3), or a pharmaceutically acceptable salt thereof, ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted. In some embodiments, ring A is optionally substituted C_{6-14} aryl. In some embodiments, ring A is optionally substituted phenyl. In some embodiments, ring A is optionally substituted 5- to 12-membered heteroaryl. In some embodiments, ring A is optionally substituted 6-membered heteroaryl. In some embodiments, ring A is optionally substituted 5-membered heteroaryl. In some embodiments, ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted. In some embodiments, ring A is optionally substituted thiophenyl.

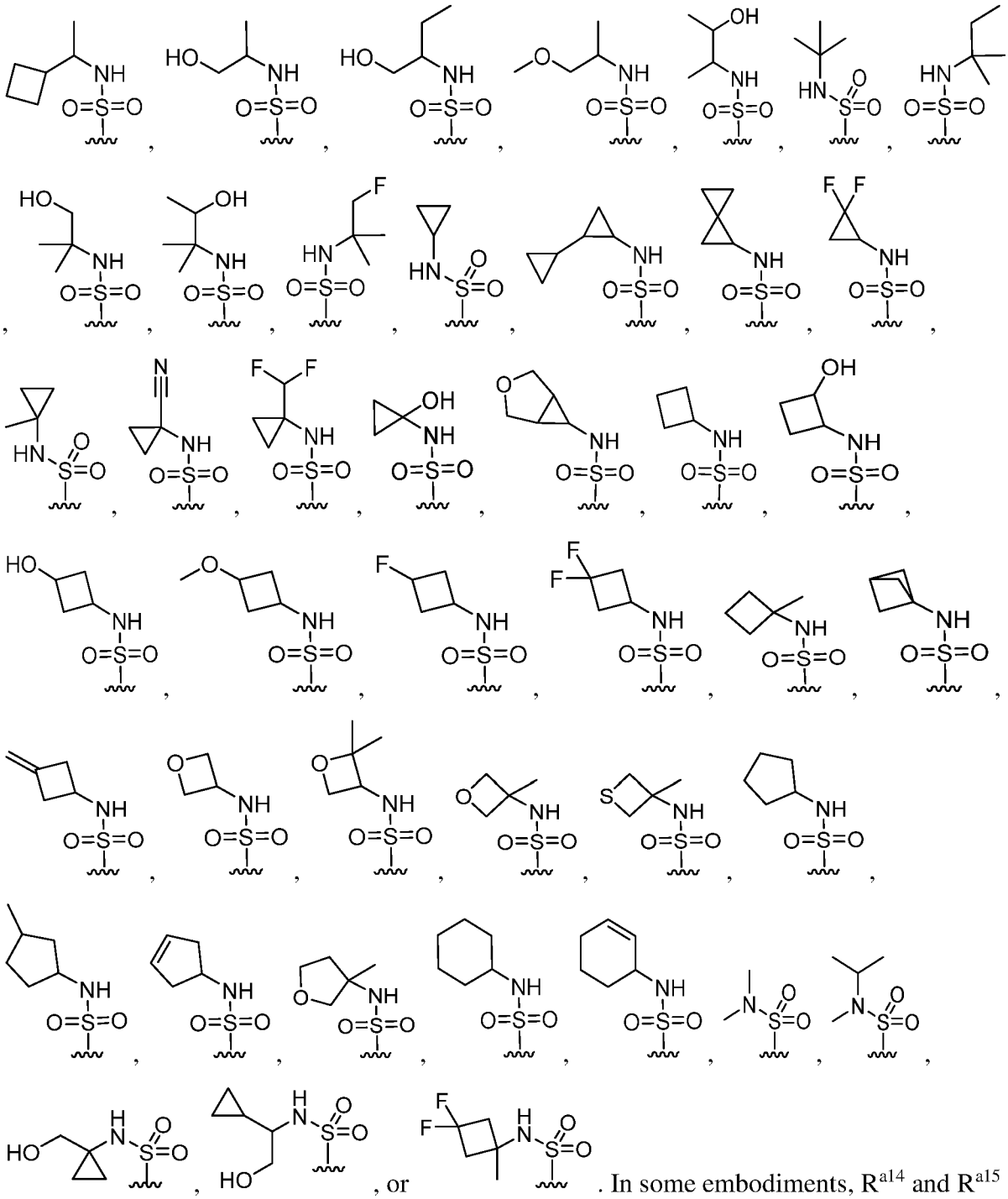
[0057] In some embodiments Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3) Formula (II), ring A is optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo. In some embodiments, R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one, two, three, four, five, or

more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl.

[0058] In some embodiments, the 3- to 10-membered heterocycloalkyl is piperidinyl. In some embodiments, the 3- to 10-membered heterocycloalkyl is  . In some embodiments, R^{a1} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a1} is hydrogen. In some embodiments, R^{a2} and R^{a3} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a2} and R^{a3} are each independently hydrogen, cyclopropyl, ethyl, or isopropyl. In some embodiments, R^{a4} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a4} is hydrogen. In some embodiments, R^{a5} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a5} is *tert*-butyl.. In some embodiments, R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl. In some embodiments, R^{a6} and R^{a7} are each independently hydrogen, imidazolyl, methylimidazolyl, or pyrimidinyl. In some embodiments, -N=S(O)$R^{a8}R^{a9}$ is  . In some embodiments, R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a8} and R^{a9} are each independently methyl or cyclopentyl. In some embodiments, -OR^{a10} is  . In some embodiments, R^{a10} is C_{3-10} cycloalkyl. In some embodiments, R^{a10} is cyclopentyl. In some embodiments, -S(O)R^{a11} is  . In some embodiments, R^{a11} is C_{3-10} cycloalkyl. In some embodiments, R^{a11} is cyclopentyl. In some embodiments, -S(O)(NR^{a12})R^{a13} is  or  . In some embodiments, R^{a12} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a12} is hydrogen or methyl. In some embodiments, R^{a13} is C_{3-10} cycloalkyl. In some embodiments, R^{a13} is cyclopentyl. In some embodiments, -S(O)$_2$N$R^{a14}R^{a15}$ is 

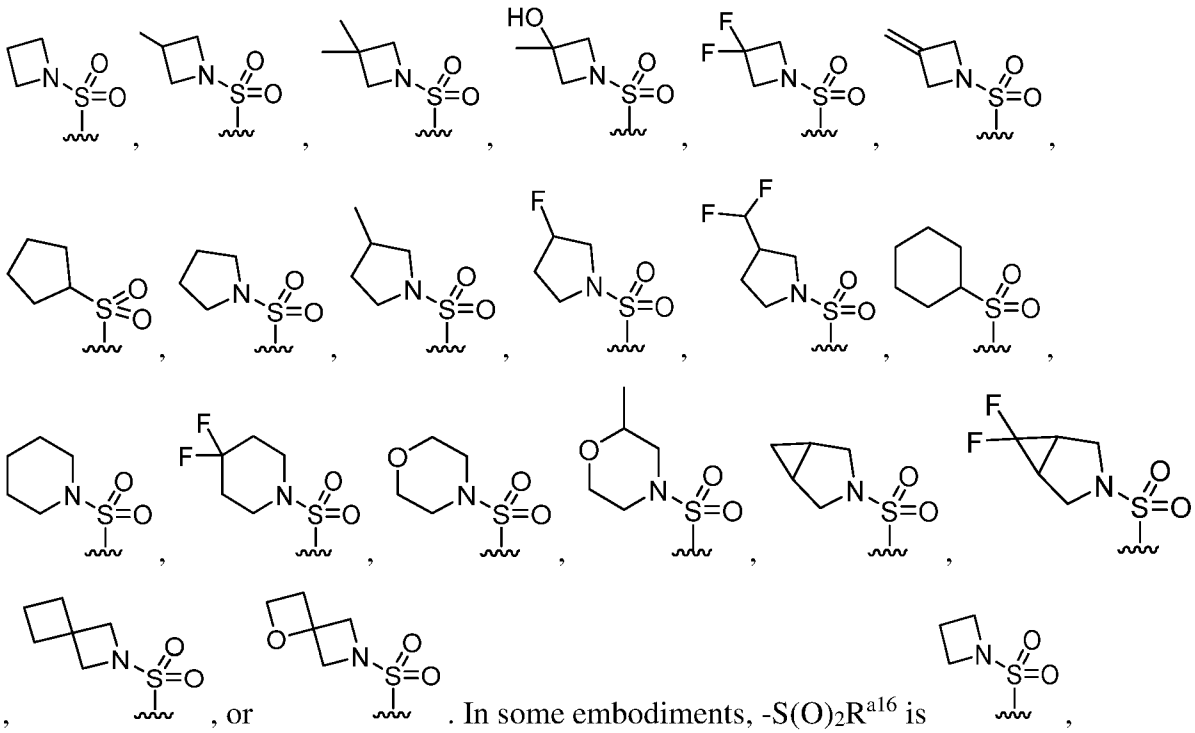











, or . In some embodiments, -$S(O)_2NR^{a14}R^{a15}$ is .

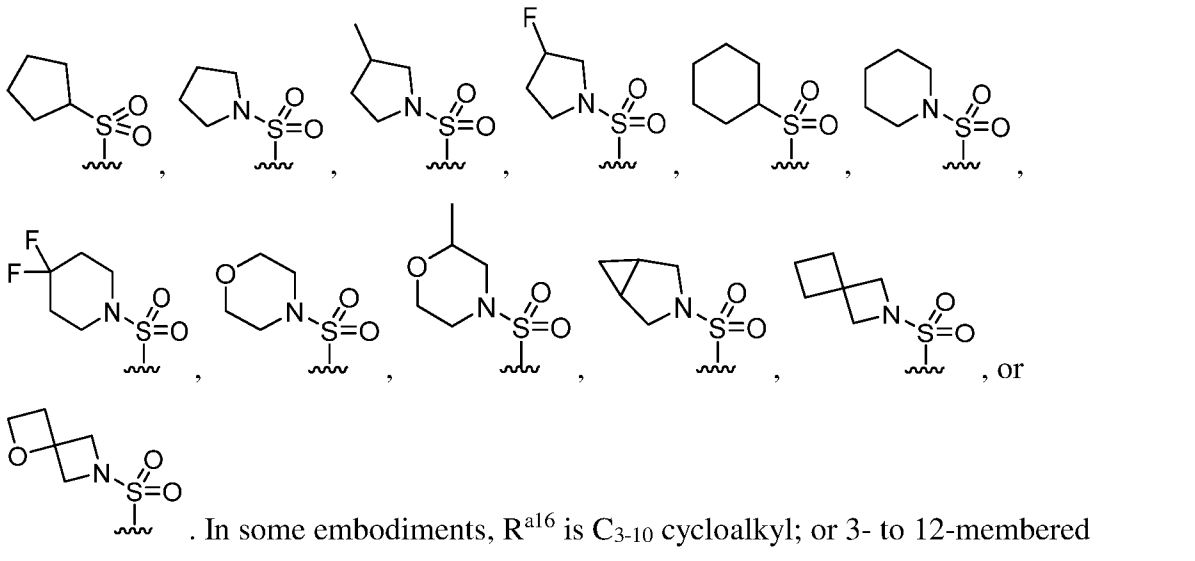


. In some embodiments, R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -

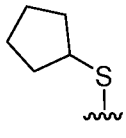
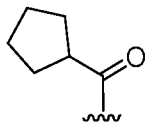
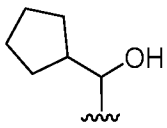
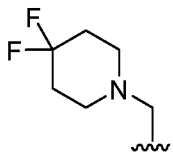
OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more C_{1-6} alkyl. In some embodiments, R^{a14} and R^{a15} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is butyl. In some embodiments, R^{a15} is *tert*-butyl. In some embodiments, -$S(O)_2R^{a16}$ is

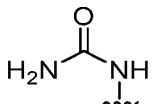
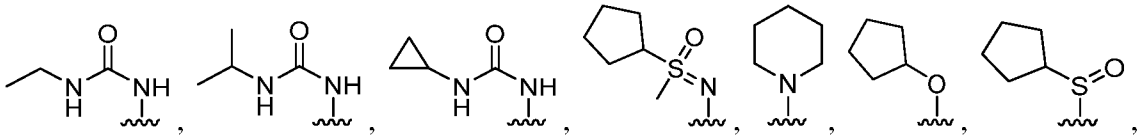
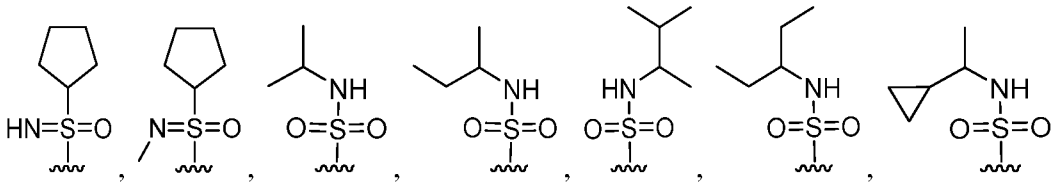


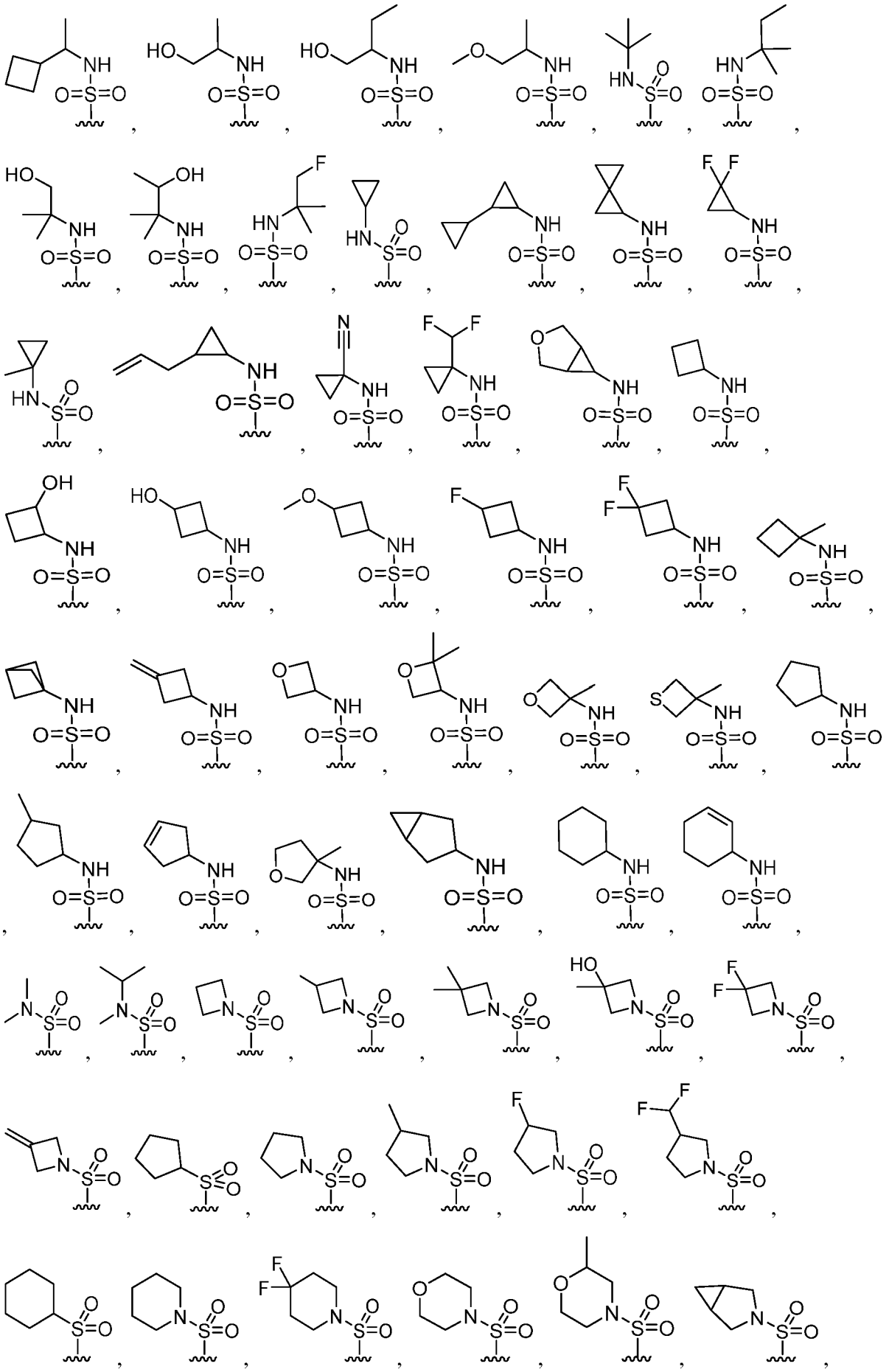
. In some embodiments, -$S(O)_2R^{a16}$ is

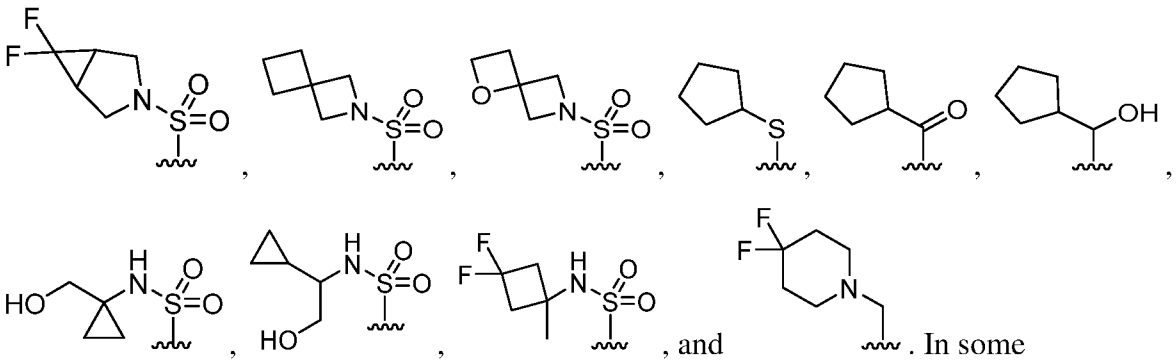


. In some embodiments, R^{a16} is C_{3-10} cycloalkyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo. In some embodiments, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$ is -$C(O)NR^{a19}R^{a20}$ or -$(CR^{a17}R^{a18})C(O)NR^{a19}R^{a20}$. In some embodiments, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$ is -$C(O)NR^{a19}R^{a20}$. In some embodiments, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$ is -$(CR^{a17}R^{a18})C(O)NR^{a19}R^{a20}$. In some embodiments, R^{a17} and

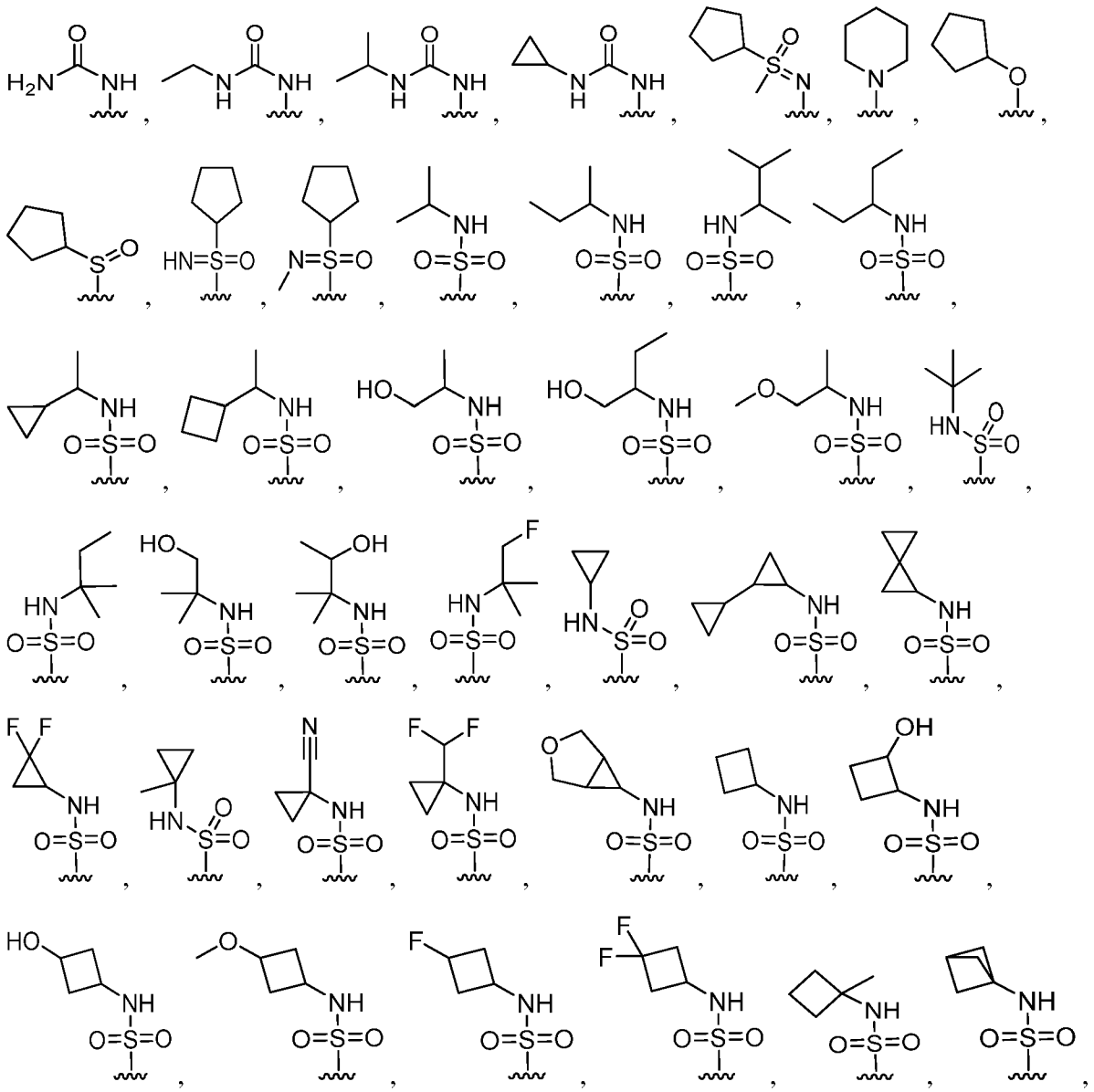
R^{a18} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{a17} and R^{a18} are each hydrogen. In some embodiments, R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a19} and R^{a20} are each independently hydrogen or cyclopropyl. In some embodiments, $-SR^{a21}$ is  . In some embodiments, R^{a21} is C_{3-10} cycloalkyl. In some embodiments, $-C(O)R^{a22}$ is  . In some embodiments, R^{a22} is C_{3-10} cycloalkyl. In some embodiments, the optionally substituted C_{1-6} alkyl is  or  . In some embodiments, C_{1-6} alkyl is optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more halo. In some embodiments, the 3- to 10-membered heterocycloalkyl is piperidinyl optionally substituted with one, two, three, four, five, or more halo. In some embodiments, the 3- to 10-membered heterocycloalkyl is optionally substituted with one, two, three, four, five, or more fluoro. In some embodiments, the 3- to 10-membered heterocycloalkyl is piperidinyl optionally substituted with one, two, three, four, five, or more fluoro.

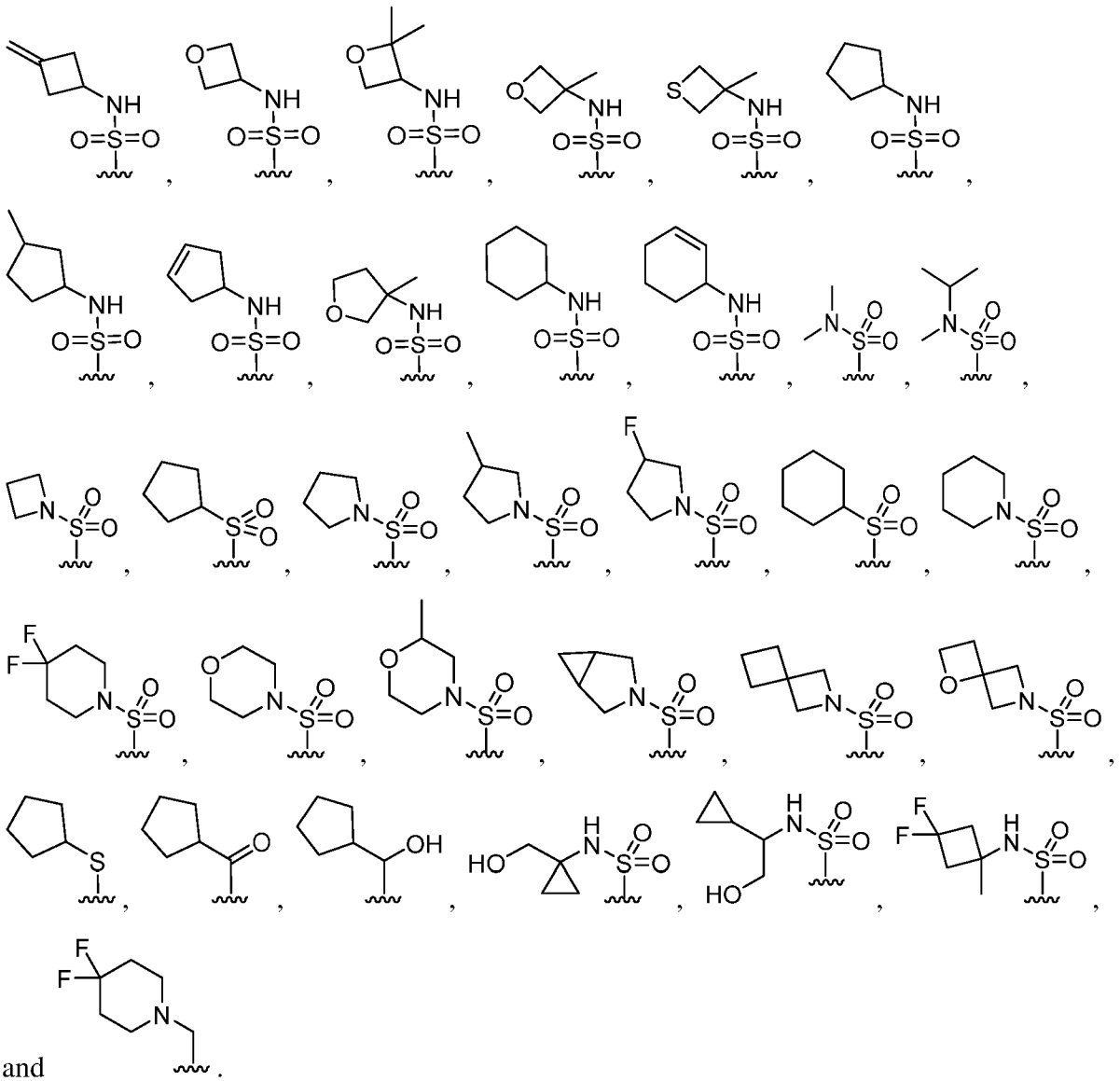
[0059] In some embodiments, ring A is substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, -OH, amino,  ,  ,  .

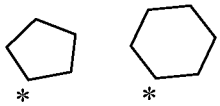


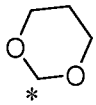


. In some embodiments, ring A is optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of fluoro, chloro, -OH, amino,



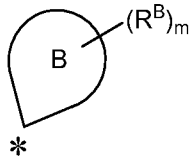


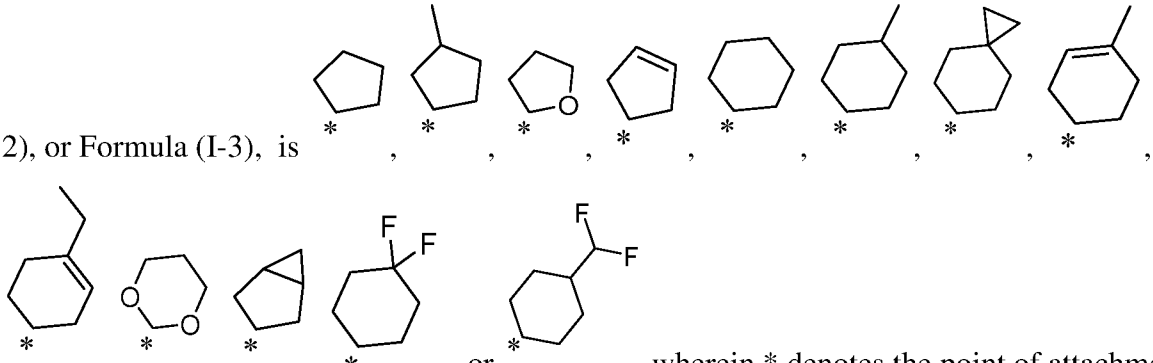
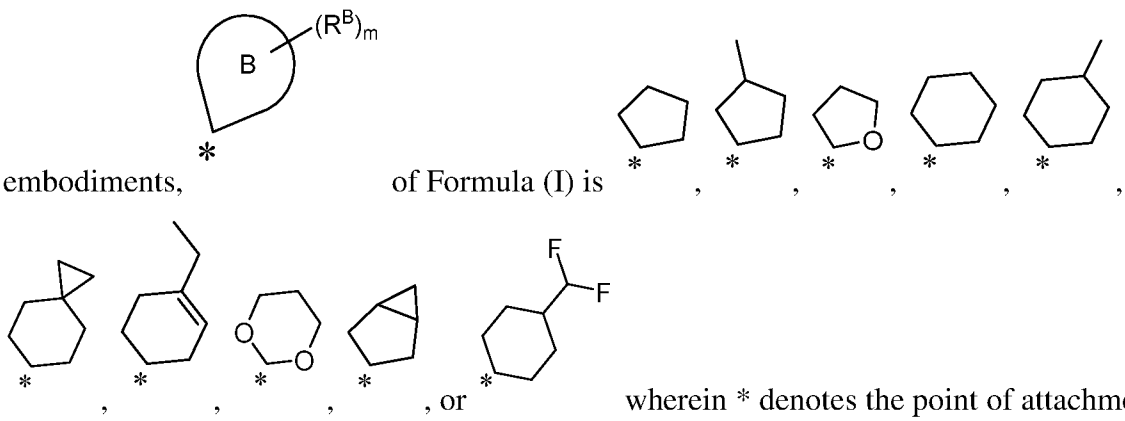
[0060] In some embodiments of Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3), or a pharmaceutically acceptable salt thereof, ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon. In some embodiments, ring B is C_{5-7} cycloalkyl. In some embodiments, ring B is cyclopentyl, cyclohexyl, or cycloheptyl. In some embodiments, ring B is  or , wherein * denotes the point of attachment to the rest of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3). In some embodiments, ring B is C_{5-7} cycloalkenyl. In some embodiments, ring B is cyclopentenyl, cyclohexenyl, or

cycloheptenyl. In some embodiments, ring B is  , wherein * denotes the point of attachment to the rest of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3). In some embodiments, ring B is  , wherein * denotes the point of attachment to the rest of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3). In some embodiments, ring B is 5- to 7-membered heterocycloalkyl. In some embodiments, ring B is 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon. In some embodiments, ring B is tetrahydrofuranyl or 1,3-dioxanyl. In some embodiments, ring B is  or  , wherein * denotes the point of attachment to the rest of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3).

[0061] In some embodiments, ring B is substituted with m R^B groups, wherein each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl. In some embodiment, an R^B group is methyl or ethyl. In some embodiment, two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form cyclopropyl. In some embodiments, two geminal R^B groups are taken together with the carbon atom to which they are attached to form cyclopropyl.

[0062] In some embodiments, m is 0, 1, 2, 3, or 4. In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1.



[0063] In some embodiments, of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3), is  , wherein * denotes the point of attachment to the rest of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3). In some embodiments, of Formula (I) is  , wherein * denotes the point of attachment to the rest of Formula (I), Formula (I-1), Formula (I-2), or Formula (I-3).

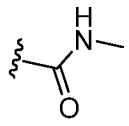
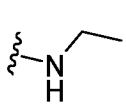
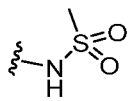
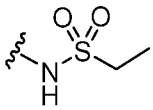
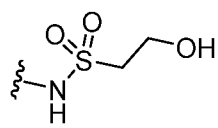
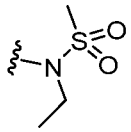
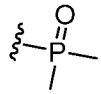
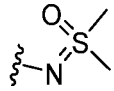
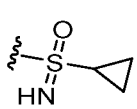
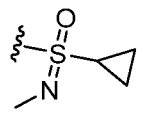
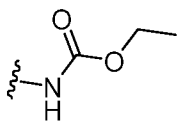
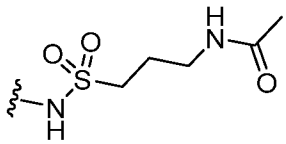
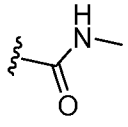
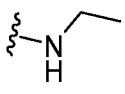
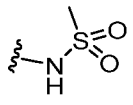
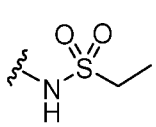
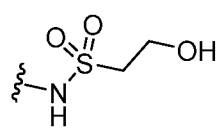
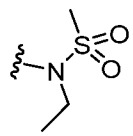
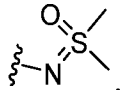
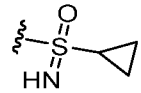
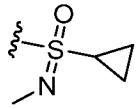
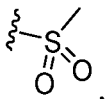
[0064] In some embodiments of Formula (I), Formula (I-1), Formula (I-2), and Formula (I-3), or a pharmaceutically acceptable salt thereof, Y^1 is N or CR^{C1}; Y^2 is N or CR^{C2}; Y^3 is N or CR^{C3}; and Y^4 is N or CR^{C4}. In some embodiments, no more than three of Y^1, Y^2, Y^3, and Y^4 are N. In some embodiments, no more than two of Y^1, Y^2, Y^3, and Y^4 are N. In some embodiments, no more than one of Y^1, Y^2, Y^3, and Y^4 is N. In some embodiments, Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}. In some embodiments, Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}. In some embodiments, Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

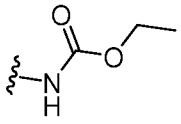
[0065] In some embodiments, R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6}

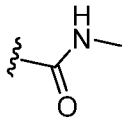
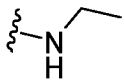
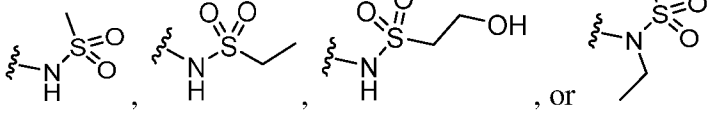
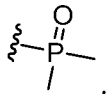
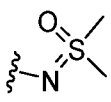
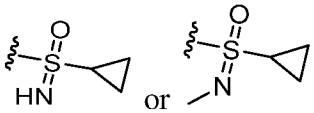
alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH.

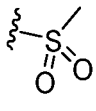
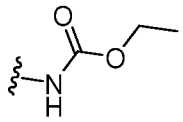
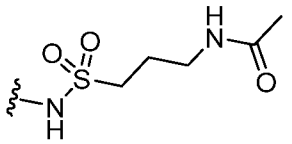
[0066] In some embodiments, R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH.

[0067] In some embodiments, R^{C1} is hydrogen or halo. In some embodiments, R^{C1} is hydrogen or fluoro. In some embodiments, R^{C3} is hydrogen. In some embodiments, R^{C4} is hydrogen or $-NH_2$. In some embodiments, R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

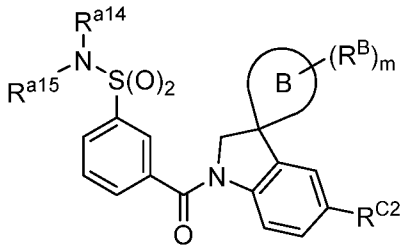
[0068] In some embodiments, R^{C2} is cyano, -OH, $-CH_2OH$, bromo, $-NO_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{C2} is cyano, -OH, $-CH_2OH$, bromo, $-NO_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

or  . In some embodiments, R^{C2} is cyano, -OH, halo, $-NO_2$, $C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{C2} is cyano, -OH, halo, $-NO_2$, $C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH.

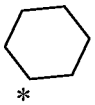
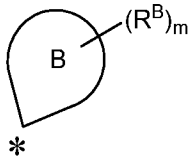
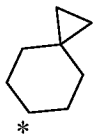
[0069] In some embodiments, $-C(O)NR^{c1}R^{c2}$ is  . In some embodiments, R^{c1} and R^{c2} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c1} and R^{c2} are each independently hydrogen, methyl, or ethyl. In some embodiments, $-NR^{c3}R^{c4}$ is  . In some embodiments, R^{c3} and R^{c4} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c1} and R^{c2} are each independently hydrogen, methyl, or ethyl. In some embodiments, $-NR^{c5}S(O)_2R^{c6}$ is  . In some embodiments, R^{c5} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{c5} is hydrogen, methyl, or ethyl. In some embodiments, R^{c6} is hydrogen or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from halo and -OH. In some embodiments, R^{c5} is methyl or $-CH_2CH_2OH$. In some embodiments, R^{c5} is hydrogen. In some embodiments, R^{c6} is ethyl. In some embodiments, $-P(O)R^{c7}R^{c8}$ is  . In some embodiments, R^{c7} and R^{c8} are each independently C_{1-6} alkyl. In some embodiments, R^{c7} and R^{c8} are each methyl. In some embodiments, $-N=S(O)R^{c9}R^{c10}$ is  . In some embodiments, R^{c9} and R^{c10} are each independently C_{1-6} alkyl. In some embodiments, R^{c9} and R^{c10} are each methyl. In some embodiments, $-S(O)(NR^{c11})R^{c12}$ is  . In

some embodiments, R^{c11} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{c11} is hydrogen or methyl. In some embodiments, R^{c12} is C_{1-6} alkyl or C_{3-10} cycloalkyl. In some embodiments, R^{c12} is cyclopropyl. In some embodiments, $-S(O)_2R^{c13}$ is  . In some embodiments, R^{c13} is C_{1-6} alkyl. In some embodiments, R^{c13} is methyl. In some embodiments, $NR^{c14}C(O)OR^{c15}$ is  . In some embodiments, R^{c14} and R^{c15} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c14} is hydrogen. In some embodiments, R^{c15} is ethyl. In some embodiments, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ is  . In some embodiments, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ is $-NR^{c16}S(O)_2(CH_2)_{1-3}NR^{c17}C(O)R^{c18}$. In some embodiments, R^{c16}, R^{c17} and R^{c18} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c16} and R^{c17} are hydrogen. In some embodiments, R^{c18} is methyl.

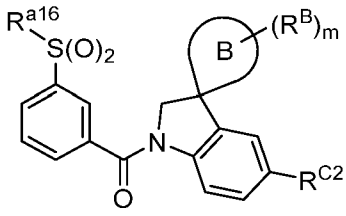
[0070] In one aspect, provided are compounds of Formula (Ia1):


(Ia1),

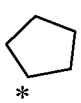
or a pharmaceutically acceptable salt thereof, wherein R^{a14}, R^{a15}, ring B, R^B, m, and R^{C2} are as defined for Formula (I) or any variation or embodiment thereof. In some embodiments, R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and –OH. In some embodiments, R^{C2} is $-NR^{c5}S(O)_2R^{c6}$. In some embodiments, R^{c5} is hydrogen and R^{c6} is C_{1-6} alkyl. In some embodiments, R^{c5} is hydrogen and R^{c6} is ethyl. In some embodiments, R^{c5} is

hydrogen. In some embodiments, R^{c6} is ethyl. In some embodiments, R^{c6} is methyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is C_{1-6} alkyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is *tert*-butyl. In some embodiments, R^{a14} is hydrogen. In some embodiments, R^{a15} is *tert*-butyl. In some embodiments, ring B is  , wherein * denotes the point of attachment to the rest of Formula (Ia1). In some embodiments,  of Formula (Ia1) is  .

[0071] In one aspect, provided are compounds of Formula (Ia2):


(Ia2),

or a pharmaceutically acceptable salt thereof, wherein R^{a16}, ring B, R^B, m, and R^{C2} are as defined for Formula (I) or any variation or embodiment thereof. In some embodiments, R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and –OH.

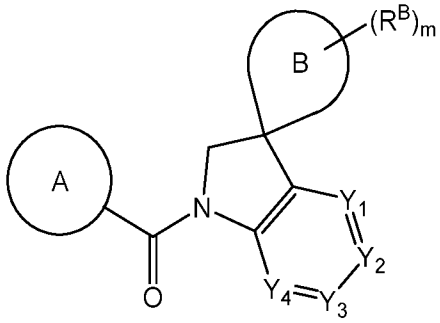
[0072] In some embodiments, ring B is not  , wherein * denotes the point of attachment to the rest of Formula (I). In some embodiments, R^{C1} is not fluoro. In some

embodiments, R^{C2} is not hydrogen. In some embodiments, ring B is not  , wherein * denotes the point of attachment to the rest of Formula (I); or R^{C1} is not fluoro; or R^{C2} is not hydrogen.

[0073] In some embodiments, the compound is not 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; or [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea.

[0074] In some embodiments, the compound is not a salt of 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; or [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea.

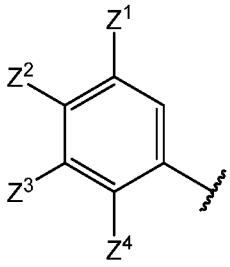
[0075] In another aspect, provided herein is a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

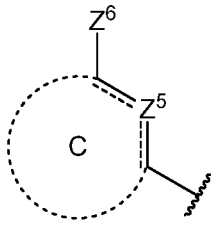
ring A is

(i)  , wherein Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl,

provided that

(1) when Z^4 is hydrogen, then at least one of Z^1 and Z^3 is R^D; and

(2) when Z^4 is R^D, then Z^1 is R^D, or

(ii)  , wherein

 is a single bond or a double bond,

Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl.

Z^6 is $-NR^{a26}C(O)NR^{a27}R^{a28}$, $-NR^{a29}C(O)OR^{a30}$, $-N=S(O)R^{a31}R^{a32}$, $-S(O)R^{a33}$, $-S(O)(NR^{a34})R^{a35}$, $-S(O)_2NR^{a36}R^{a37}$, $-S(O)_2R^{a38}$, $-SR^{a39}$, $-C(O)R^{a40}$, 3- to 10-membered heterocycloalkyl, or $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo, and

ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl;

R^{a4}-R^{a40} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo or C_{1-6} alkyl optionally substituted with one or more halo; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together to form a $=CR^{1a3}R^{1a4}$ group, wherein R^{1a3} and R^{1a4} are each independently hydrogen or C_{1-6} alkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

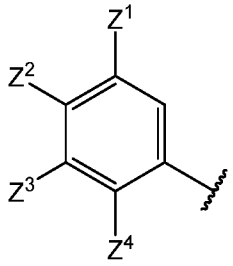
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

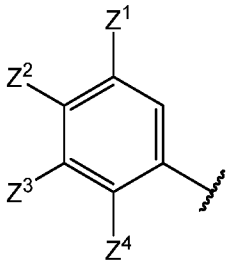
R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, - $NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, -O-$S(O)_2R^{c19}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and -OH, and

R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -O(C_{1-6} alkyl), - NHC(O)(C_{1-6} alkyl), and -OH;

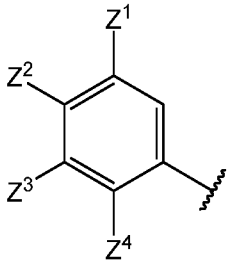
provided that

(1) when ring B is unsubstituted cyclopentyl, then ring A is 

, wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) substituted with one or more halo,

(2) when ring B is unsubstituted cyclohexyl and ring A is 

, then at least one of R^{C1}-R^{C4} is R^F, and

(3) when ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4 R^B, then ring A is 

, wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) optionally substituted with one or more halo.

[0076] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, with one, two, three, or four Z^1-Z^4 are independently selected from the group consisting of -SR^{a21}, -$C(O)R^{a22}$, and C_{1-6} alkyl substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more halo. In some embodiments, ring A is substituted with -SR^{a21}, -$C(O)R^{a22}$, or C_{1-6} alkyl substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more halo. In some embodiments, R^{a21} and R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl.

[0077] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, -$NR^{a4}C(O)OR^{a5}$, -$NR^{a6}R^{a7}$, -$N=S(O)R^{a8}R^{a9}$, -OR^{a10}, -$S(O)R^{a11}$, -$S(O)(NR^{a12})R^{a13}$, -$S(O)_2NR^{a14}R^{a15}$, -$S(O)_2R^{a16}$, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, -$SR^{a21}$, -$C(O)R^{a22}$, -$P(O)(R^{a23})(R^{a24})$, -$C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl, wherein R^{a4}-R^{a25} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl.

[0078] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, Z^4 is hydrogen and at least one of Z^1 and Z^3 is R^D wherein R^D is as defined elsewhere herein. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, Z^4 is when Z^4 is R^D and Z^1 is R^D wherein R^D is as defined elsewhere herein.

[0079] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl. In some embodiments, X is H. In some embodiments, X is C_{1-6}alkyl. In some embodiments, X is methyl. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl, Z^6 is $-NR^{a26}C(O)NR^{a27}R^{a28}$, $-NR^{a29}C(O)OR^{a30}$, $-N{=}S(O)R^{a31}R^{a32}$, $-S(O)R^{a33}$, $-S(O)(NR^{a34})R^{a35}$, $-S(O)_2NR^{a36}R^{a37}$, $-S(O)_2R^{a38}$, $-SR^{a39}$, 3- to 10-membered heterocycloalkyl, $C(O)R^{a40}$, or $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo, and ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl; and R^{a26}-R^{a40} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl.

[0080] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, one or more R^B groups are independently C_{1-6} alkyl substituted with one, two, three, four, five, or more halo. In some embodiments, an R^B group is C_{1-6} alkyl substituted with one, two, three, four, five, or more halo.

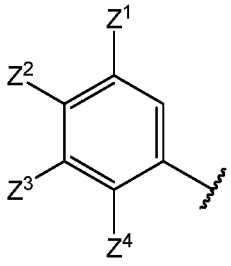
[0081] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each

carbon. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, one or more R^B groups are independently halo or C_{1-6} alkyl optionally substituted with one or more halo. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together to form a $=CR^{1a3}R^{1a4}$ group, wherein R^{1a3} and R^{1a4} are each independently hydrogen or C_{1-6} alkyl.

[0082] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, R^{C2} is $-NR^{c14}C(O)OR^{c15}$, wherein R^{c14} and R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0083] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, $-O-S(O)_2R^{c19}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and –OH; and R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, $-O(C_{1-6}$ alkyl), $-NHC(O)(C_{1-6}$ alkyl), and –OH. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and –OH, and R^{c1}-R^{c19} are as defined elsewhere herein. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, R^{C1}-R^{C4} are each independently $-O-S(O)_2R^{c19}$, wherein R^{c19} is as defined elsewhere herein.

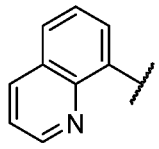
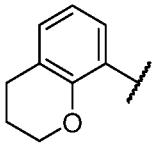
[0084] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring B is unsubstituted cyclopentyl and at least one of Z^1-Z^4 is $-S(O)_2$-(3- to 10-membered heterocycloalkyl) is substituted with one or more halo. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring B is unsubstituted

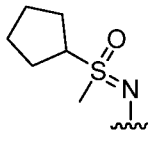
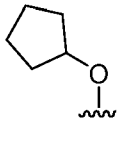
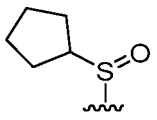
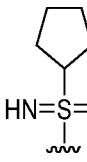
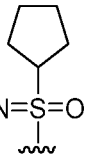
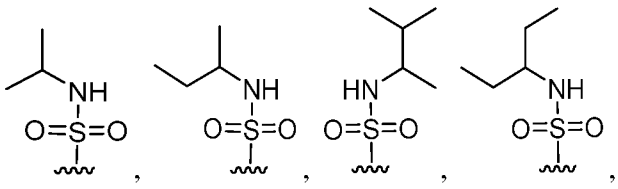
cyclohexyl, ring A is  and at least one of R^{C1}-R^{C4} is R^F, wherein R^{C1}-R^{C4} and R^F are as as defined elsewhere herein. In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4 R^B, and at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) is optionally substituted with one or more halo, wherein R^B is as defined elsewhere herein.

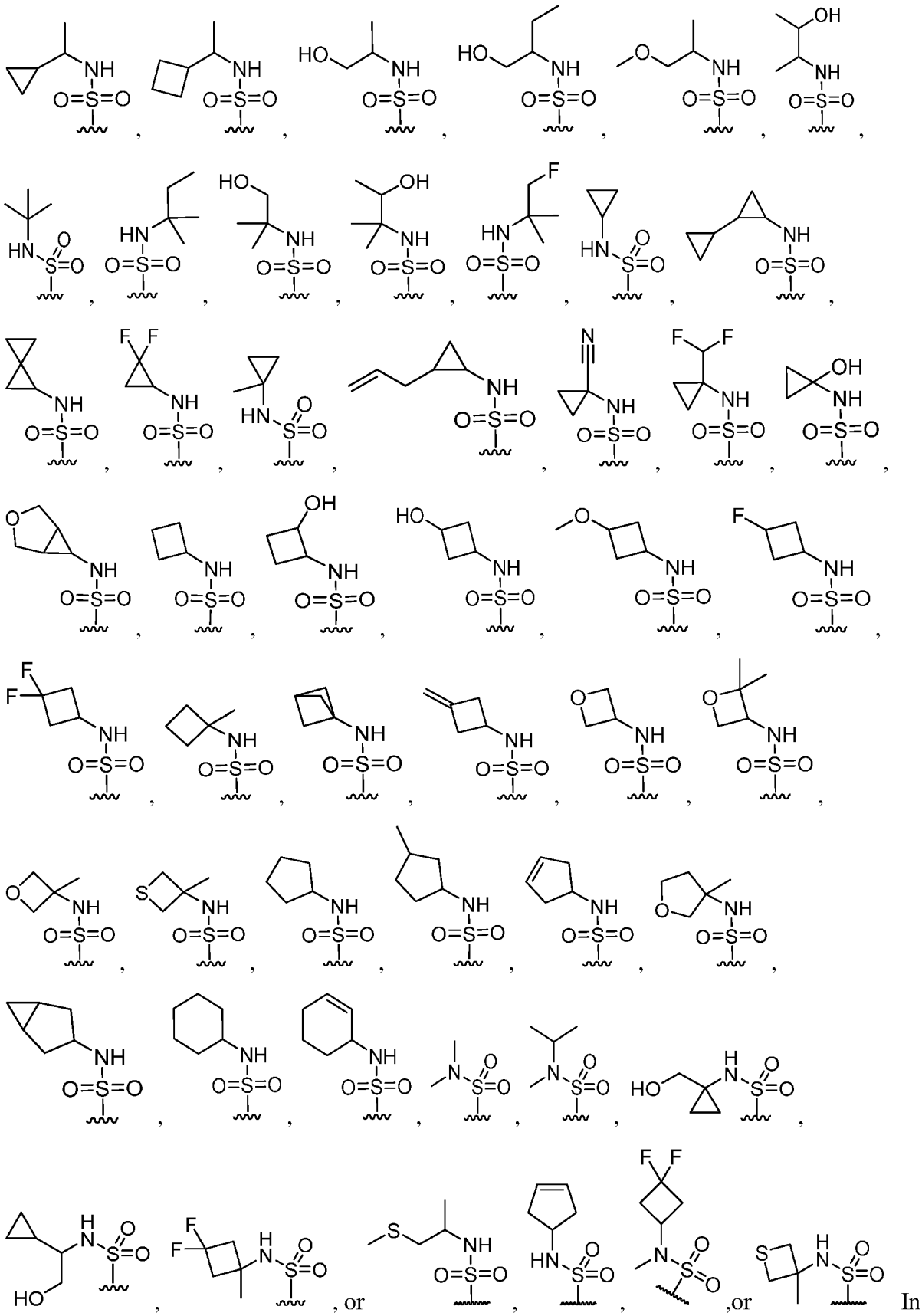
[0085] In some embodiments, cycloalkyl or heterocycloalkyl groups include spiro groups. In some embodiments, cycloalkyl or heterocycloalkyl groups include fused groups.

[0086] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted. In some embodiments, ring A is optionally substituted C_{6-14} aryl. In some embodiments, ring A is optionally substituted phenyl. In some embodiments, ring A is optionally substituted 5- to 12-membered heteroaryl. In some embodiments, ring A is optionally substituted 6-membered heteroaryl. In some embodiments, ring A is optionally substituted 5-membered heteroaryl. In some embodiments, ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted. In some embodiments, ring A is optionally substituted thiophenyl.

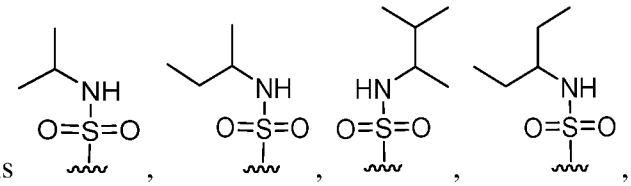
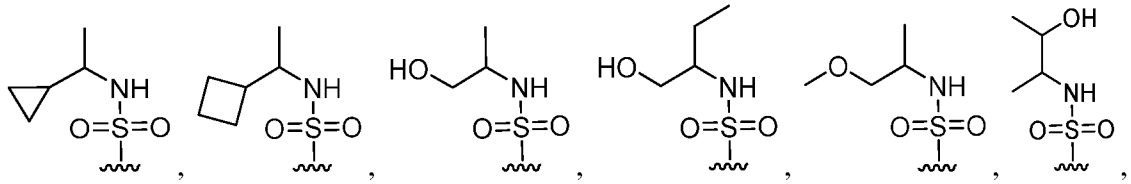
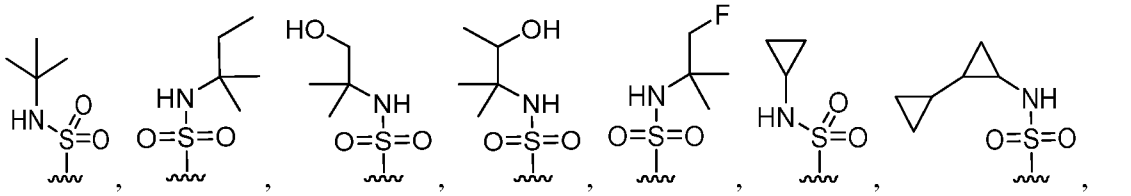
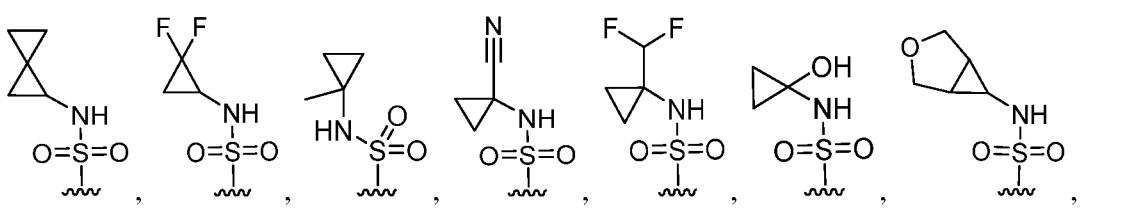
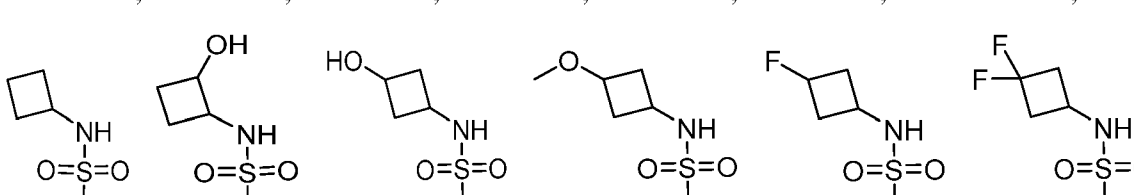
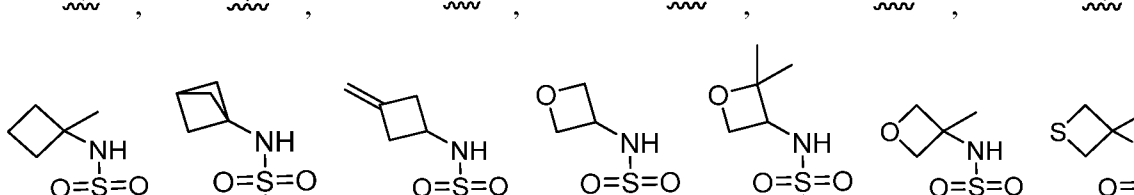
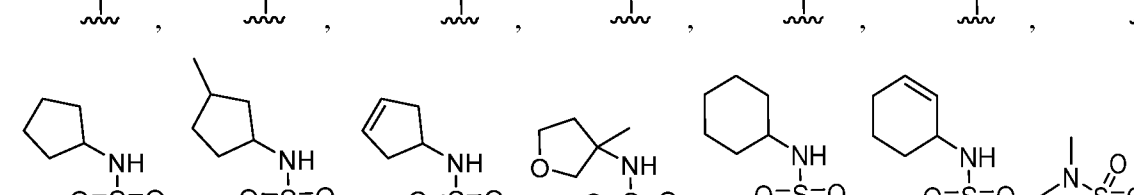
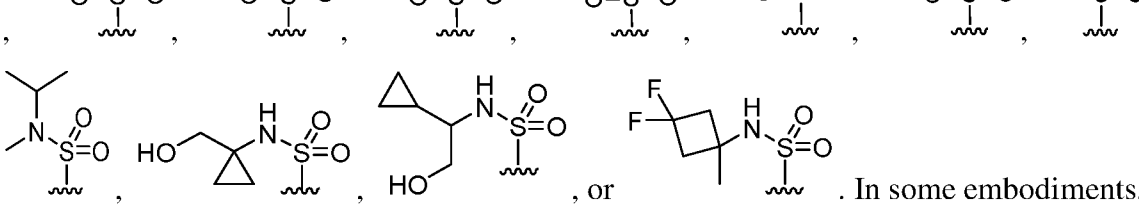
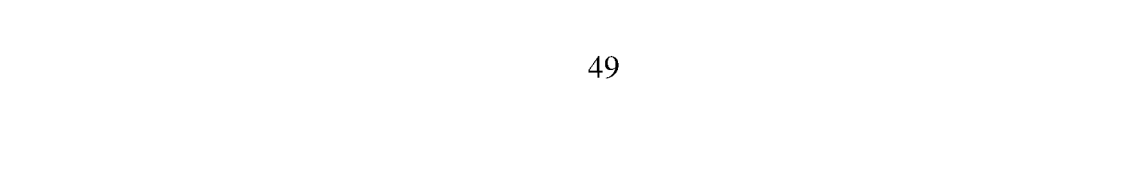
[0087] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring A is optionally substituted phenyl. In some embodiments, ring A is optionally substituted 5- to 12-membered heteroaryl. In some embodiments, ring A is optionally substituted 6-membered heteroaryl. In some embodiments, ring A is optionally substituted 5-membered heteroaryl. In some embodiments, ring A is pyridinyl, thiophenyl, furanyl,

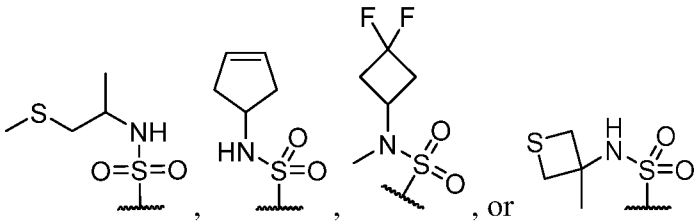
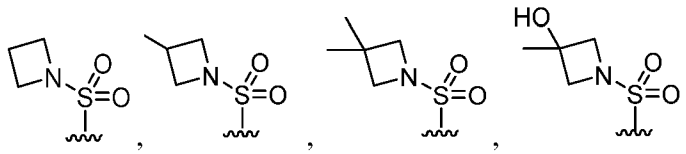
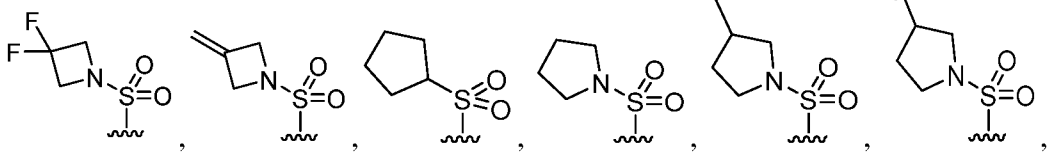
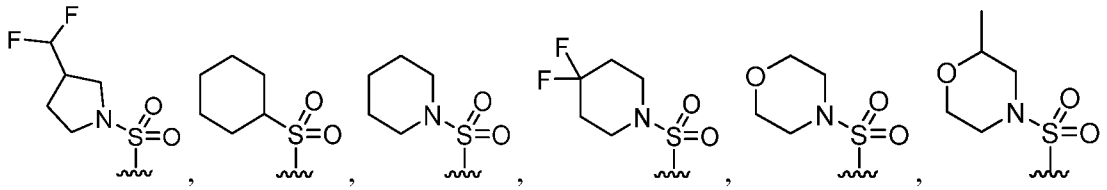
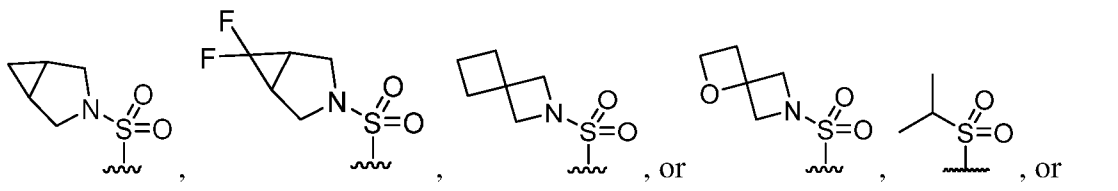
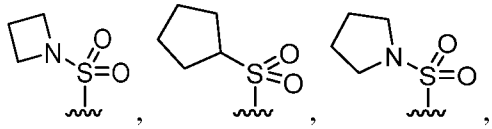
pyrazolyl, pyrrolyl, or oxazolyl. In some embodiments, ring A is is  or  .

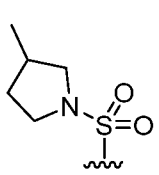
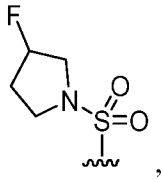
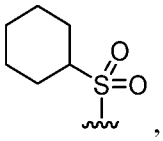
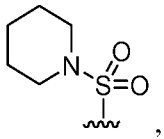
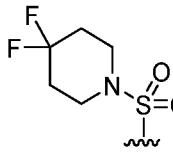
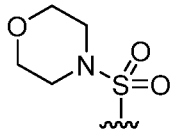
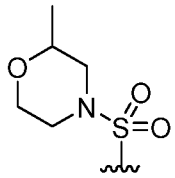
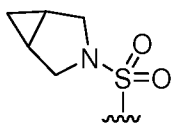
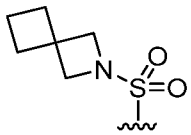
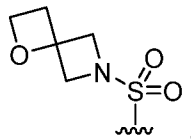
[0088] In some embodiments of Formula (II), R^{a4} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a4} is hydrogen. In some embodiments, R^{a5} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a5} is *tert*-butyl. In some embodiments, R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl. In some embodiments, R^{a6} and R^{a7} are each independently hydrogen, imidazolyl, methylimidazolyl, or pyrimidinyl. In some embodiments, $-N=S(O)R^{a8}R^{a9}$ is  . In some embodiments, R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a8} and R^{a9} are each independently methyl or cyclopentyl. In some embodiments, $-OR^{a10}$ is  . In some embodiments, R^{a10} is C_{3-10} cycloalkyl. In some embodiments, R^{a10} is cyclopentyl. In some embodiments, $-S(O)R^{a11}$ is  . In some embodiments, R^{a11} is C_{3-10} cycloalkyl. In some embodiments, R^{a11} is cyclopentyl. In some embodiments, $-S(O)(NR^{a12})R^{a13}$ is  or  . In some embodiments, R^{a12} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a12} is hydrogen or methyl. In some embodiments, R^{a13} is C_{3-10} cycloalkyl. In some embodiments, R^{a13} is cyclopentyl. In some embodiments, $-S(O)_2NR^{a14}R^{a15}$ is  ,

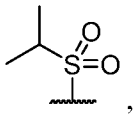
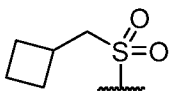
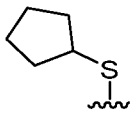
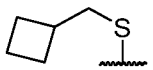
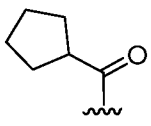


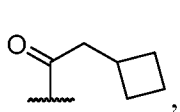
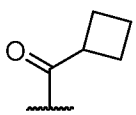
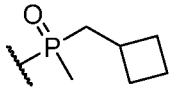
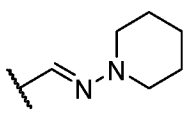
In

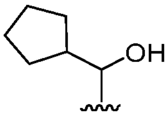
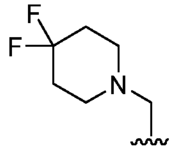
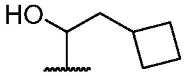
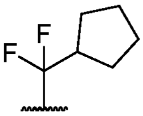
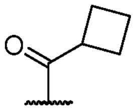
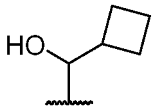
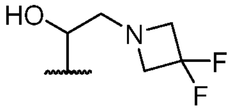
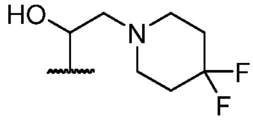
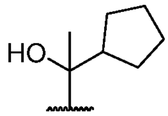
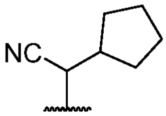
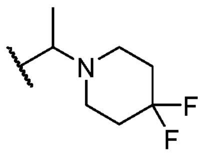
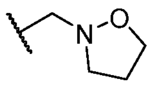
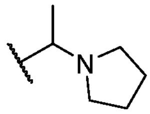
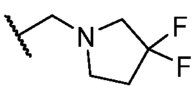
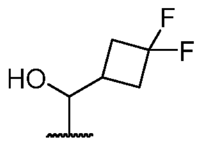
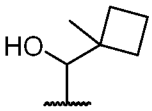
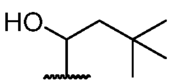
some embodiments, -$S(O)_2NR^{a14}R^{a15}$ is  ,  ,  ,  ,  ,  ,  ,  , ,  , , or . In some embodiments, -

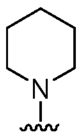
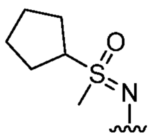
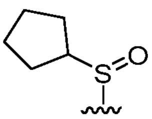
$S(O)_2NR^{a14}R^{a15}$ is  . In some embodiments, R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more C_{1-6} alkyl. In some embodiments, R^{a14} and R^{a15} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is butyl. In some embodiments, R^{a15} is *tert*-butyl. In some embodiments, $-S(O)_2R^{a16}$ is  ,  ,  ,  . In some embodiments, $-S(O)_2R^{a16}$ is  .

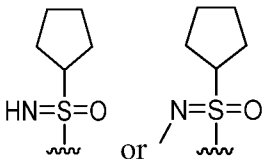
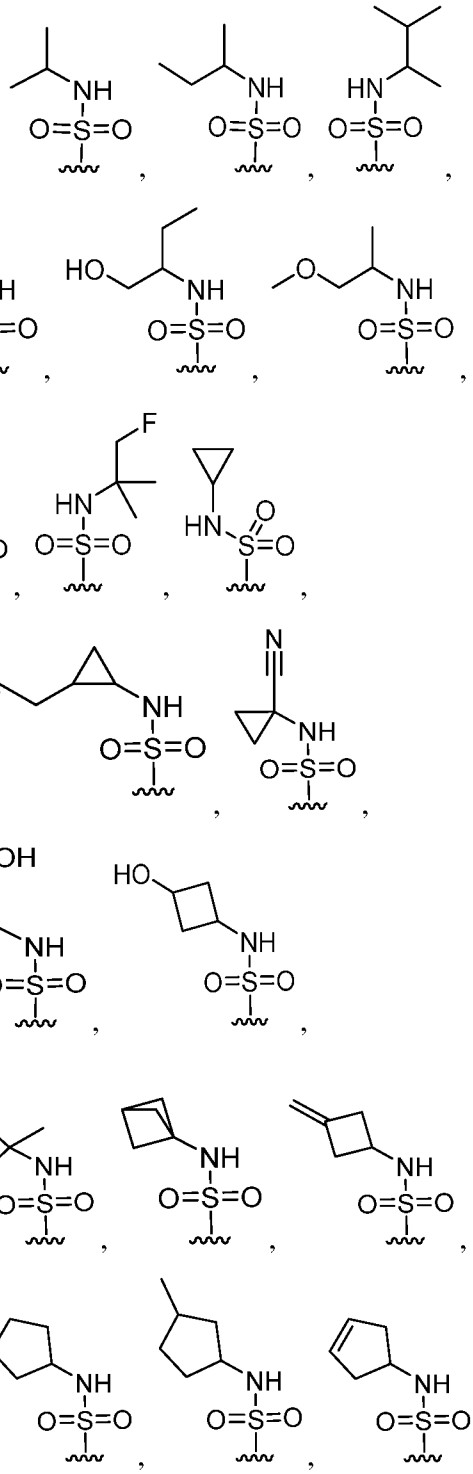











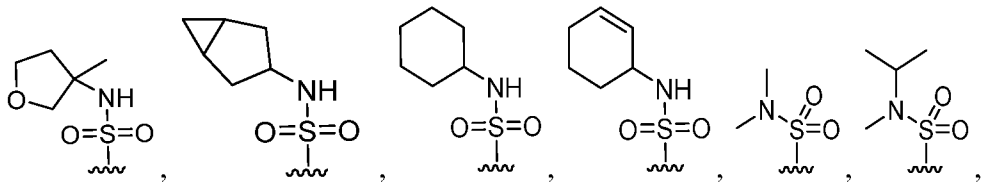
. In some embodiments, -$S(O)_2R^{a16}$ is  , or  . In some embodiments, R^{a16} is C_{3-10} cycloalkyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo. In some embodiments, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$ is -$C(O)NR^{a19}R^{a20}$ or -$(CR^{a17}R^{a18})C(O)NR^{a19}R^{a20}$. In some embodiments, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$ is -$C(O)NR^{a19}R^{a20}$. In some embodiments, -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$ is -$(CR^{a17}R^{a18})C(O)NR^{a19}R^{a20}$. In some embodiments, R^{a17} and R^{a18} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{a17} and R^{a18} are each hydrogen. In some embodiments, R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a21} is hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more C_{3-10} cycloalkyl. In some embodiments, -SR^{a21} is  or  . In some embodiments, R^{a22} is hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more C_{3-10} cycloalkyl. In some embodiments, -$C(O)R^{a22}$ is  ,

 , or  . In some embodiments, R^{a23} and R^{a24} are each indeendently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more C_{3-10} cycloalkyl. In some embodiments, -$P(O)(R^{a23})(R^{a24})$is  . In some embodiments, R^{24} is hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more C_{3-10} cycloalkyl. In some embodiments, -$C=NR^{a25}$ is  . In some embodiments, Z^1-Z^4

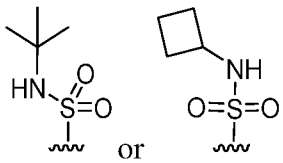
are each independently C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl. In some embodiments, Z^1-Z^4 are each indepednetly  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0089] In some embodiments of Formula (II), Z^6 is 3- to 10-membered heterocycloalkyl. In some embodiments, Z^6 is  . In some embodiments, R^{a26} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a27} is hydrogen. In some embodiments, R^{a27} and R^{a28} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a27} and R^{a28} are each independently hydrogen, cyclopropyl, ethyl, or isopropyl. In some embodiments, R^{a29} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a29} is hydrogen. In some embodiments, R^{a30} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a30} is *tert*-butyl. In some embodiments, -N=S(O)$R^{a31}R^{a32}$ is  . In some embodiments, R^{a31} and R^{a32} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl. In some embodiments, R^{a31} and R^{a32} are each independently methyl or cyclopentyl. In some embodiments, -S(O)R^{a33} is  . In some embodiments, R^{a33} is C_{3-10} cycloalkyl. In some embodiments, R^{a33} is

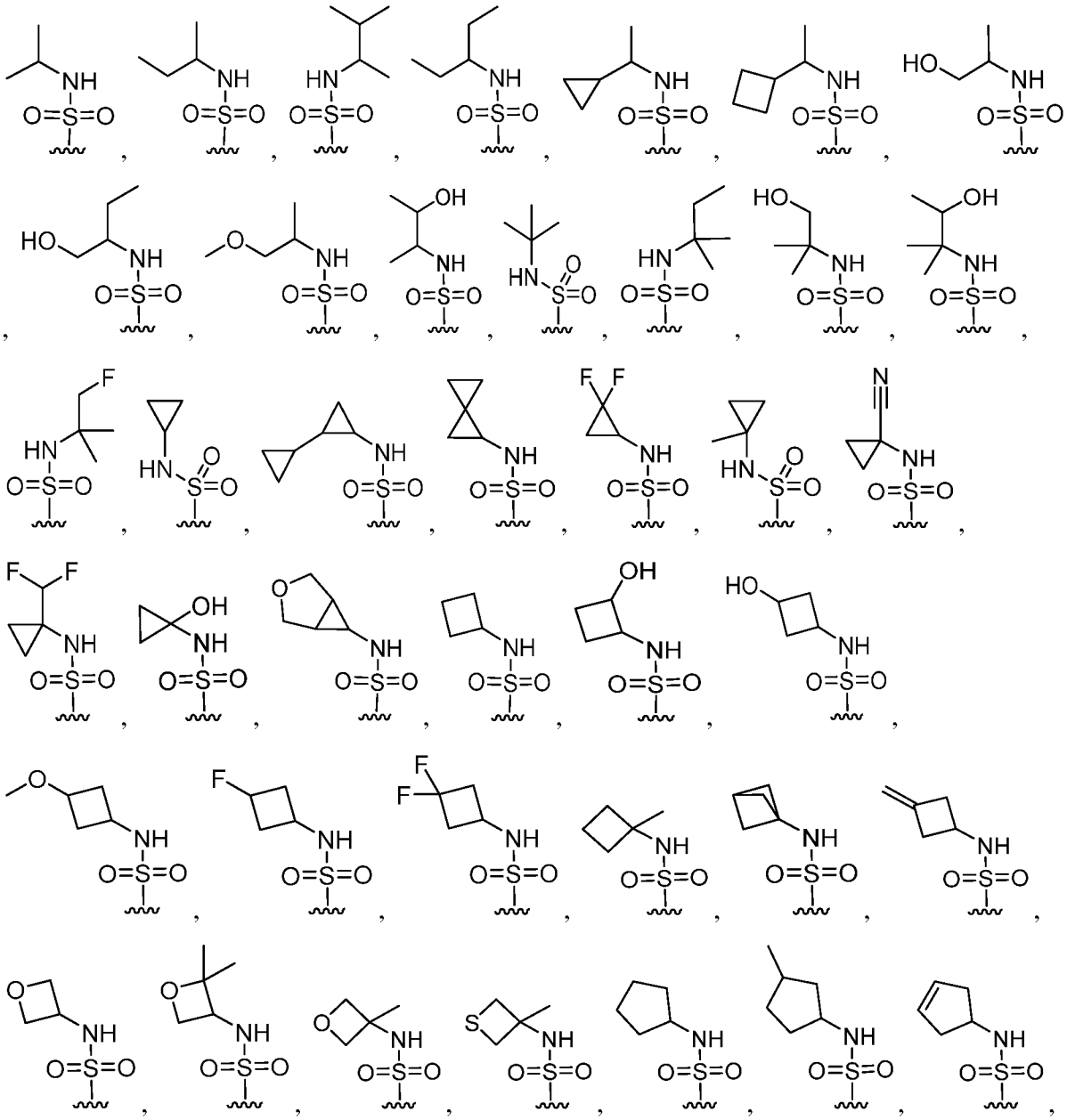
cyclopentyl. In some embodiments, -S(O)(NR^{a34})R^{a35} is  . In some embodiments, R^{a34} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{a34} is hydrogen or methyl. In some embodiments, R^{a35} is C_{3-10} cycloalkyl. In some embodiments, R^{a35} is cyclopentyl. In some embodiments, -S(O)$_2$NR^{a34}R^{a35}is 

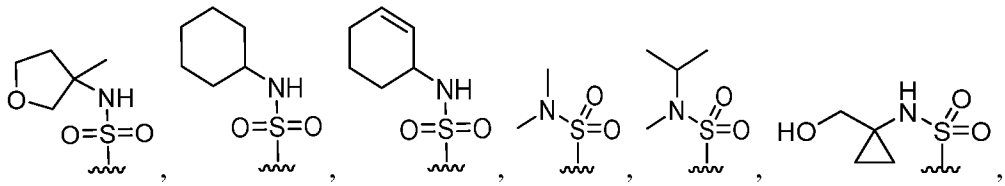
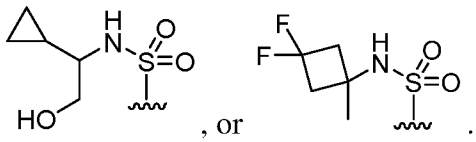


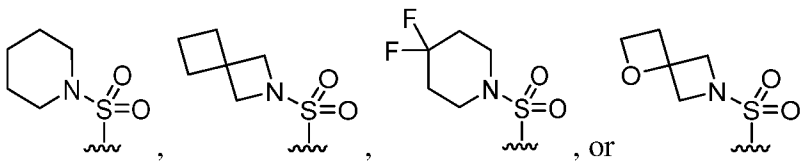
, or . In some embodiments, -

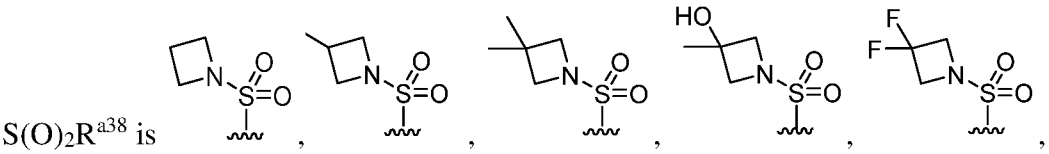
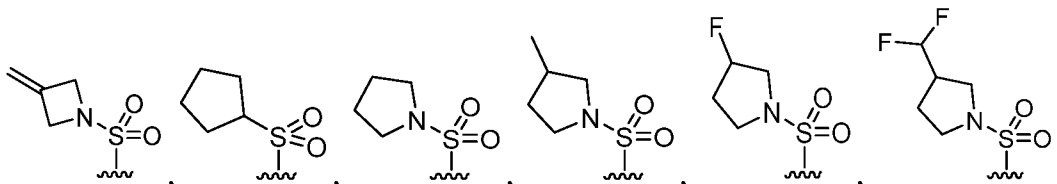
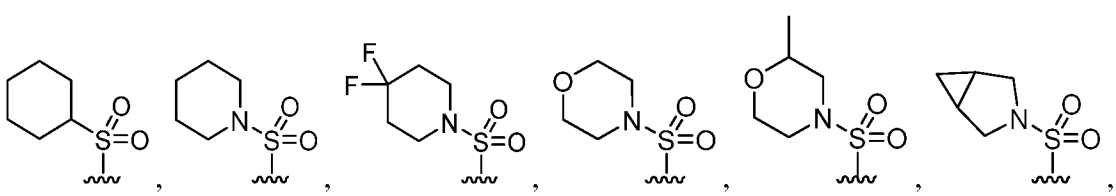


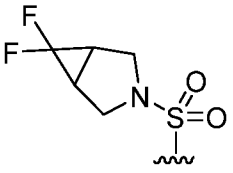
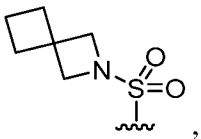
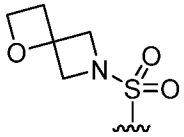
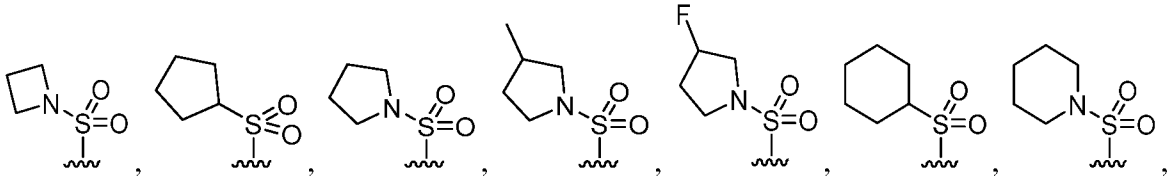
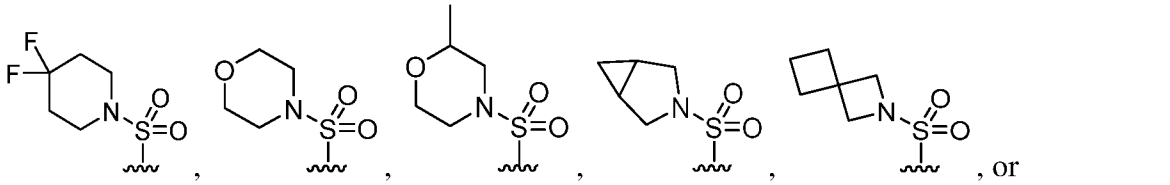
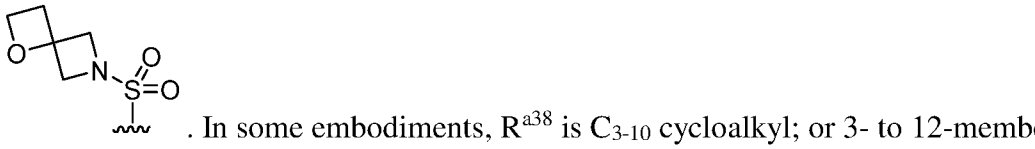
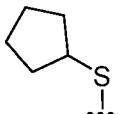
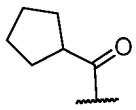
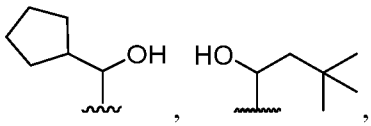
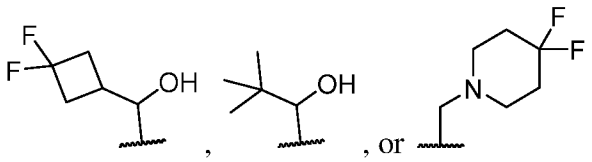
$S(O)_2NR^{a34}R^{a35}$ is or . In some embodiments, $-S(O)_2NR^{a34}R^{a35}$ is

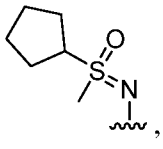
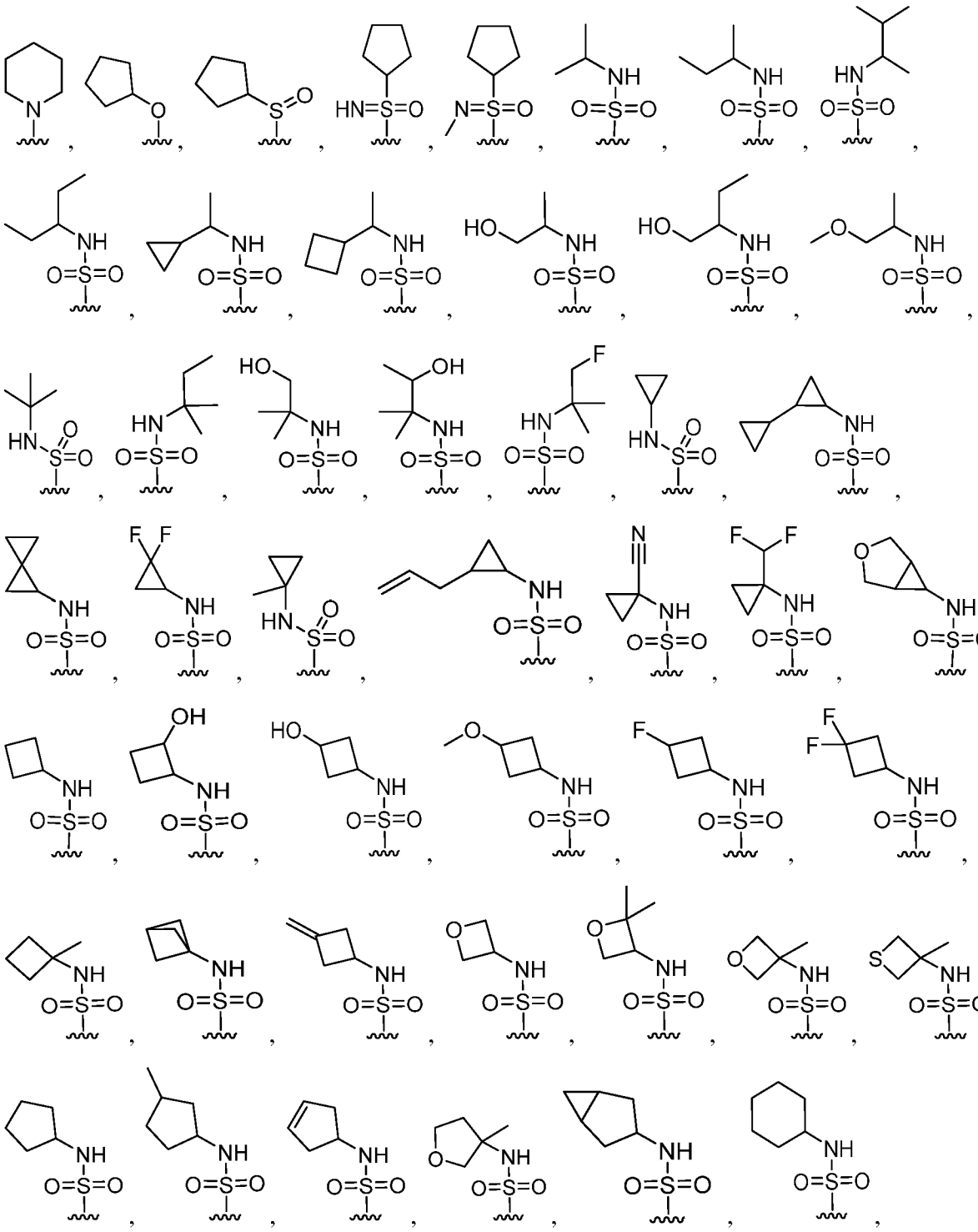


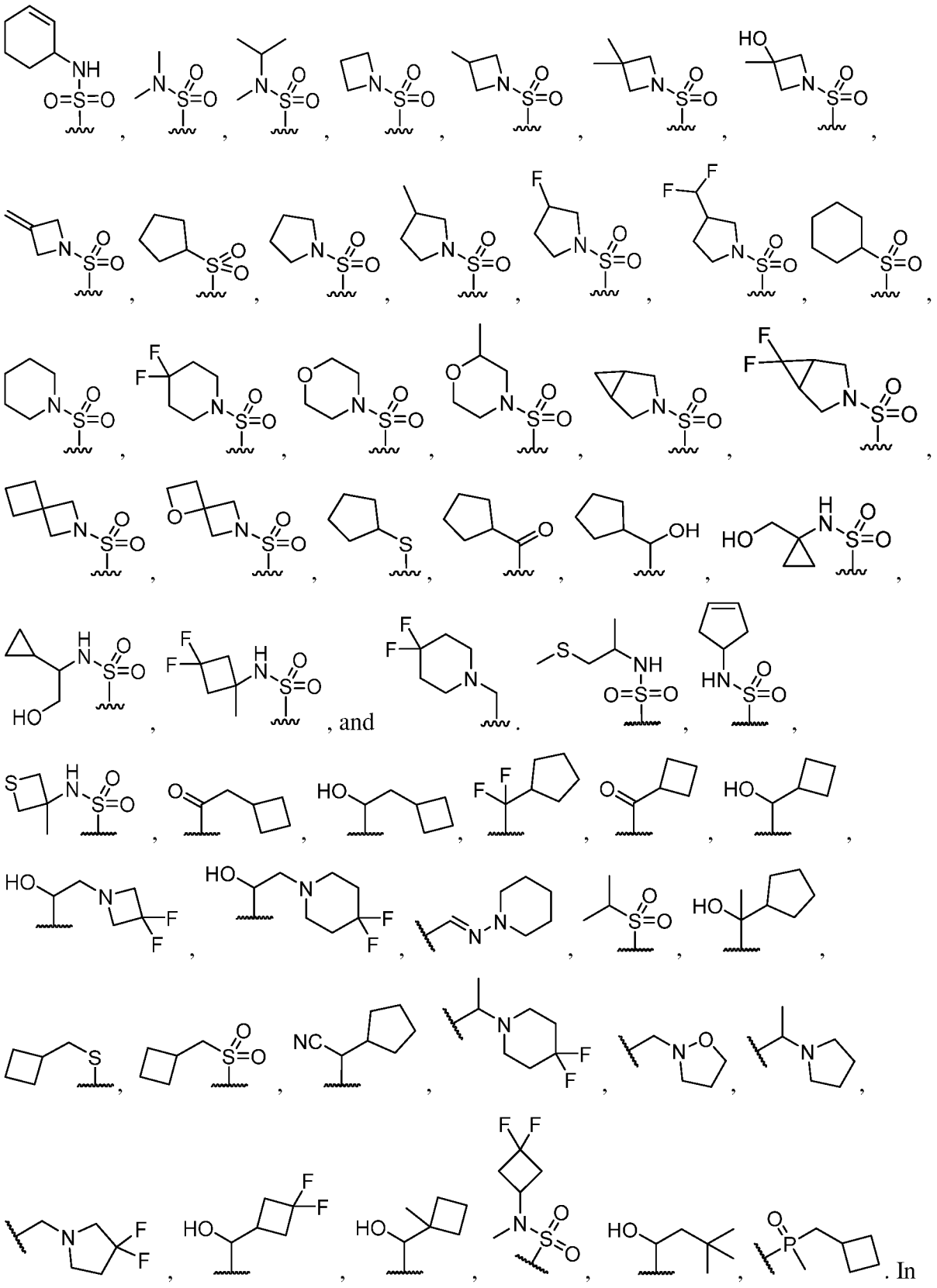


, or . In some embodiments, R^{a36} and R^{a37} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), =$CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more C_{1-6} alkyl. In some embodiments, R^{a36} and R^{a37} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{a36} is hydrogen and R^{a37} is butyl. In some embodiments, R^{a37} is *tert*-butyl. In some embodiments, -$S(O)_2R^{a38}$ is


, or . In some embodiments, -$S(O)_2R^{a38}$ is

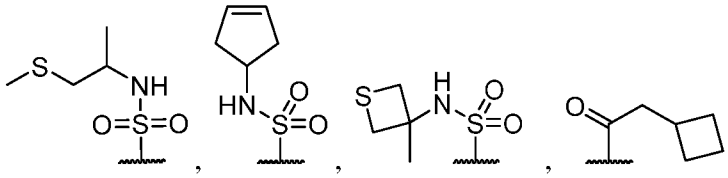
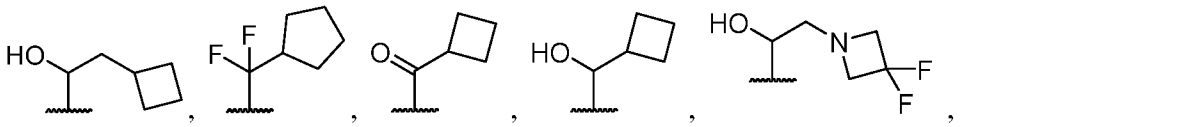
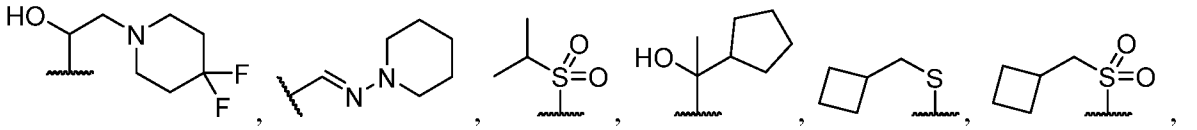
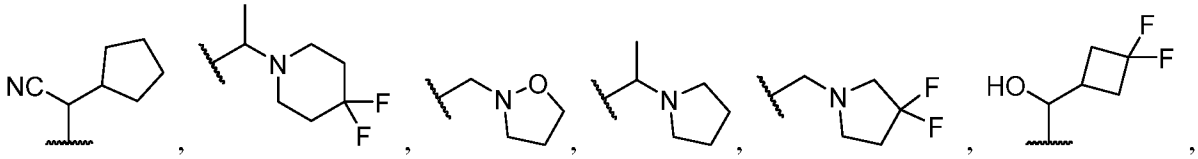
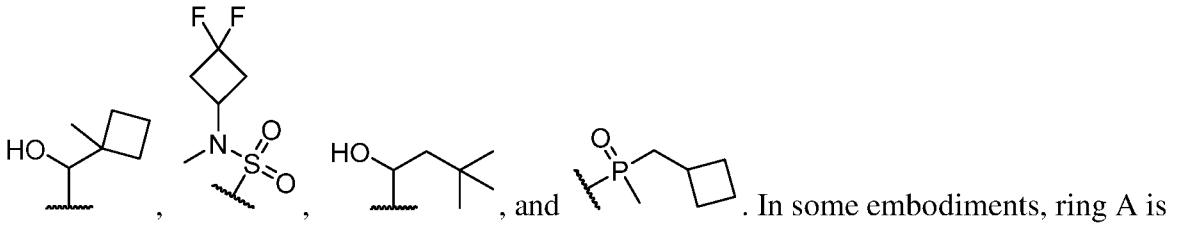
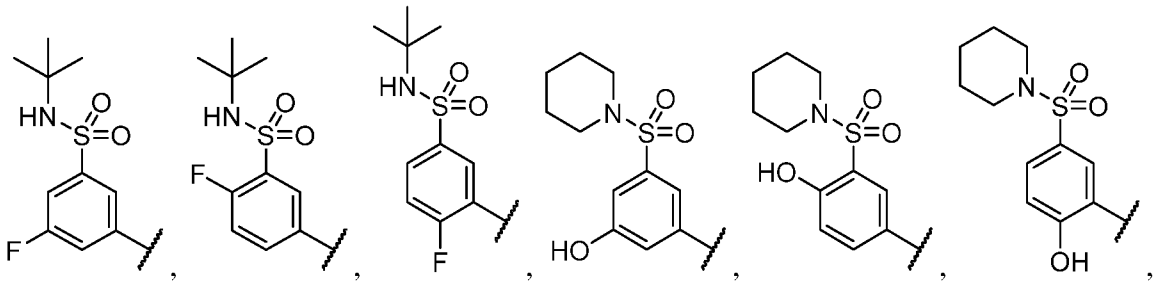
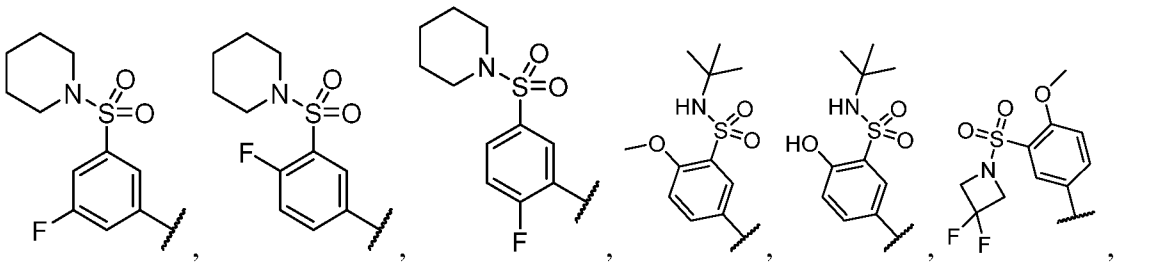
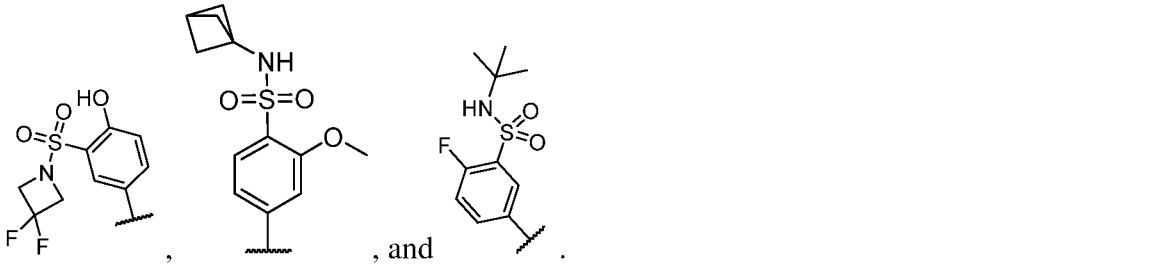




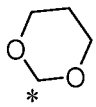


, or  . In some embodiments, $-S(O)_2R^{a38}$ is 


, or . In some embodiments, R^{a38} is C_{3-10} cycloalkyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo. In some embodiments, $-SR^{a39}$ is  . In some embodiments, R^{a39} is C_{3-10} cycloalkyl. In some embodiments, R^{a40} is C_{3-10}cycloalkyl. In some embodiments, $-C(O)R^{a40}$ is  . In some embodiments, $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo. In some embodiments, Z^7 is -OH. In some embodiments, Z^7 is H. In some embodiments, Z^8 is C_{1-6} alkyl. In some embodiments, Z^8 is C_{3-10} cycloalkyl optionally substituted with one ore more halo. In some embodiments, Z^8 is 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo. In some embodiments, $-CH(Z^7)(Z^8)$ is 

, or .

[0090] In some embodiments of Formula (II), Z^1, Z^2, Z^3, and Z^4 are each independently selected from the group consisting of fluoro, chloro, -OH, amino, $-CH_2OH$,  , 



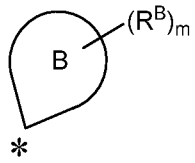
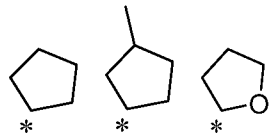
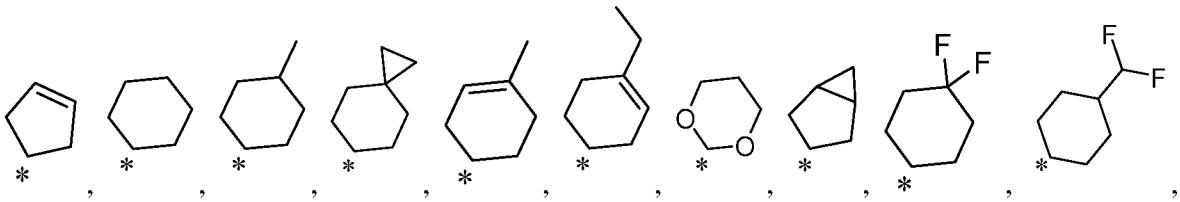
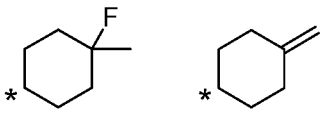
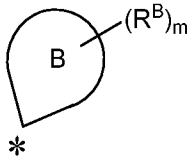
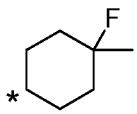
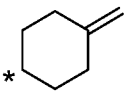
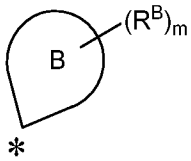
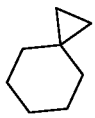
, and . In some embodiments, Z^1, Z^2, Z^3, and Z^4 are each independently selected from the group

consisting of –CH_2OH,  ,  ,  ,  ,  , and . In some embodiments, ring A is bi-subsittuted phenyl. In some embodiments, ring A is selected from the group consisting of  ,  ,  , and .

[0091] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon. In some embodiments, ring B is C_{5-7} cycloalkyl. In some embodiments, ring B is cyclopentyl, cyclohexyl, or cycloheptyl. In some embodiments, ring B is  or  , wherein * denotes the point of attachment to the rest of Formula (II). In some embodiments, ring B is C_{5-7} cycloalkenyl. In some embodiments, ring B is cyclopentenyl, cyclohexenyl, or cycloheptenyl. In some embodiments, ring B is  , wherein * denotes the point of attachment to the rest of Formula (II). In some embodiments, ring B is  , wherein * denotes the point of attachment to the rest of Formula (II). In some embodiments, ring B is 5- to 7-membered heterocycloalkyl. In some embodiments, ring B is 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon. In some embodiments, ring B is tetrahydrofuranyl or 1,3-dioxanyl. In some embodiments, ring B is  or  , wherein * denotes the point of attachment to the rest of Formula (II).

[0092] In some embodiments of Formula (II), ring B is substituted with m R^B groups, wherein each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl. In some embodiment, an R^B group is methyl or ethyl. In some embodiment, two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form cyclopropyl. In some embodiments, two geminal R^B groups are taken together with the carbon atom to which they are attached to form cyclopropyl.

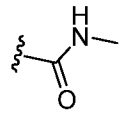
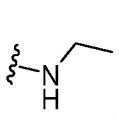
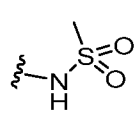
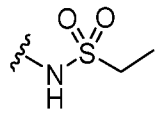
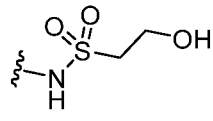
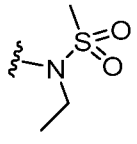
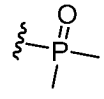
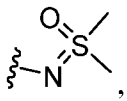
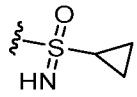
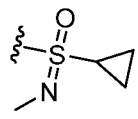
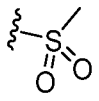
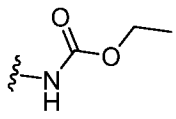
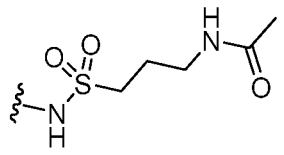
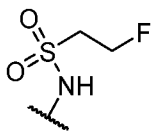
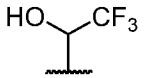
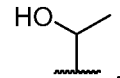
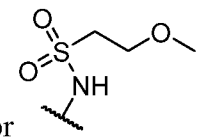
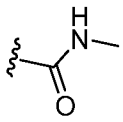
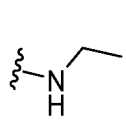
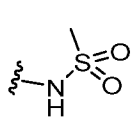
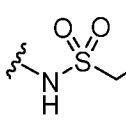
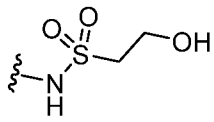
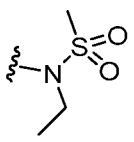
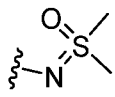
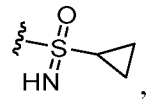
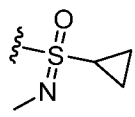
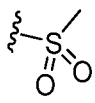
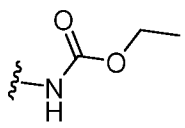
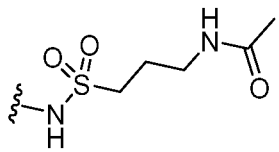
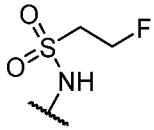
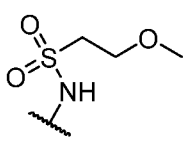
[0093] In some embodiments of Formula (II), m is 0, 1, 2, 3, or 4. In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1.

[0094] In some embodiments,  of Formula (II) is  ,  ,  , or wherein * denotes the point of attachment to the rest of Formula (II). In some embodiments,  of Formula (II) is  , or  wherein * denotes the point of attachment to the rest of Formula (II). In some embodiments,  is  , wherein of * denotes the point of attachment to the rest of Formula (II).

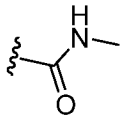
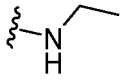
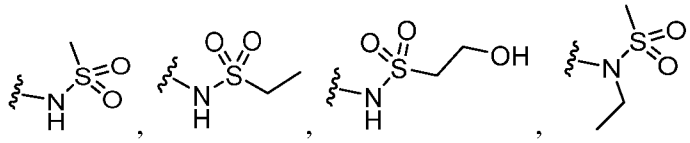
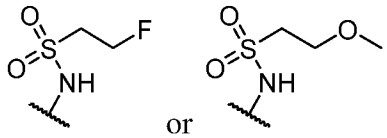
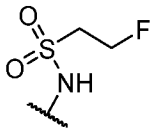
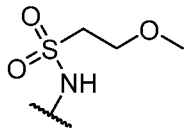
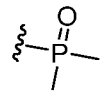
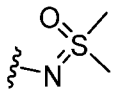
[0095] In some embodiments of Formula (II), or a pharmaceutically acceptable salt thereof, Y^1 is N or CR^{C1}; Y^2 is N or CR^{C2}; Y^3 is N or CR^{C3}; and Y^4 is N or CR^{C4}. In some embodiments, no more than three of Y^1, Y^2, Y^3, and Y^4 are N. In some embodiments, no more than two of Y^1, Y^2, Y^3, and Y^4 are N. In some embodiments, no more than one of Y^1, Y^2, Y^3, and Y^4 is N. In some embodiments, Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}. In some embodiments, Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}. In some embodiments, Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

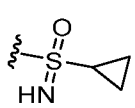
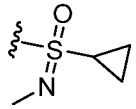
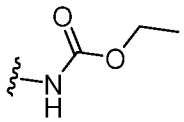
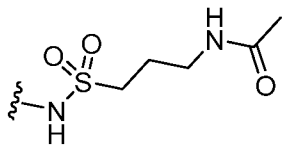
[0096] In some embodiments of Formula (II), R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, - $NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -$P(O)R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)$(NR^{c11})R^{c12}$, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, -O-$S(O)_2R^{c19}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and –OH.

[0097] In some embodiments of Formula (II), R^{C1} is hydrogen or halo. In some embodiments, R^{C1} is hydrogen or fluoro. In some embodiments, R^{C3} is hydrogen. In some embodiments, R^{C4} is hydrogen or -NH_2. In some embodiments, R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or -NH_2.

[0098] In some embodiments of Formula (II), R^{C2} is cyano, -OH, -CH_2OH, fluro, bromo, -NO_2,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , or  .  ,  ,  , or  . In some embodiments, R^{C2} is cyano, -OH, -CH_2OH, bromo, -NO_2,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{C2} is  ,  ,  ,  , or  . In some embodiments, R^{C2} is cyano, -OH, halo, -NO_2, C(O)$NR^{c1}R^{c2}$, - $NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -$P(O)R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)$(NR^{c11})R^{c12}$, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted

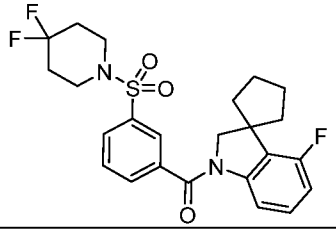
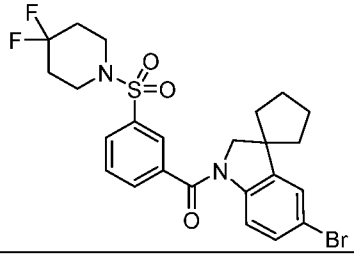
with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{C2} is cyano, -OH, halo, $-NO_2$, $C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{C2} is $-O-S(O)_2R^{c19}$.

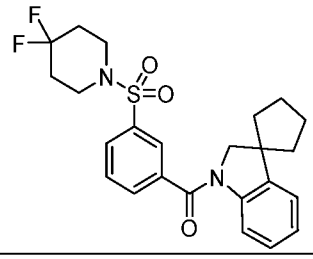
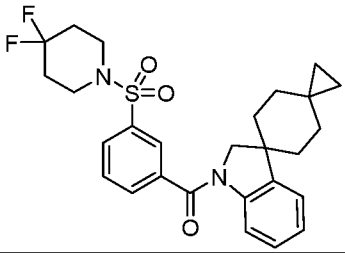
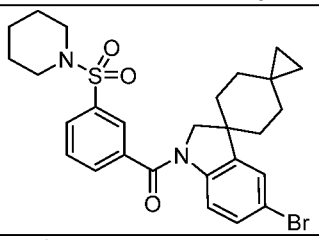
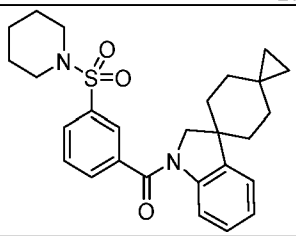
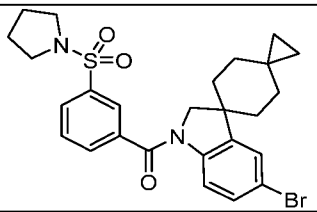
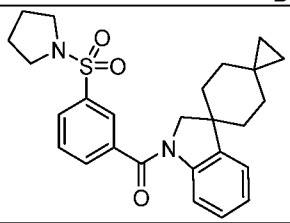
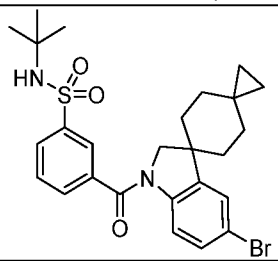
[0099] In some embodiments, $-C(O)NR^{c1}R^{c2}$ is  . In some embodiments, R^{c1} and R^{c2} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c1} and R^{c2} are each independently hydrogen, methyl, or ethyl. In some embodiments, $-NR^{c3}R^{c4}$ is  . In some embodiments, R^{c3} and R^{c4} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c1} and R^{c2} are each independently hydrogen, methyl, or ethyl. In some embodiments, $-NR^{c5}S(O)_2R^{c6}$ is  ,  or . In some embodiments, $-NR^{c5}S(O)_2R^{c6}$ is  or  . In some embodiments, R^{c5} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{c5} is hydrogen, methyl, or ethyl. In some embodiments, R^{c6} is hydrogen or C_{1-6} alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from halo, –OH, $-O(C_{1-6}$ alkyl), and $–NHC(O)(C_{1-6}$ alky). In some embodiments, R^{c5} is methyl or $-CH_2CH_2OH$. In some embodiments, R^{c5} is hydrogen. In some embodiments, R^{c6} is ethyl. In some embodiments, R^{c6} is $–CH_2CH_2F$. In some embodiments, R^{c6} is $–OCH_3$. In some embodiments, $-P(O)R^{c7}R^{c8}$ is  . In some embodiments, R^{c7} and R^{c8} are each independently C_{1-6} alkyl. In some embodiments, R^{c7} and R^{c8} are each methyl. In some embodiments, $-N{=}S(O)R^{c9}R^{c10}$ is  . In some embodiments, R^{c9} and R^{c10} are each

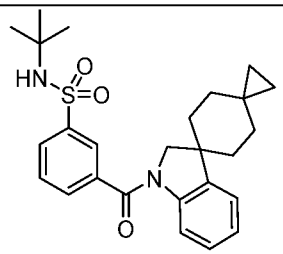
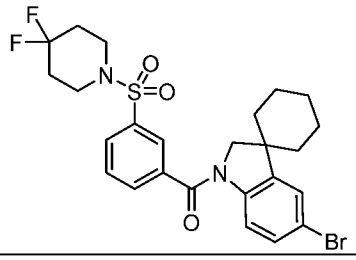
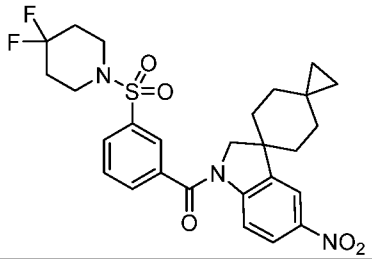
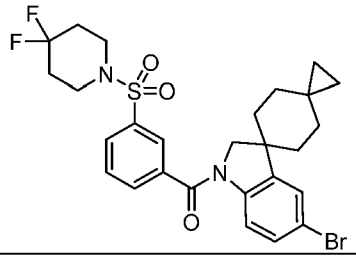
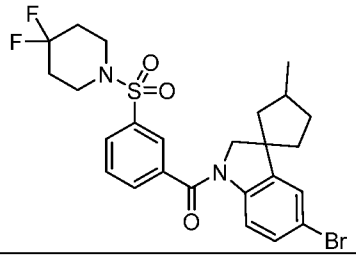
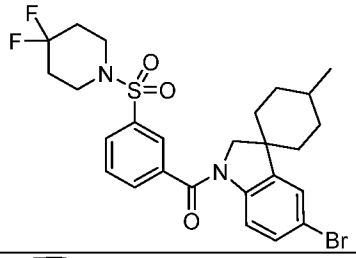
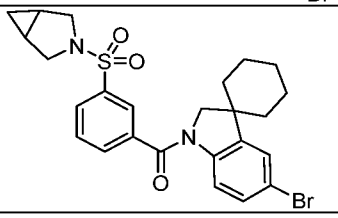
independently C_{1-6} alkyl. In some embodiments, R^{c9} and R^{c10} are each methyl. In some embodiments, $-S(O)(NR^{c11})R^{c12}$ is  or  . In some embodiments, R^{c11} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{c11} is hydrogen or methyl. In some embodiments, R^{c12} is C_{1-6} alkyl or C_{3-10} cycloalkyl. In some embodiments, R^{c12} is cyclopropyl. In some embodiments, $-S(O)_2R^{c13}$ is  . In some embodiments, R^{c13} is C_{1-6} alkyl. In some embodiments, R^{c13} is methyl. In some embodiments, $NR^{c14}C(O)OR^{c15}$ is  . In some embodiments, R^{c14} and R^{c15} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c14} is hydrogen. In some embodiments, R^{c15} is ethyl. In some embodiments, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ is  . In some embodiments, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ is $-NR^{c16}S(O)_2(CH_2)_{1-3}NR^{c17}C(O)R^{c18}$. In some embodiments, R^{c16}, R^{c17} and R^{c18} are each independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{c16} and R^{c17} are hydrogen. In some embodiments, R^{c18} is methyl.

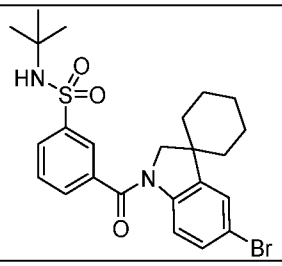
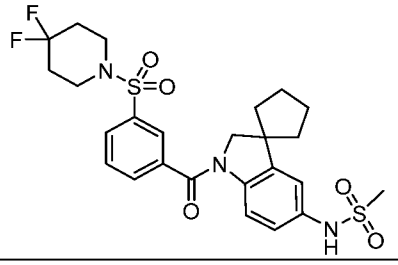
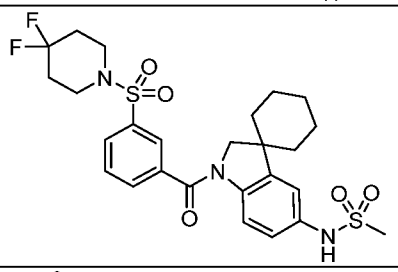
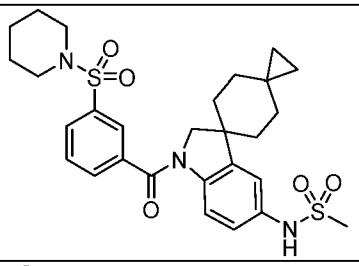
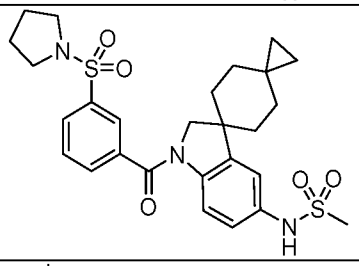
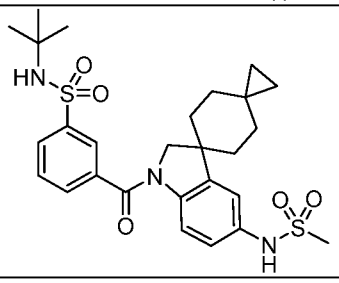
[0100] In some embodiments, provided herein are compounds and pharmaceutically acceptable salts thereof described in **Table 1**.

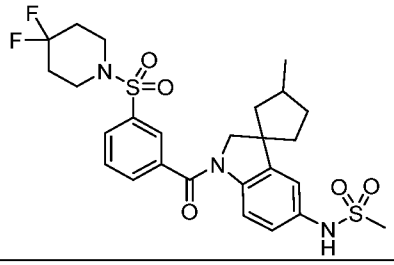
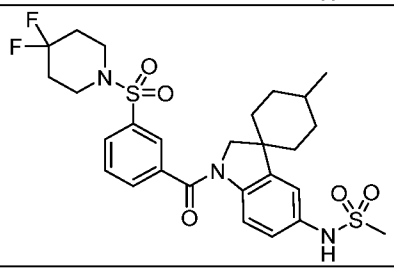
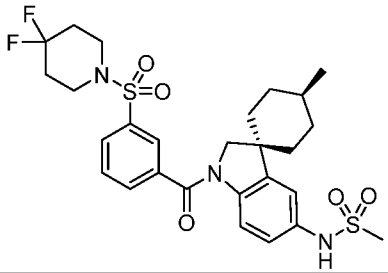
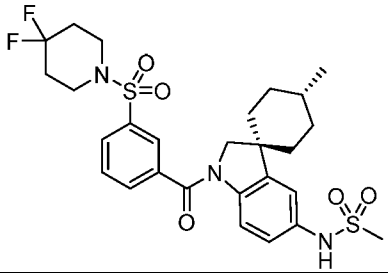
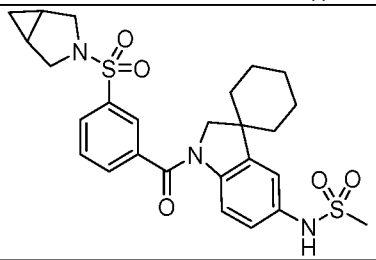
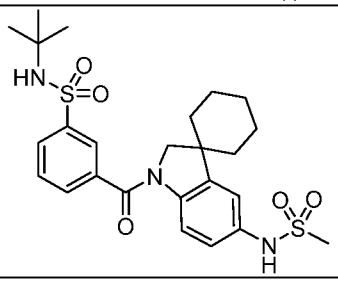
Table 1.

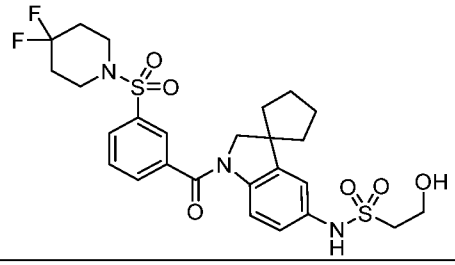
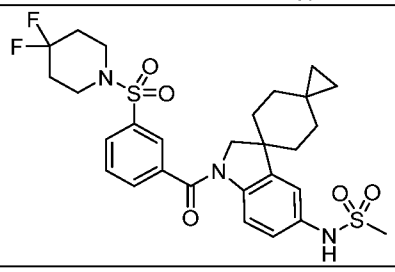
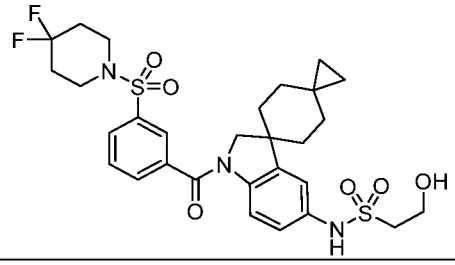
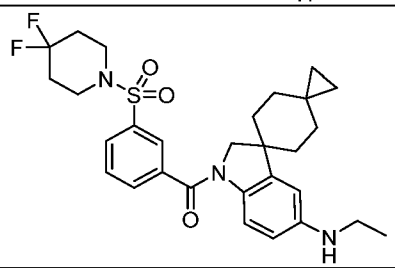
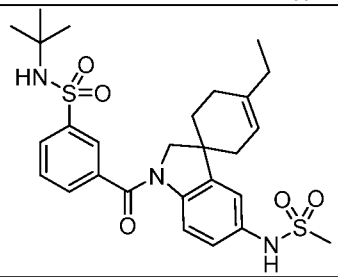
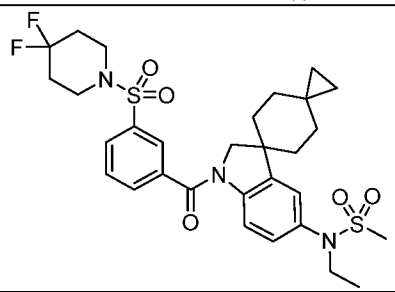
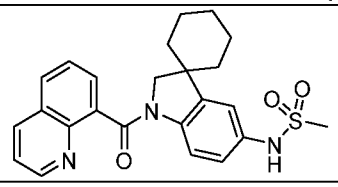
Compound No.	Structure	Name
Compound 1		(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)methanone
Compound 2		(5'-bromospiro[cyclopentane-1,3'-indolin]-1'-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone

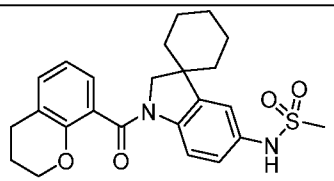
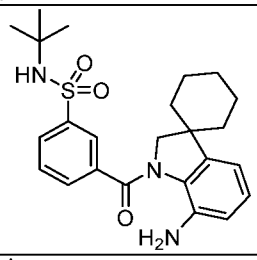
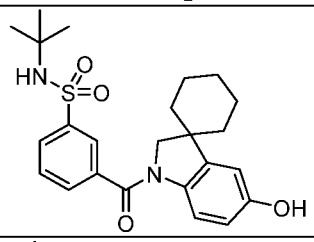
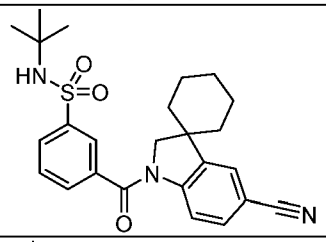
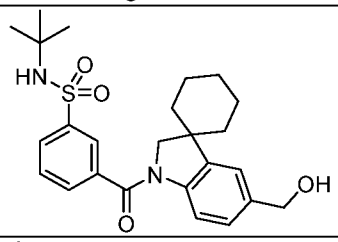
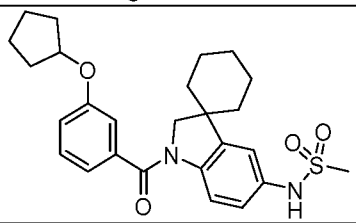
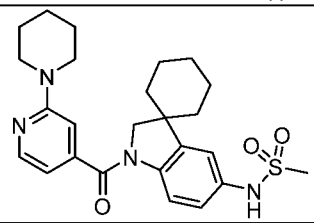
Compound No.	Structure	Name
Compound 3		(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(spiro[cyclopentane-1,3'-indolin]-1'-yl)methanone
Compound 4		(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)methanone
Compound 5		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-(piperidin-1-ylsulfonyl)phenyl)methanone
Compound 6		dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl(3-(piperidin-1-ylsulfonyl)phenyl)methanone
Compound 7		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-(pyrrolidin-1-ylsulfonyl)phenyl)methanone
Compound 8		dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl(3-(pyrrolidin-1-ylsulfonyl)phenyl)methanone
Compound 9		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-butyl)benzenesulfonamide

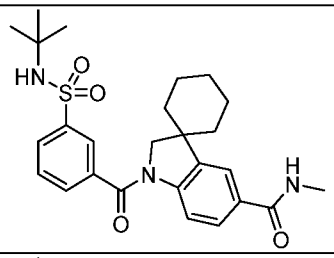
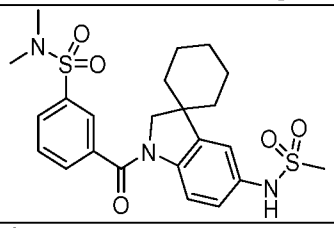
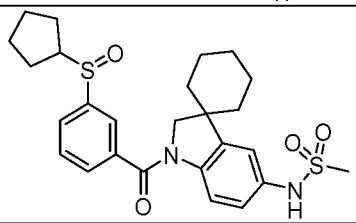
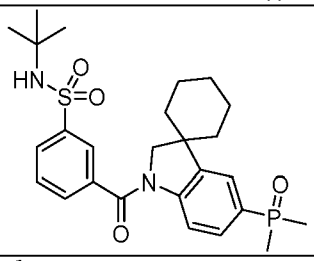
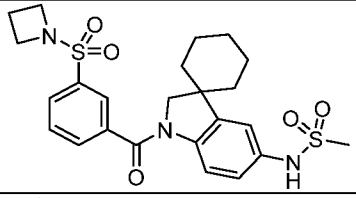
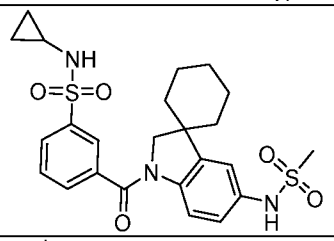
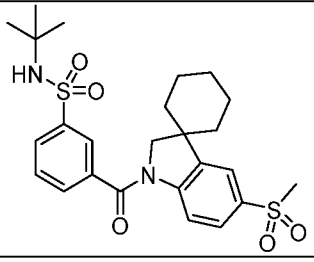
Compound No.	Structure	Name
Compound 10		N-(tert-butyl)-3-(dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 11		(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone
Compound 12		(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(5"-nitrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)methanone
Compound 13		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone
Compound 14		(5'-bromo-3-methylspiro[cyclopentane-1,3'-indolin]-1'-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone
Compound 15		(5'-bromo-4-methylspiro[cyclohexane-1,3'-indolin]-1'-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone
Compound 16		(3-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)phenyl)(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)methanone

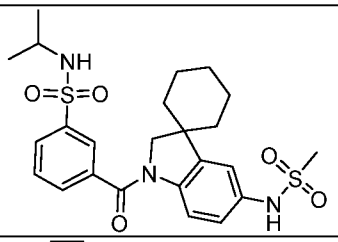
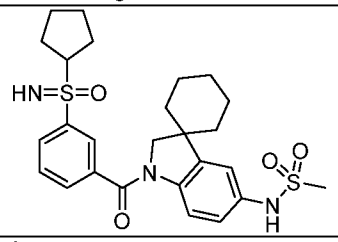
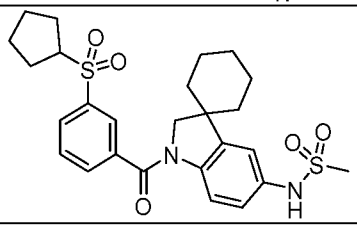
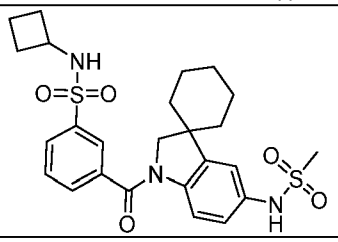
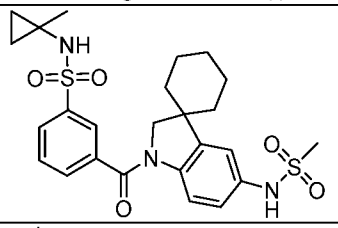
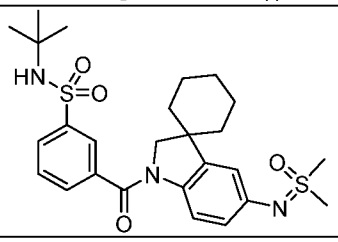
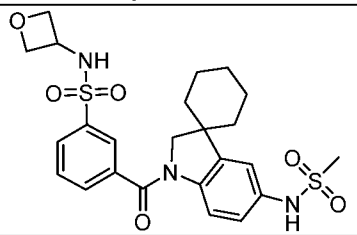
Compound No.	Structure	Name
Compound 17		3-(5'-bromospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 18		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 19		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 20		N-(1''-(3-(piperidin-1-ylsulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 21		N-(1''-(3-(pyrrolidin-1-ylsulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 22		N-(tert-butyl)-3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide

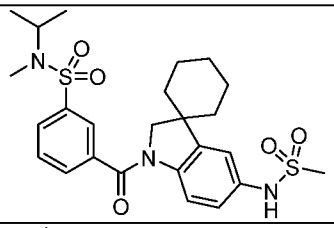
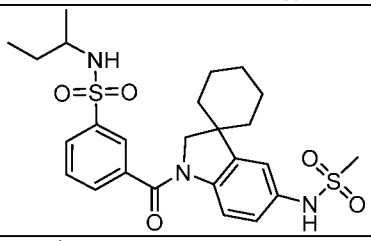
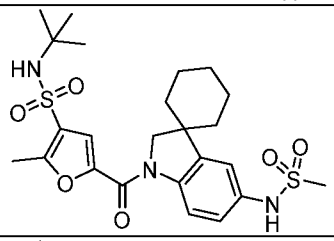
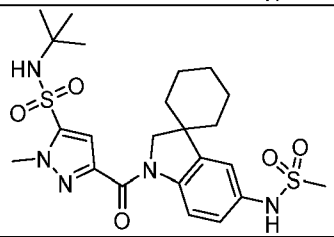
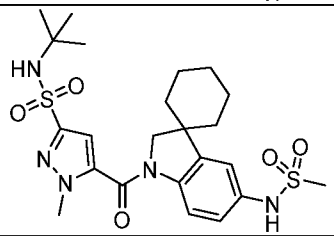
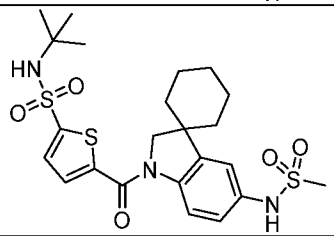
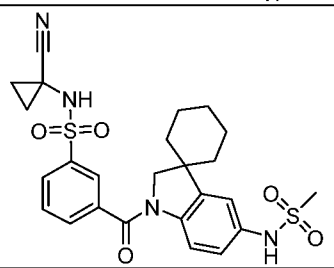
Compound No.	Structure	Name
Compound 23		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)-3-methylspiro[cyclopentane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 24		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)-4-methylspiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
(1s,4s)-Compound 24		N-((1s,4s)-1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)-4-methylspiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
(1r,4r)-Compound 24		N-((1r,4r)-1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)-4-methylspiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 25		N-(1'-(3-((3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 26		N-(tert-butyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

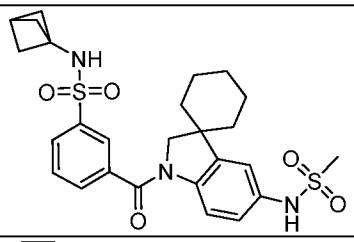
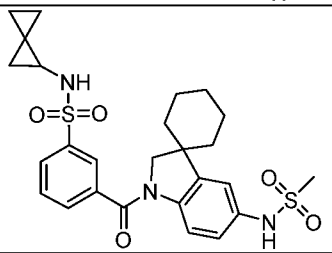
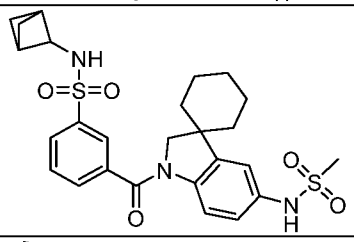
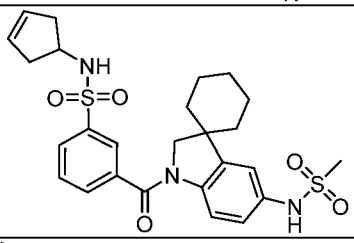
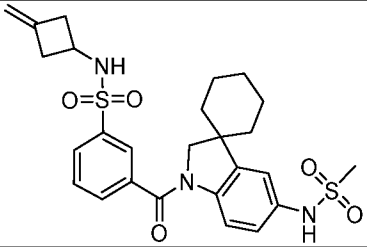
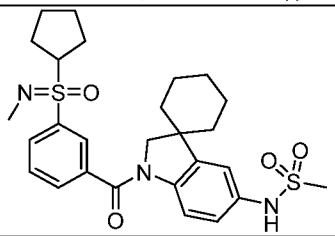
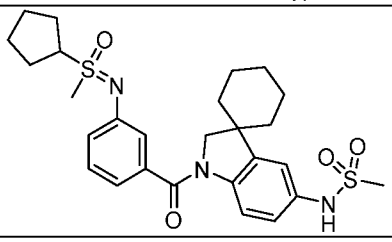
Compound No.	Structure	Name
Compound 27		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)-2-hydroxyethane-1-sulfonamide
Compound 28		N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 29		N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)-2-hydroxyethane-1-sulfonamide
Compound 30		(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(5''-(ethylamino)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)methanone
Compound 31		N-(tert-butyl)-3-(4-ethyl-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indolin]-3-en-1'-carbonyl)benzenesulfonamide
Compound 32		N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)-N-ethylmethanesulfonamide
Compound 33		N-(1'-(quinoline-8-carbonyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide

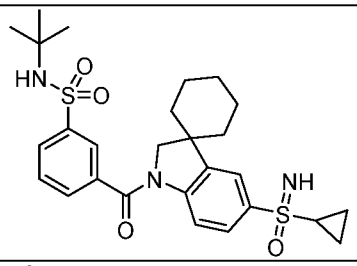
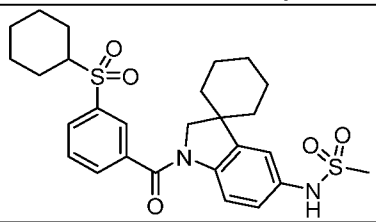
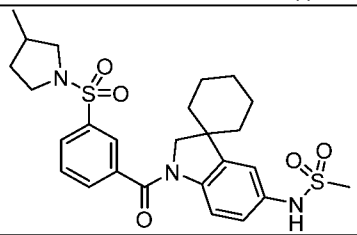
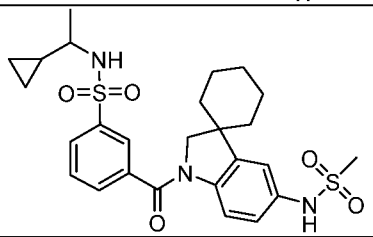
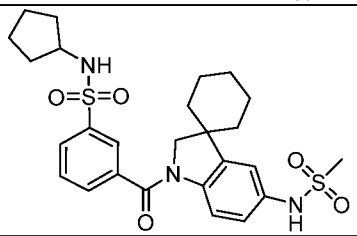
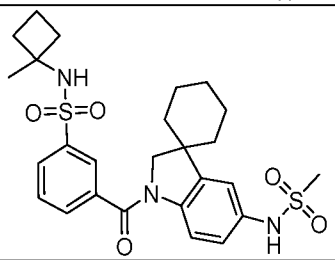
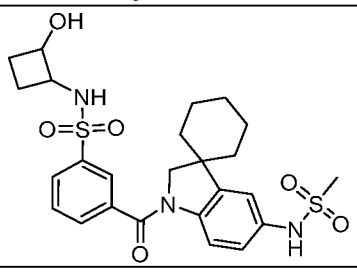
Compound No.	Structure	Name
Compound 34		N-(1'-(chromane-8-carbonyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 35		3-(7'-aminospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 36		N-(tert-butyl)-3-(5'-hydroxyspiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 37		N-(tert-butyl)-3-(5'-cyanospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 38		N-(tert-butyl)-3-(5'-(hydroxymethyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 39		N-(1'-(3-(cyclopentyloxy)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 40		N-(1'-(2-(piperidin-1-yl)isonicotinoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide

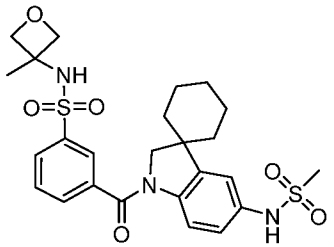
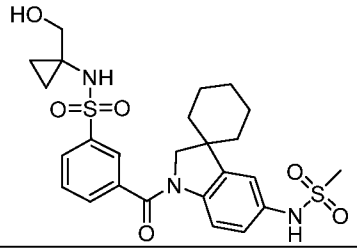
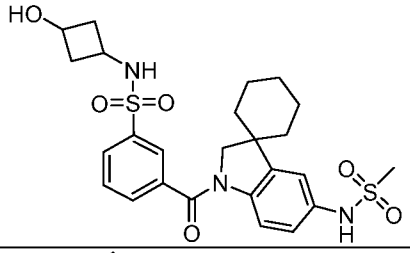
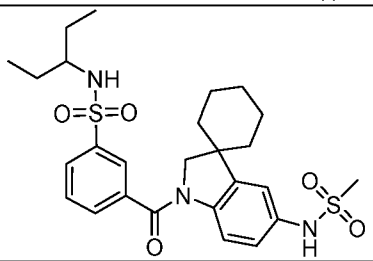
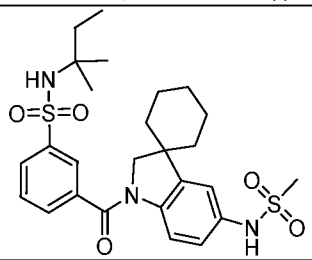
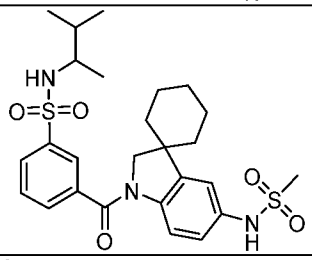
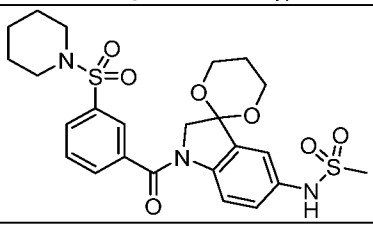
Compound No.	Structure	Name
Compound 41		1'-(3-(N-(tert-butyl)sulfamoyl)benzoyl)-N-methylspiro[cyclohexane-1,3'-indoline]-5'-carboxamide
Compound 42		N,N-dimethyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 43		N-(1'-(3-(cyclopentylsulfinyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 44		N-(tert-butyl)-3-(5'-(dimethylphosphoryl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 45		N-(1'-(3-(azetidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 46		N-cyclopropyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 47		N-(tert-butyl)-3-(5'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

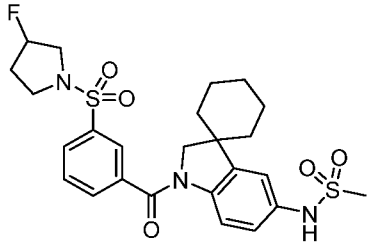
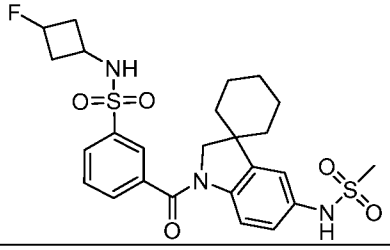
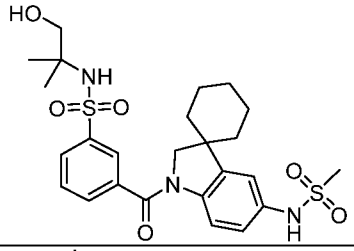
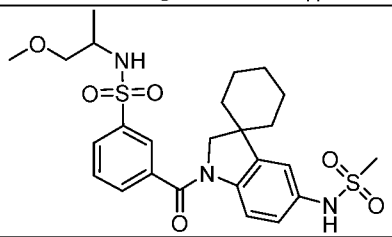
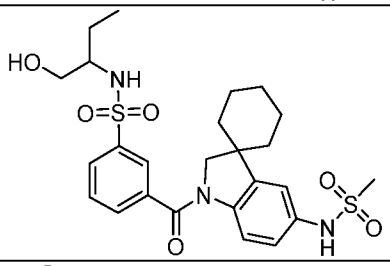
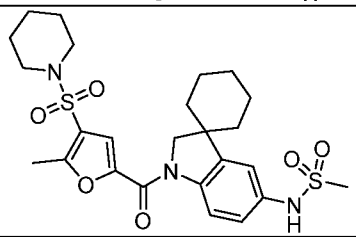
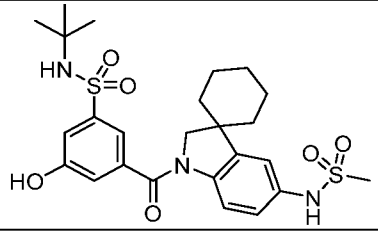
Compound No.	Structure	Name
Compound 48		N-isopropyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 49		N-(1'-(3-(cyclopentanesulfonimidoyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 50		N-(1'-(3-(cyclopentylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 51		N-cyclobutyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 52		3-({5'-methanesulfonamido-1',2'-dihydrospiro[cyclohexane-1,3'-indol]-1'-yl}carbonyl)-N-(1-methylcyclopropyl)benzene-1-sulfonamide
Compound 53		N-(tert-butyl)-3-(5'-((dimethyl(oxo)-λ^6-sulfaneylidene)amino)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 54		3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(oxetan-3-yl)benzenesulfonamide

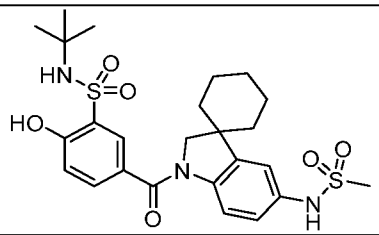
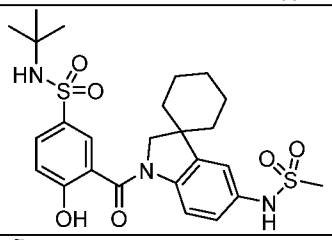
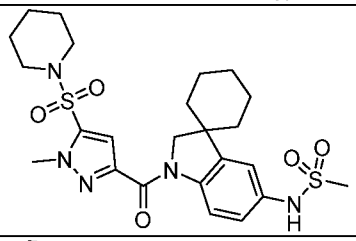
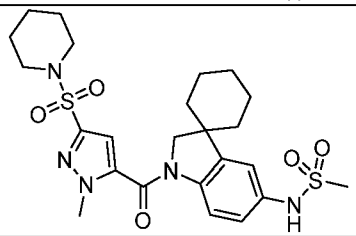
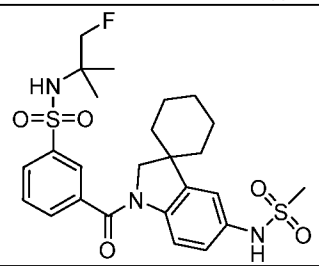
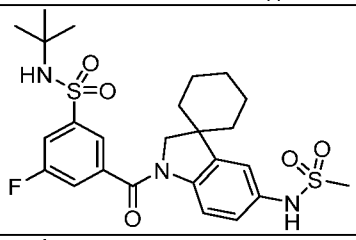
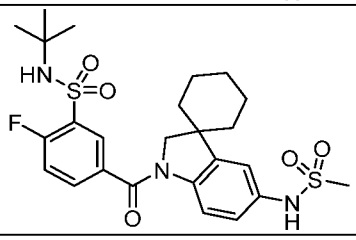
Compound No.	Structure	Name
Compound 55		N-isopropyl-N-methyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 56		N-(sec-butyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 57		N-(tert-butyl)-2-methyl-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)furan-3-sulfonamide
Compound 58		N-(tert-butyl)-1-methyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-1H-pyrazole-5-sulfonamide
Compound 59		N-(tert-butyl)-1-methyl-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-1H-pyrazole-3-sulfonamide
Compound 60		N-(tert-butyl)-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)thiophene-2-sulfonamide
Compound 61		N-(1-cyanocyclopropyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

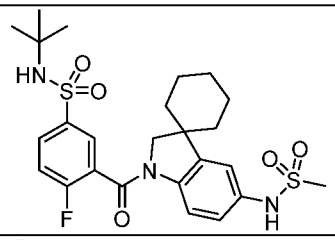
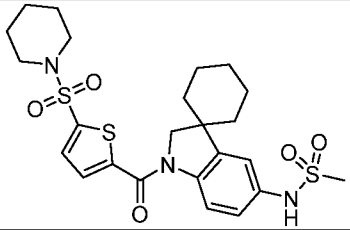
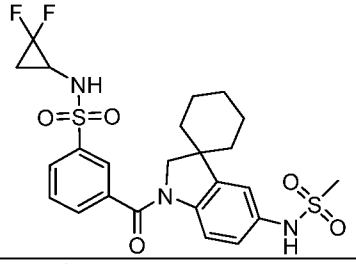
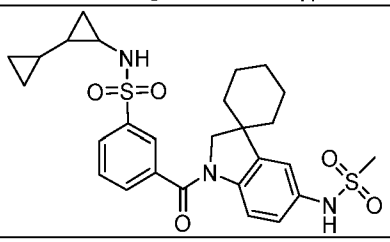
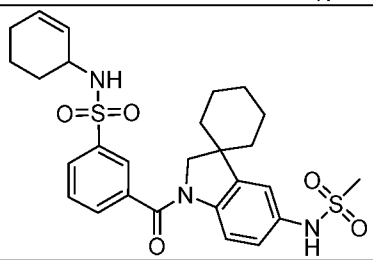
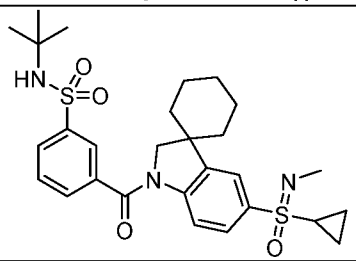
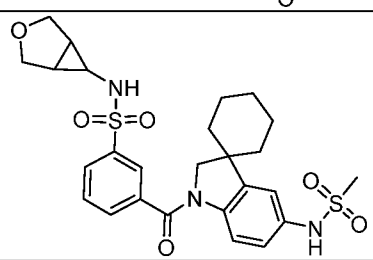
Compound No.	Structure	Name
Compound 62		N-(bicyclo[1.1.1]pentan-1-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 63		3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(spiro[2.2]pentan-1-yl)benzenesulfonamide
Compound 64		N-(bicyclo[1.1.1]pentan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 65		N-(cyclopent-3-en-1-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 66		N-(3-methylenecyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 67		N-(1'-(3-(N-methylcyclopentanesulfonimidoyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 68		N-(1'-(3-((cyclopentyl(methyl)(oxo)-λ^6-sulfaneylidene)amino)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide

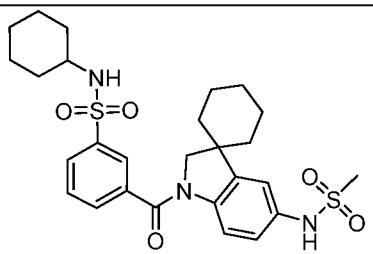
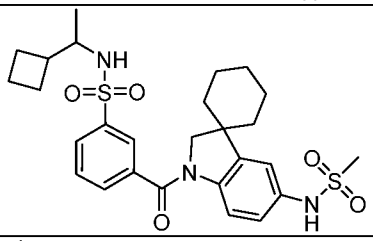
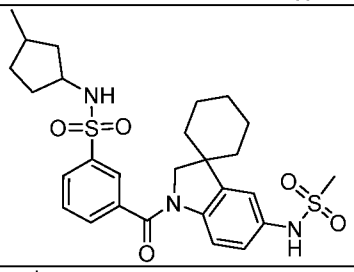
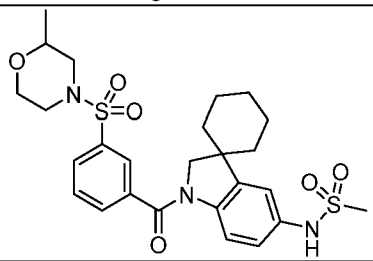
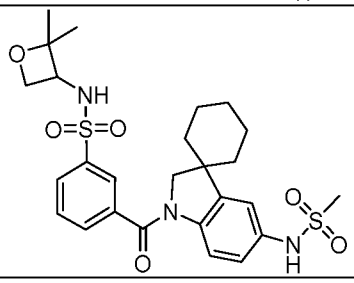
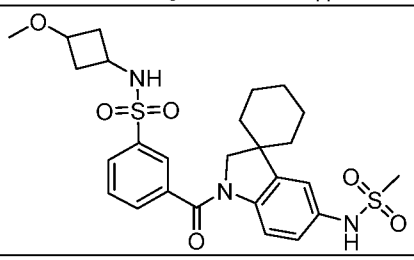
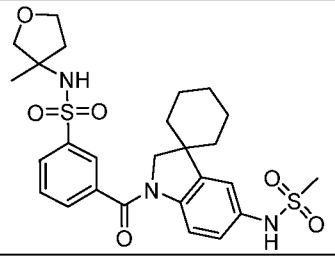
Compound No.	Structure	Name
Compound 69		N-(tert-butyl)-3-(5'-(cyclopropanesulfonimidoyl) spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 70		N-(1'-(3-(cyclohexylsulfonyl)benzoyl) spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 71		N-(1'-(3-((3-methylpyrrolidin-1-yl)sulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 72		N-(1-cyclopropylethyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 73		N-cyclopentyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 74		N-(1-methylcyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 75		N-(2-hydroxycyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

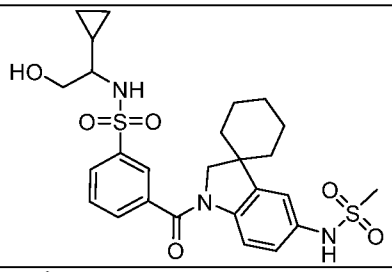
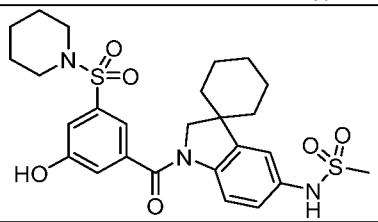
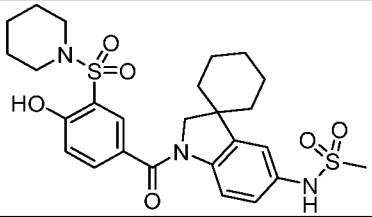
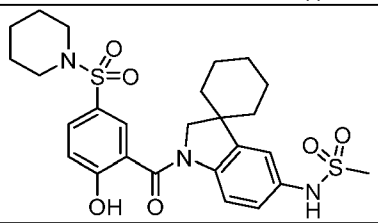
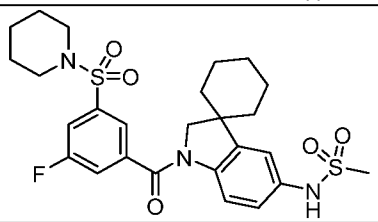
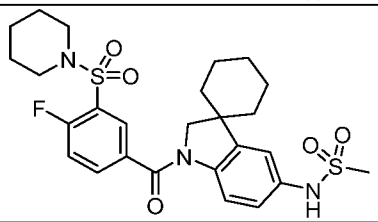
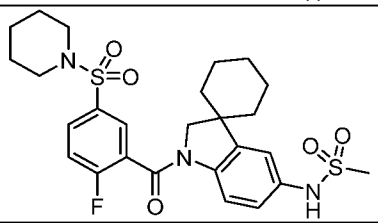
Compound No.	Structure	Name
Compound 76		N-(3-methyloxetan-3-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 77		N-(1-(hydroxymethyl)cyclopropyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 78		N-(3-hydroxycyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 79		3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(pentan-3-yl)benzenesulfonamide
Compound 80		3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-pentyl)benzenesulfonamide
Compound 81		N-(3-methylbutan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 82		N-(1-(3-(piperidin-1-ylsulfonyl)benzoyl)spiro[indoline-3,2'-[1,3]dioxan]-5-yl)methanesulfonamide

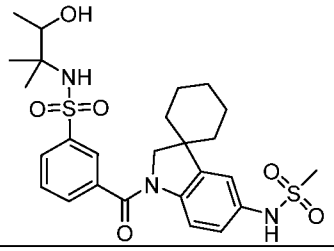
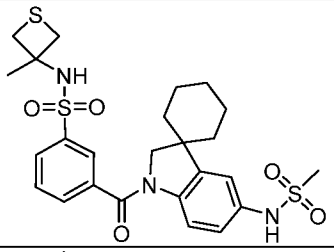
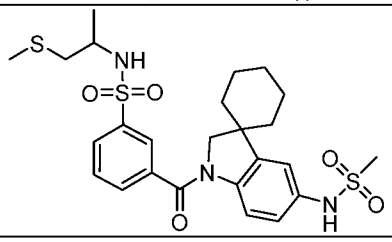
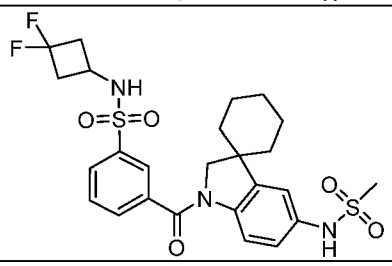
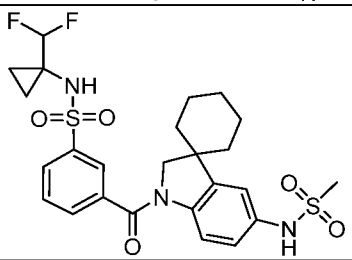
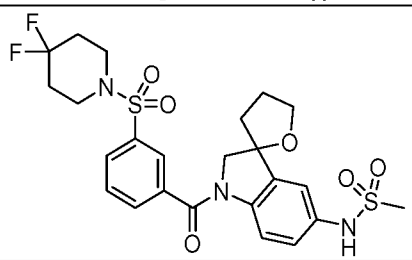
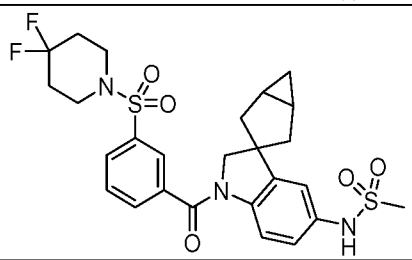
Compound No.	Structure	Name
Compound 83		N-(1'-(3-((3-fluoropyrrolidin-1-yl)sulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 84		N-(3-fluorocyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 85		N-(1-hydroxy-2-methylpropan-2-yl)-3-(5'-(methylsulfonamido) spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 86		N-(1-methoxypropan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 87		N-(1-hydroxybutan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 88		N-(1'-(5-methyl-4-(piperidin-1-ylsulfonyl)furan-2-carbonyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 89		N-(tert-butyl)-3-hydroxy-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

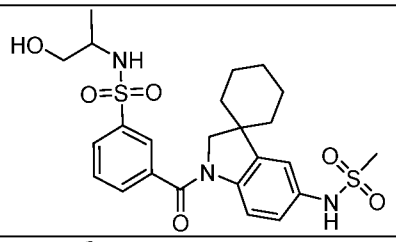
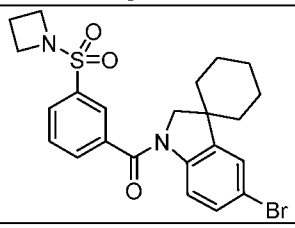
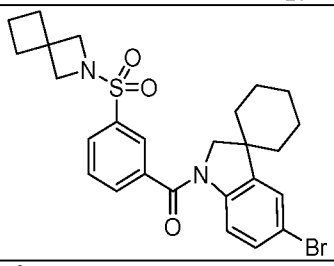
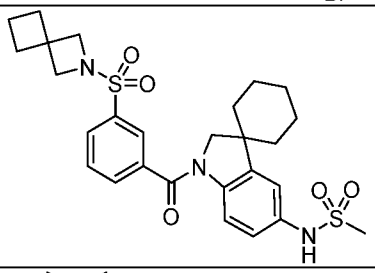
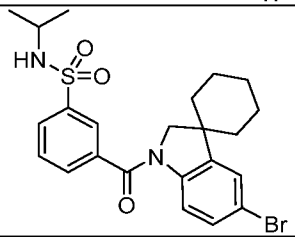
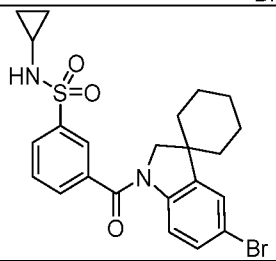
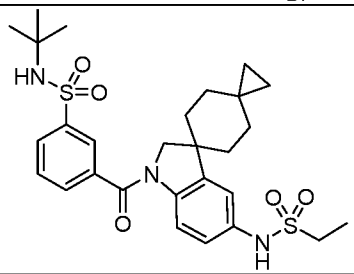
Compound No.	Structure	Name
Compound 90		N-(tert-butyl)-2-hydroxy-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 91		N-(tert-butyl)-4-hydroxy-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 92		N-(1'-(1-methyl-5-(piperidin-1-ylsulfonyl)-1H-pyrazole-3-carbonyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 93		N-(1'-(1-methyl-3-(piperidin-1-ylsulfonyl)-1H-pyrazole-5-carbonyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 94		N-(1-fluoro-2-methylpropan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 95		N-(tert-butyl)-3-fluoro-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 96		N-(tert-butyl)-2-fluoro-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

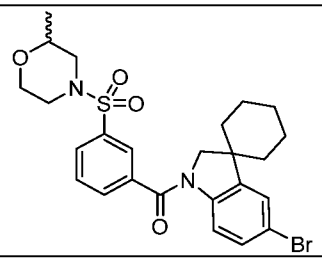
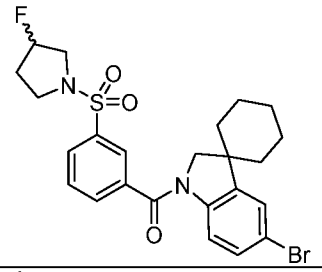
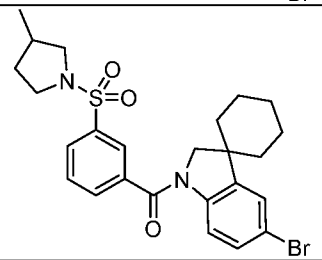
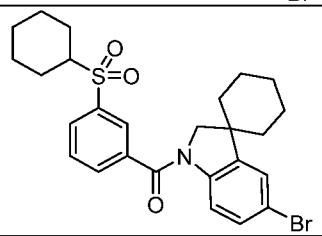
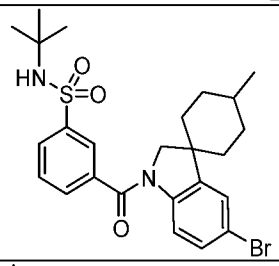
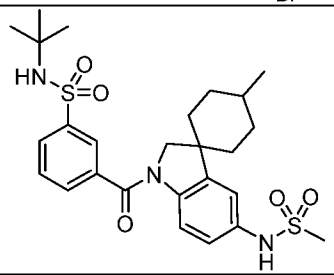
Compound No.	Structure	Name
Compound 97		N-(tert-butyl)-4-fluoro-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 98		N-(1'-(5-(piperidin-1-ylsulfonyl)thiophene-2-carbonyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 99		N-(2,2-difluorocyclopropyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 100		N-([1,1'-bi(cyclopropan)]-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 101		N-(cyclohex-2-en-1-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 102		N-(tert-butyl)-3-(5'-(N-methylcyclopropanesulfonimidoyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 103		N-(3-oxabicyclo[3.1.0]hexan-6-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

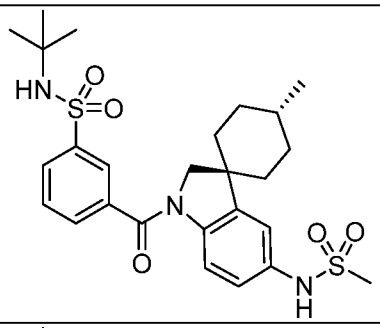
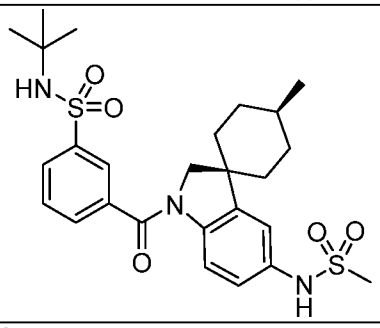
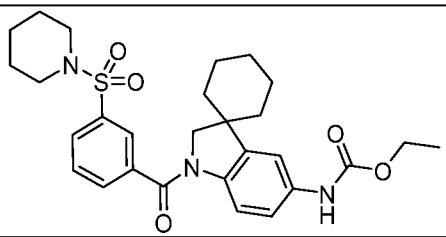
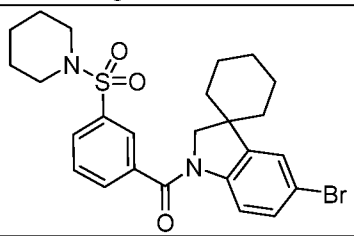
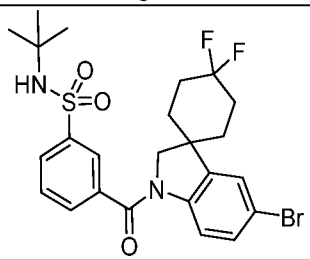
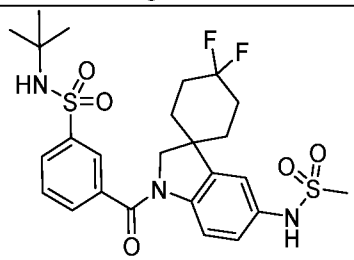
Compound No.	Structure	Name
Compound 104		N-cyclohexyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 105		N-(1-cyclobutylethyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 106		N-(3-methylcyclopentyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 107		N-(1'-(3-((2-methylmorpholino)sulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 108		N-(2,2-dimethyloxetan-3-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 109		N-(3-methoxycyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 110		3-(5'-(methylsulfonamido) spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(3-methyltetrahydrofuran-3-yl)benzenesulfonamide

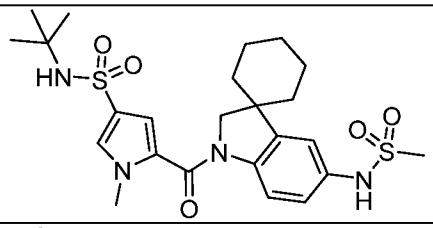
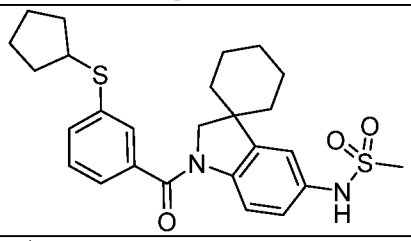
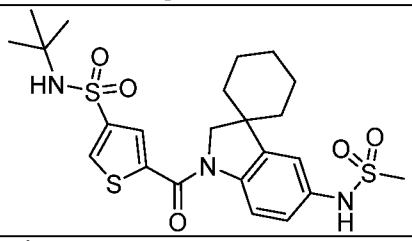
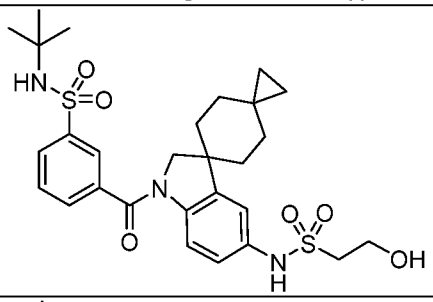
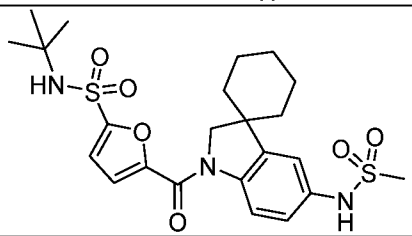
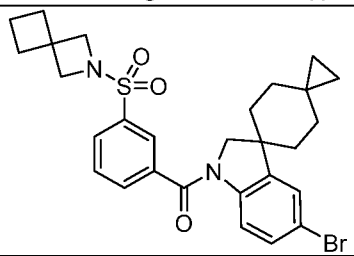
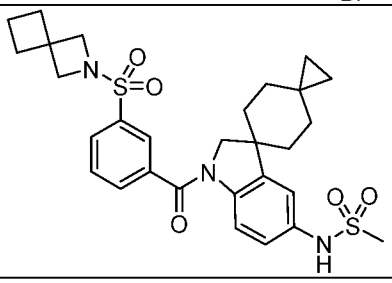
Compound No.	Structure	Name
Compound 111		N-(1-cyclopropyl-2-hydroxyethyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 112		N-(1'-(3-hydroxy-5-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 113		N-(1'-(4-hydroxy-3-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 114		N-(1'-(2-hydroxy-5-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 115		N-(1'-(3-fluoro-5-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 116		N-(1'-(4-fluoro-3-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 117		N-(1'-(2-fluoro-5-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide

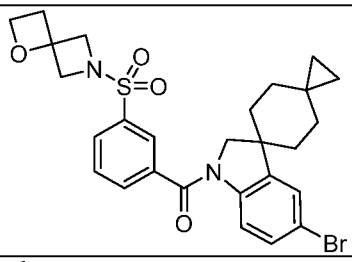
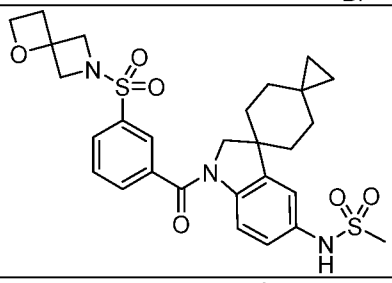
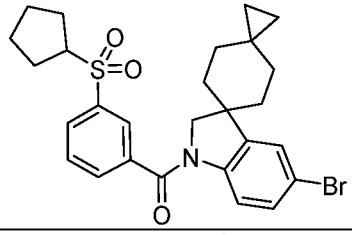
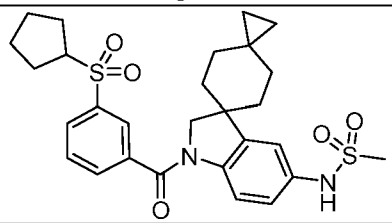
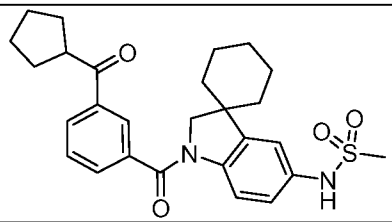
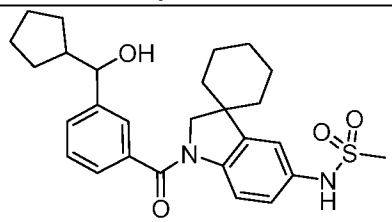
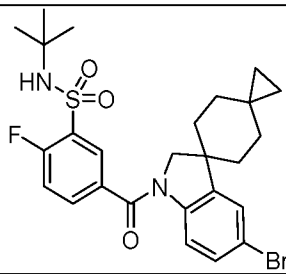
Compound No.	Structure	Name
Compound 118		N-(3-hydroxy-2-methylbutan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 119		3-(5'-(methylsulfonamido) spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(3-methylthietan-3-yl)benzenesulfonamide
Compound 120		3-(5'-(methylsulfonamido) spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(1-(methylthio)propan-2-yl)benzenesulfonamide
Compound 121		N-(3,3-difluorocyclobutyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 122		N-(1-(difluoromethyl)cyclopropyl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 123		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)-4,5-dihydro-3H-spiro[furan-2,3'-indolin]-5'-yl)methanesulfonamide
Compound 124		N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[bicyclo[3.1.0] hexane-3,3'-indolin]-5'-yl)methanesulfonamide

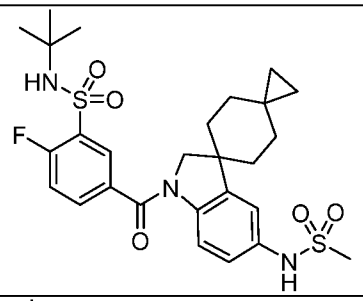
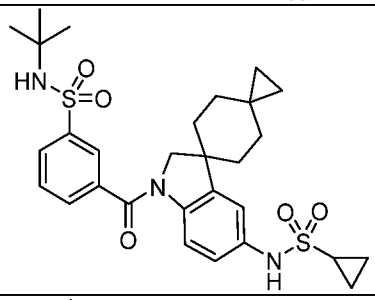
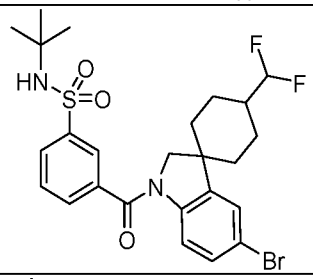
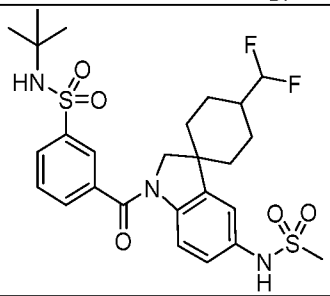
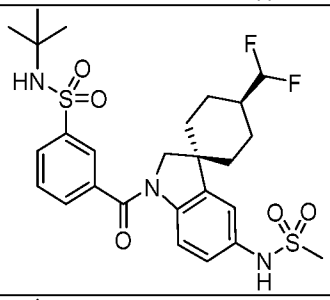
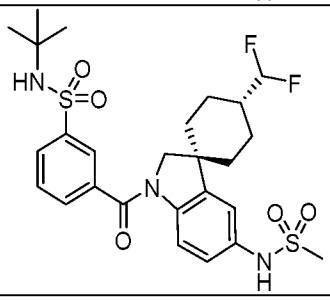
Compound No.	Structure	Name
Compound 125		N-(1-hydroxypropan-2-yl)-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 126		(3-(azetidin-1-ylsulfonyl)phenyl)(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)methanone
Compound 128		(3-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)phenyl)(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)methanone
Compound 129		N-(1'-(3-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 130		3-(5'-bromospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-isopropylbenzenesulfonamide
Compound 132		3-(5'-bromospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-cyclopropylbenzenesulfonamide
Compound 134		N-(tert-butyl)-3-(5''-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide

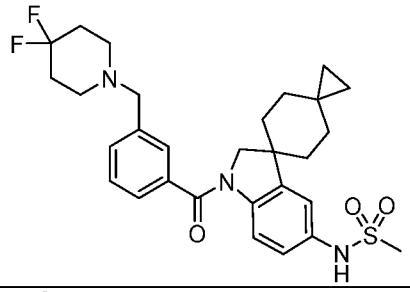
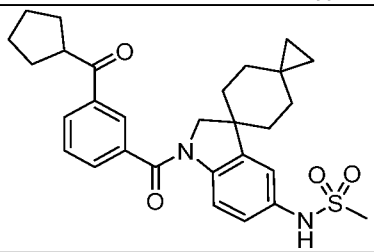
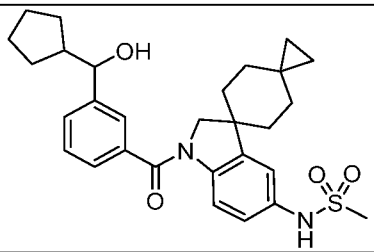
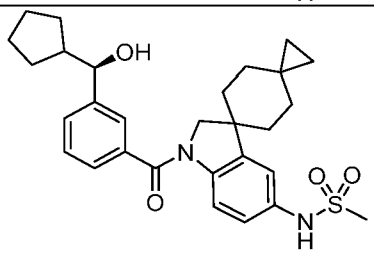
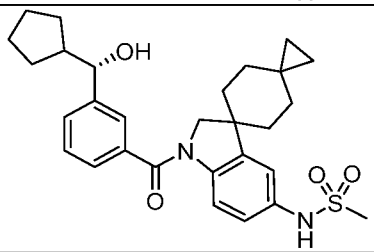
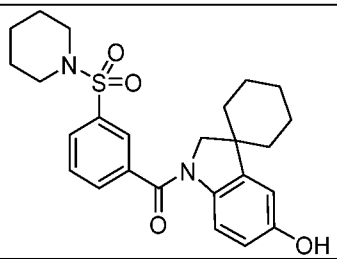
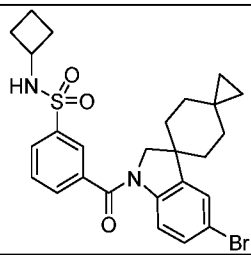
Compound No.	Structure	Name
Compound 135		(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)(3-((2-methylmorpholino) sulfonyl)phenyl)methanone
Compound 136		(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)(3-((3-fluoropyrrolidin-1-yl)sulfonyl)phenyl)methanone
Compound 137		(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)(3-((3-methylpyrrolidin-1-yl)sulfonyl)phenyl)methanone
Compound 138		(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)(3-(cyclohexylsulfonyl) phenyl)methanone
Compound 139		3-(5'-bromo-4-methylspiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 140		N-(tert-butyl)-3-(4-methyl-5'-(methylsulfonamido)spiro[cyclohexane -1,3'-indoline]-1'-carbonyl)benzenesulfonamide

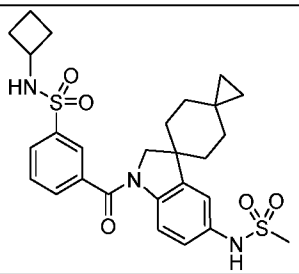
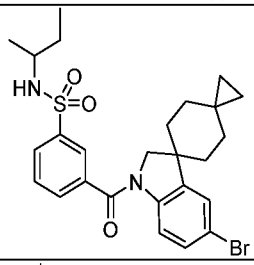
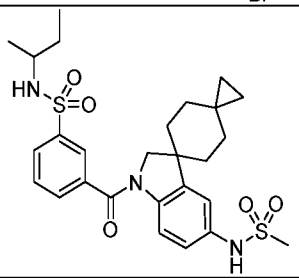
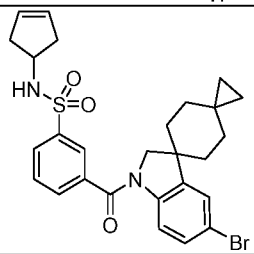
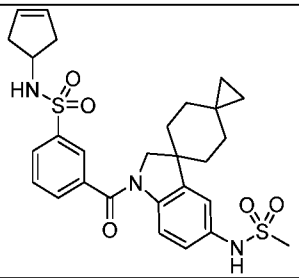
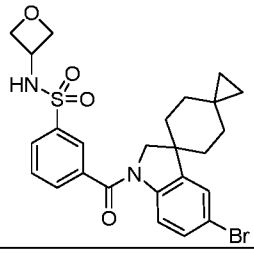
Compound No.	Structure	Name
Compound 140-(1r,4r)		N-(tert-butyl)-3-((1r,4r)-4-methyl-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 140-(1s,4s)		N-(tert-butyl)-3-((1s,4s)-4-methyl-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 141		ethyl (1'-(3-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)carbamate
Compound 142		(5'-bromospiro[cyclohexane-1,3'-indolin]-1'-yl)(3-(piperidin-1-ylsulfonyl) phenyl)methanone
Compound 143		3-(5'-bromo-4,4-difluorospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 144		N-(tert-butyl)-3-(4,4-difluoro-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

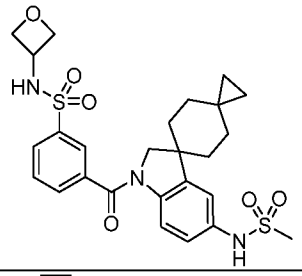
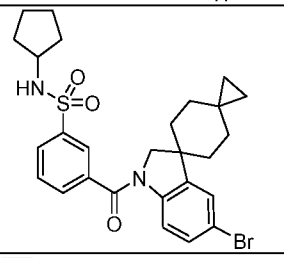
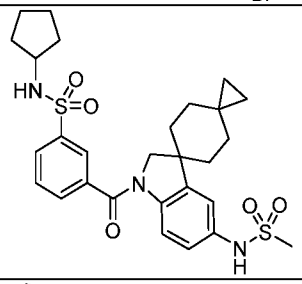
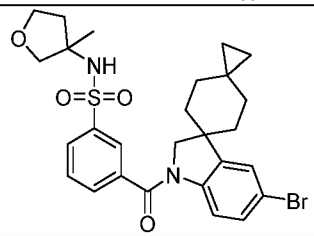
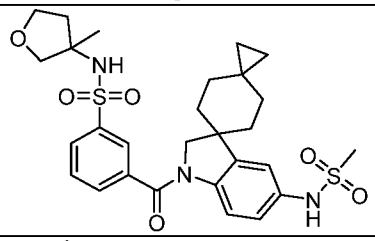
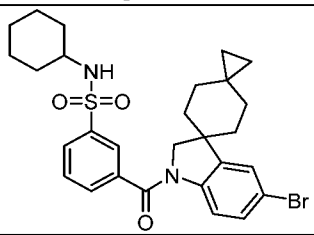
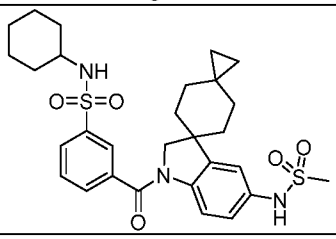
Compound No.	Structure	Name
Compound 145		N-(tert-butyl)-1-methyl-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-1H-pyrrole-3-sulfonamide
Compound 146		N-(1'-(3-(cyclopentylthio)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 147		N-(tert-butyl)-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)thiophene-3-sulfonamide
Compound 148		N-(tert-butyl)-3-(5''-((2-hydroxyethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 149		N-(tert-butyl)-5-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)furan-2-sulfonamide
Compound 150		(3-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)phenyl)(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)methanone
Compound 151		N-(1''-(3-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

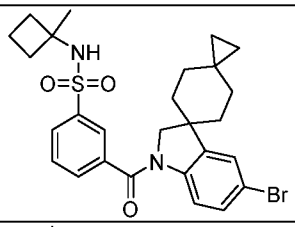
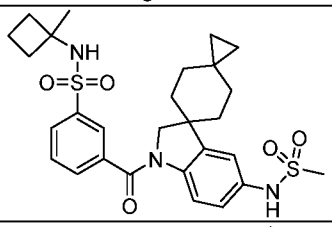
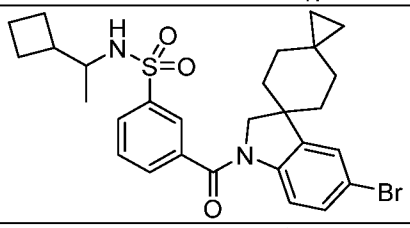
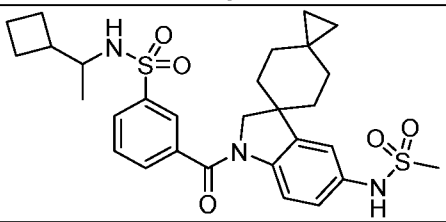
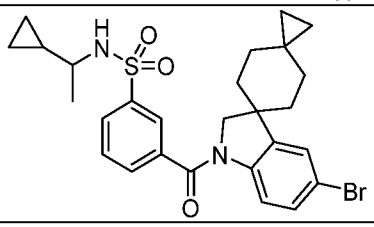
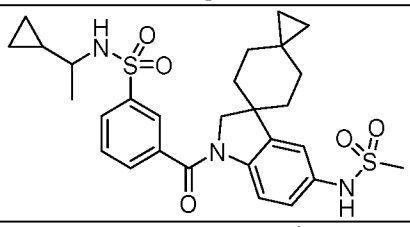
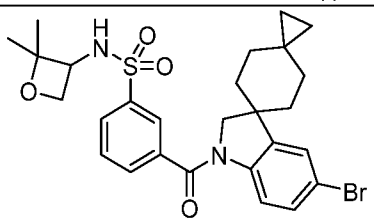
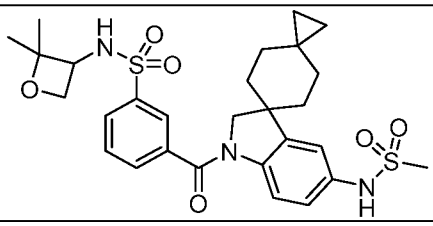
Compound No.	Structure	Name
Compound 152		(3-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)phenyl)(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)methanone
Compound 153		N-(1"-(3-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 154		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-(cyclopentylsulfonyl)phenyl)methanone
Compound 155		N-(1"-(3-(cyclopentylsulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 156		N-(1'-(3-(cyclopentanecarbonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 157		N-(1'-(3-(cyclopentyl(hydroxy)methyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 158		5-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-butyl)-2-fluorobenzenesulfonamide

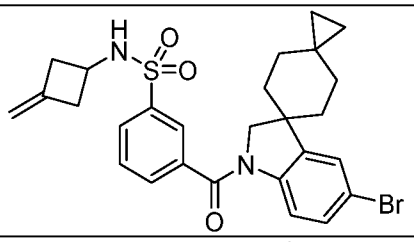
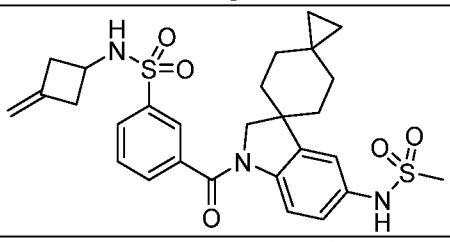
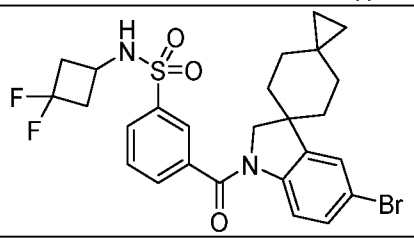
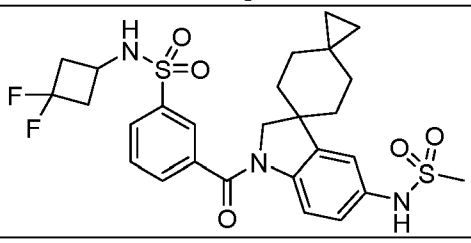
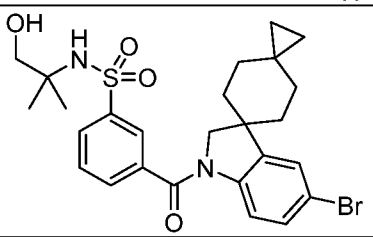
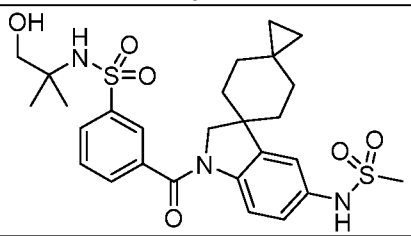
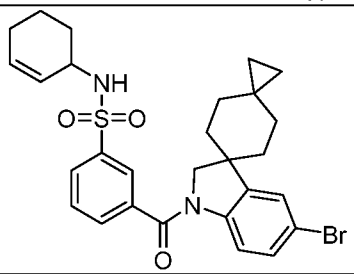
Compound No.	Structure	Name
Compound 159		N-(tert-butyl)-2-fluoro-5-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 160		N-(tert-butyl)-3-(5''-(cyclopropanesulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 161		3-(5'-bromo-4-(difluoromethyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 162		N-(tert-butyl)-3-(4-(difluoromethyl)-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1s,4s)-Compound 162		N-(tert-butyl)-3-((1s,4s)-4-(difluoromethyl)-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1r,4r)-Compound 162		N-(tert-butyl)-3-((1r,4r)-4-(difluoromethyl)-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide

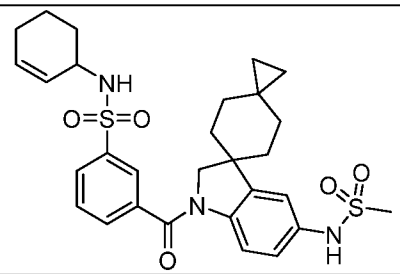
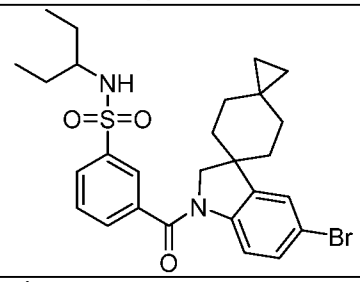
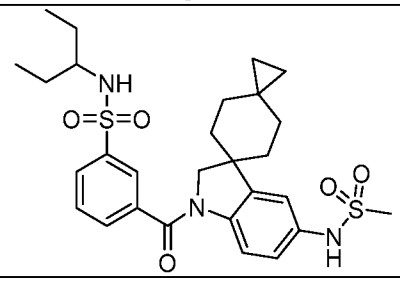
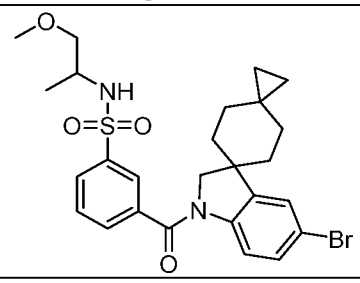
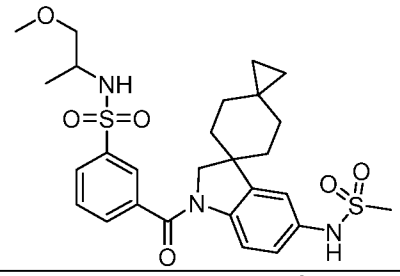
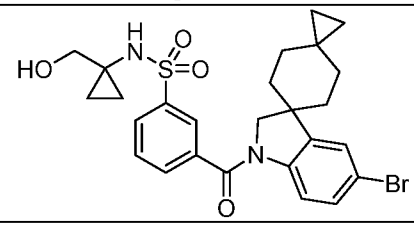
Compound No.	Structure	Name
Compound 163		N-(1"-(3-((4,4-difluoropiperidin-1-yl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 164		N-(1"-(3-(cyclopentanecarbonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 165		N-(1"-(3-(cyclopentyl(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 165		(R)-N-(1"-(3-(cyclopentyl(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 165		(S)-N-(1"-(3-(cyclopentyl(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 166		(5'-hydroxyspiro[cyclohexane-1,3'-indolin]-1'-yl)(3-(piperidin-1-ylsulfonyl)phenyl)methanone
Compound 167		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-cyclobutylbenzenesulfonamide

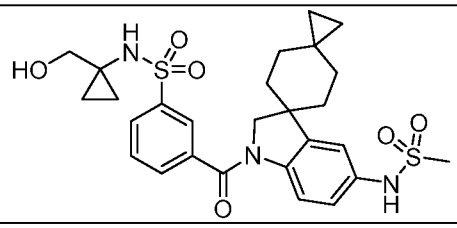
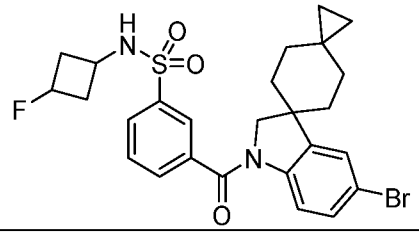
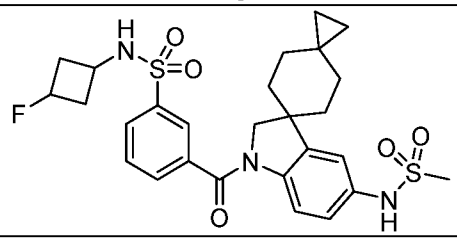
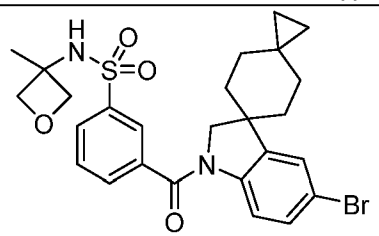
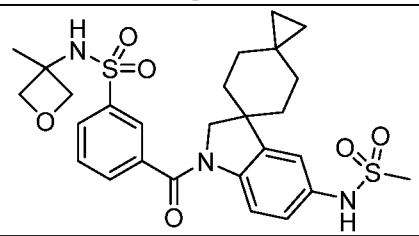
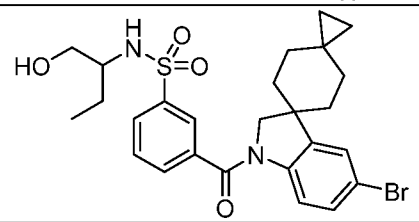
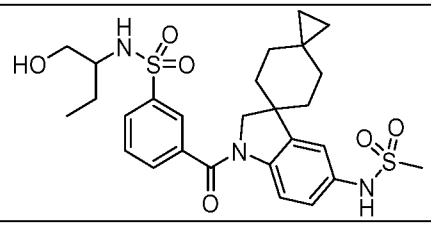
Compound No.	Structure	Name
Compound 168		N-cyclobutyl-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 169		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(sec-butyl)benzenesulfonamide
Compound 170		N-(sec-butyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 171		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(cyclopent-3-en-1-yl)benzenesulfonamide
Compound 172		N-(cyclopent-3-en-1-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 173		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(oxetan-3-yl)benzenesulfonamide

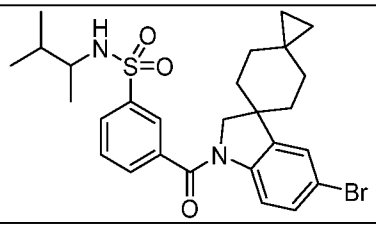
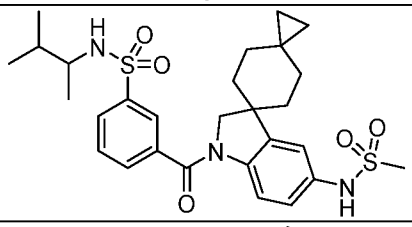
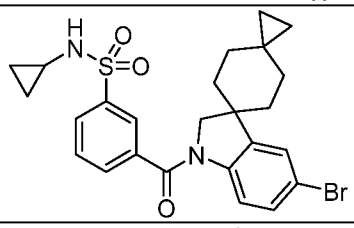
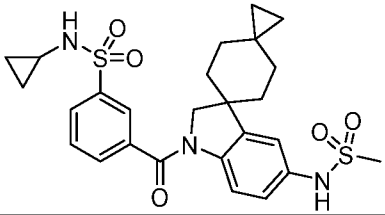
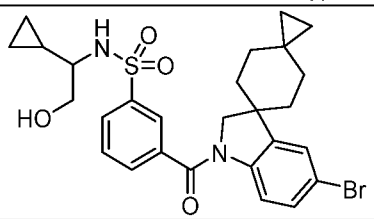
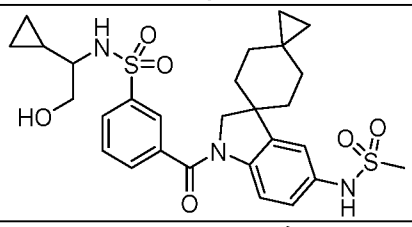
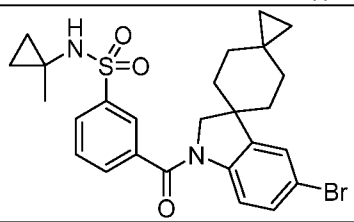
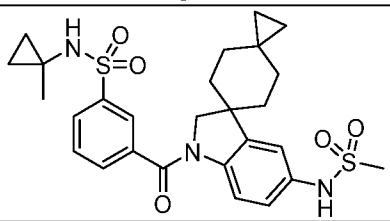
Compound No.	Structure	Name
Compound 174		3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(oxetan-3-yl)benzenesulfonamide
Compound 175		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-cyclopentylbenzenesulfonamide
Compound 176		N-cyclopentyl-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 177		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methyltetrahydrofuran-3-yl)benzenesulfonamide
Compound 178		3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methyltetrahydrofuran-3-yl)benzenesulfonamide
Compound 179		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-cyclohexylbenzenesulfonamide
Compound 180		N-cyclohexyl-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

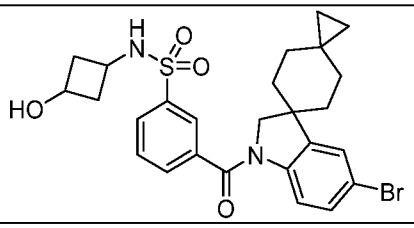
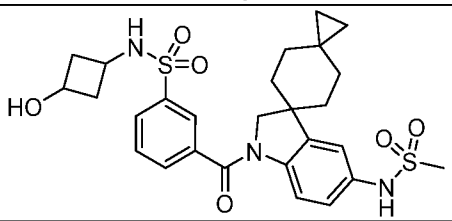
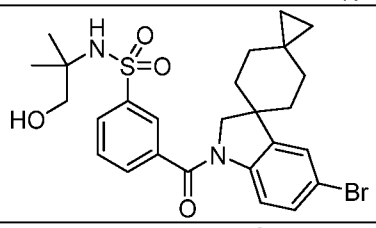
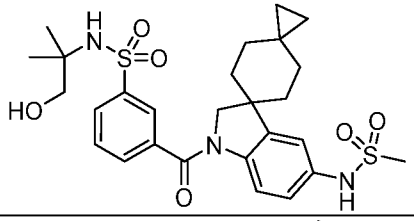
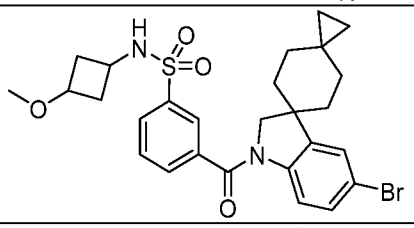
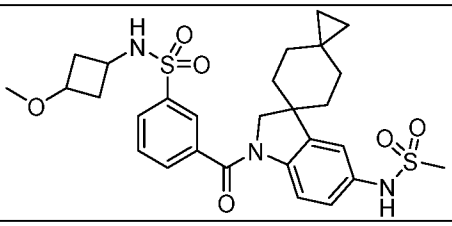
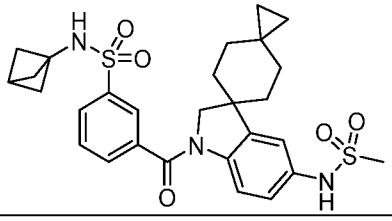
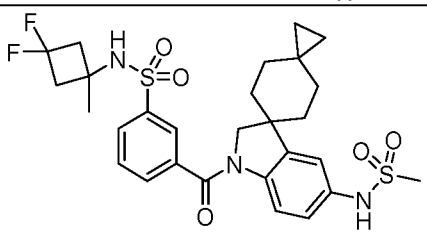
Compound No.	Structure	Name
Compound 181		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-methylcyclobutyl)benzenesulfonamide
Compound 182		N-(1-methylcyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 183		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-cyclobutylethyl)benzenesulfonamide
Compound 184		N-(1-cyclobutylethyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 185		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-cyclopropylethyl)benzenesulfonamide
Compound 186		N-(1-cyclopropylethyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 187		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(2,2-dimethyloxetan-3-yl)benzenesulfonamide
Compound 188		N-(2,2-dimethyloxetan-3-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

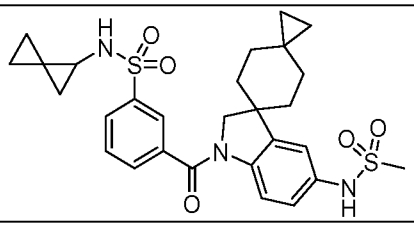
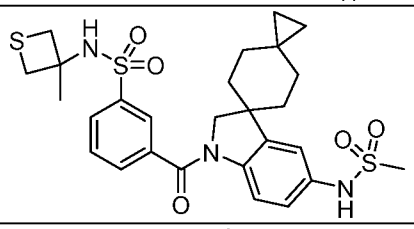
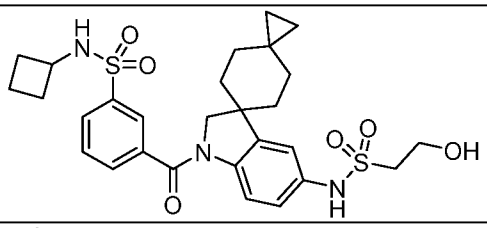
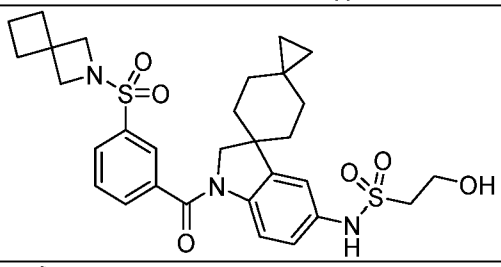
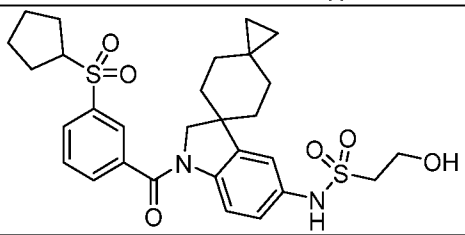
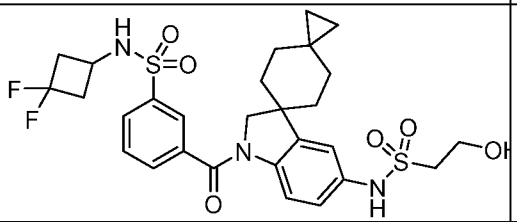
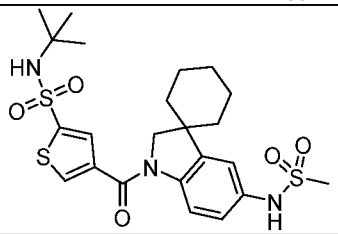
Compound No.	Structure	Name
Compound 189		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methylenecyclobutyl)benzenesulfonamide
Compound 190		N-(3-methylenecyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 191		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3,3-difluorocyclobutyl)benzenesulfonamide
Compound 192		N-(3,3-difluorocyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 193		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-hydroxy-2-methylpropan-2-yl)benzenesulfonamide
Compound 194		N-(1-hydroxy-2-methylpropan-2-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 195		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(cyclohex-2-en-1-yl)benzenesulfonamide

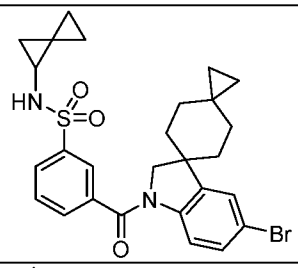
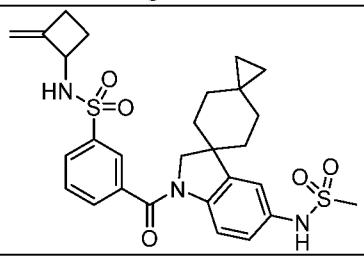
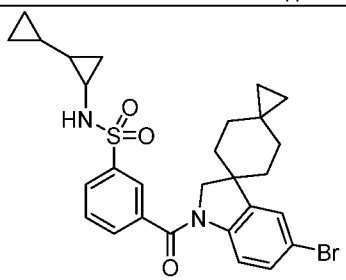
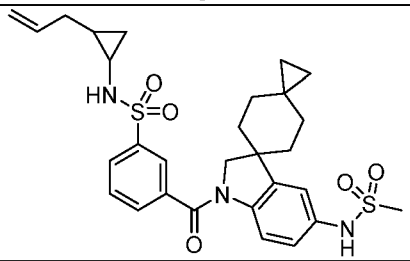
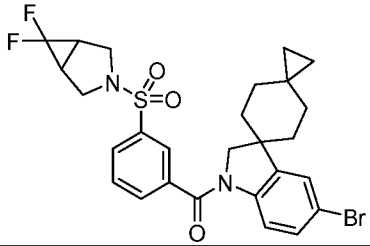
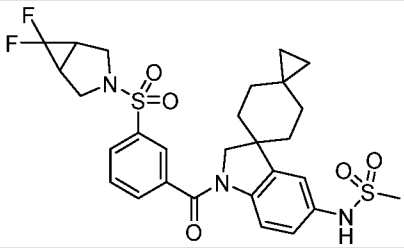
Compound No.	Structure	Name
Compound 196		N-(cyclohex-2-en-1-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 197		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(pentan-3-yl)benzenesulfonamide
Compound 198		3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(pentan-3-yl)benzenesulfonamide
Compound 199		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-methoxypropan-2-yl)benzenesulfonamide
Compound 200		N-(1-methoxypropan-2-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 201		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-(hydroxymethyl)cyclopropyl)benzenesulfonamide

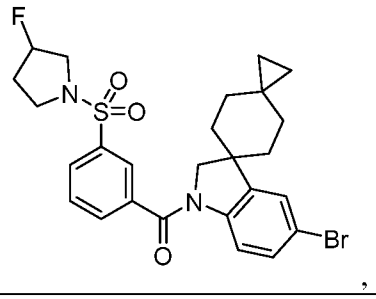
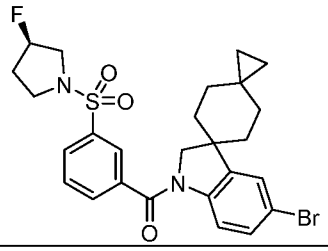
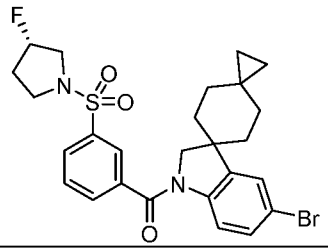
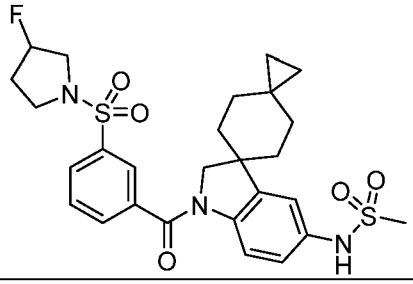
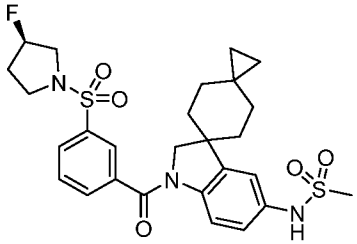
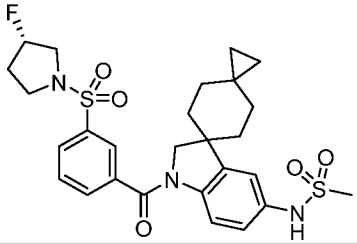
Compound No.	Structure	Name
Compound 202		N-(1-(hydroxymethyl)cyclopropyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 203		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-fluorocyclobutyl)benzenesulfonamide
Compound 204		N-(3-fluorocyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 205		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methyloxetan-3-yl)benzenesulfonamide
Compound 206		N-(3-methyloxetan-3-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 207		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-hydroxybutan-2-yl)benzenesulfonamide
Compound 208		N-(1-hydroxybutan-2-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

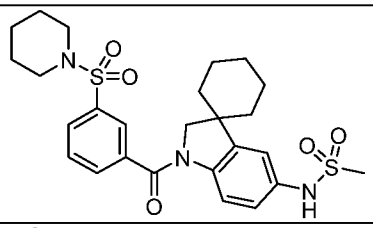
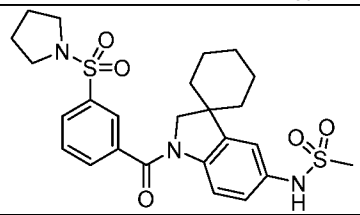
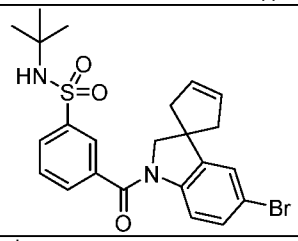
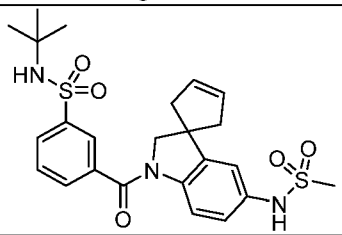
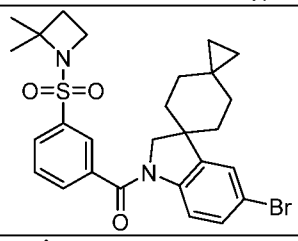
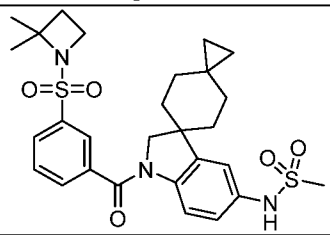
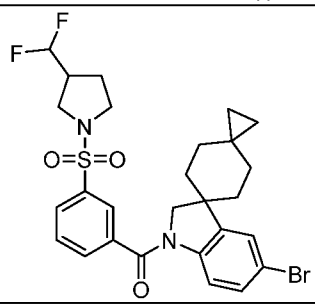
Compound No.	Structure	Name
Compound 209		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methylbutan-2-yl)benzenesulfonamide
Compound 210		N-(3-methylbutan-2-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 211		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-cyclopropylbenzenesulfonamide
Compound 212		N-cyclopropyl-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 213		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-cyclopropyl-2-hydroxyethyl)benzenesulfonamide
Compound 214		N-(1-cyclopropyl-2-hydroxyethyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 215		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-methylcyclopropyl)benzenesulfonamide
Compound 216		N-(1-methylcyclopropyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

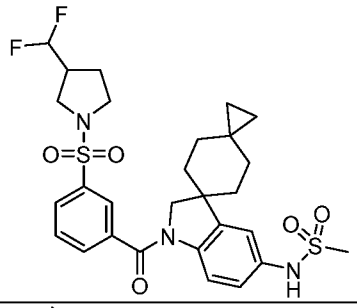
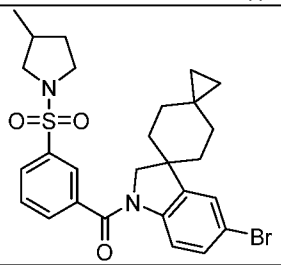
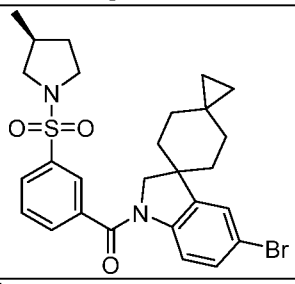
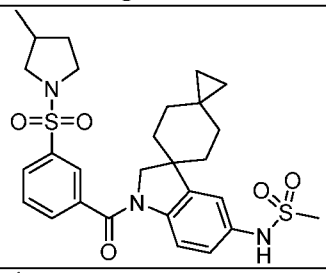
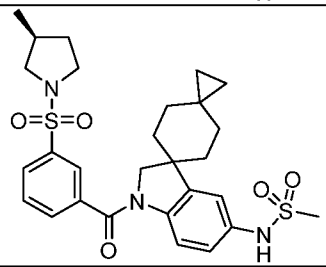
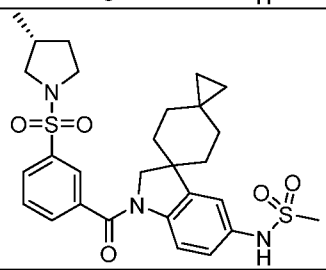
Compound No.	Structure	Name
Compound 217		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-hydroxycyclobutyl)benzenesulfonamide
Compound 218		N-(3-hydroxycyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 219		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-hydroxy-2-methylpropan-2-yl)benzenesulfonamide
Compound 220		N-(1-hydroxy-2-methylpropan-2-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 221		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methoxycyclobutyl)benzenesulfonamide
Compound 222		N-(3-methoxycyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 223		N-(bicyclo[1.1.1]pentan-1-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 224		N-(3,3-difluoro-1-methylcyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

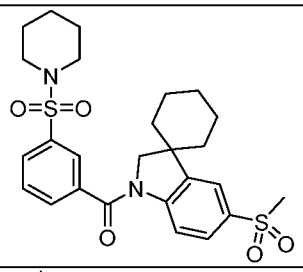
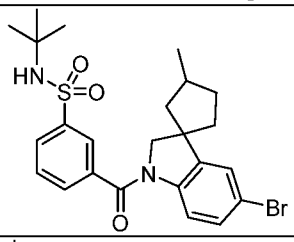
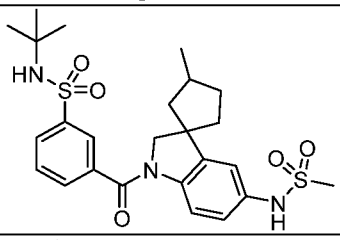
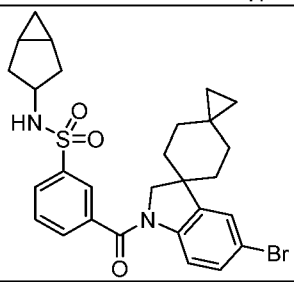
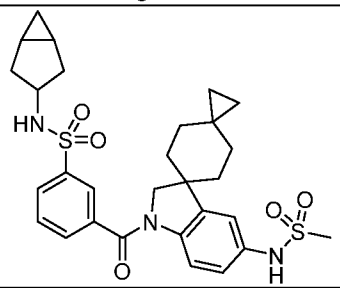
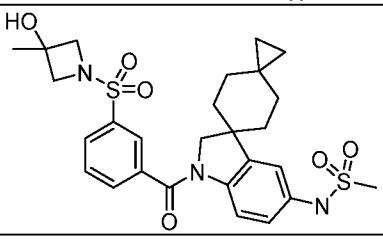
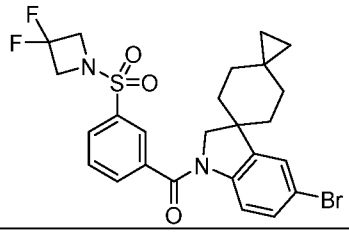
Compound No.	Structure	Name
Compound 225		3-(5"-(methylsulfonamido)dispiro [cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(spiro[2.2]pentan-1-yl)benzenesulfonamide
Compound 226		3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(3-methylthietan-3-yl)benzenesulfonamide
Compound 227		N-cyclobutyl-3-(5"-((2-hydroxyethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 228		N-(1"-(3-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)-2-hydroxyethane-1-sulfonamide
Compound 229		N-(1"-(3-(cyclopentylsulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)-2-hydroxyethane-1-sulfonamide
Compound 230		N-(3,3-difluorocyclobutyl)-3-(5"-((2-hydroxyethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 231		N-(tert-butyl)-4-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)thiophene-2-sulfonamide

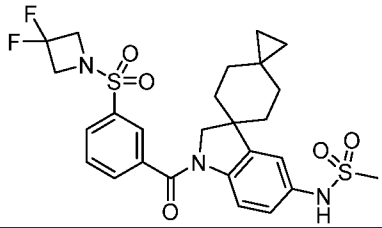
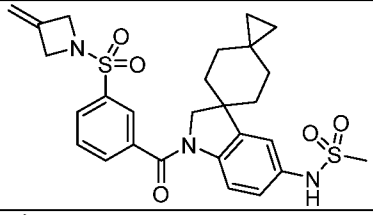
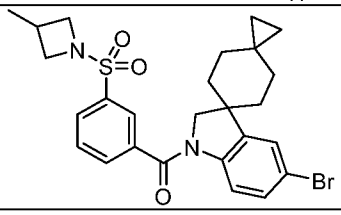
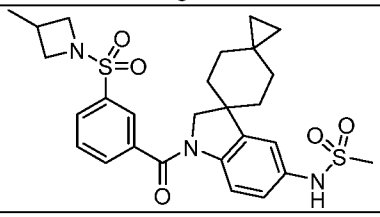
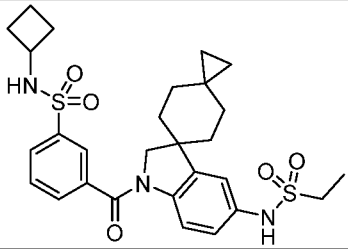
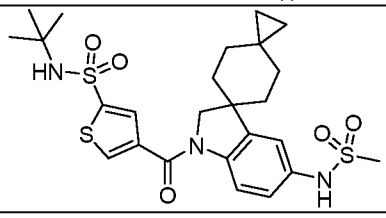
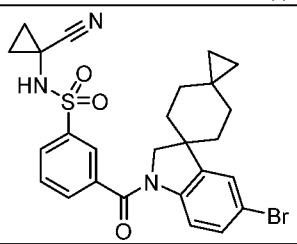
Compound No.	Structure	Name
Compound 232		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(spiro[2.2]pentan-1-yl)benzenesulfonamide
Compound 233		N-(2-methylenecyclobutyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 234		N-([1,1'-bi(cyclopropan)]-2-yl)-3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 235		N-(2-allylcyclopropyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 236		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)phenyl)methanone
Compound 237		N-(1"-(3-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

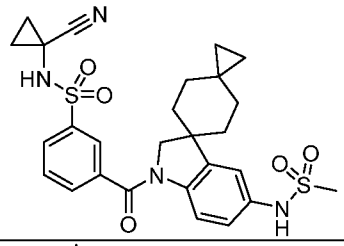
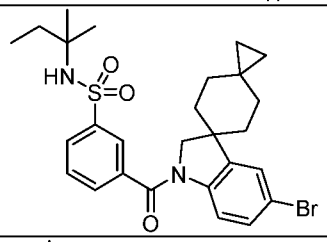
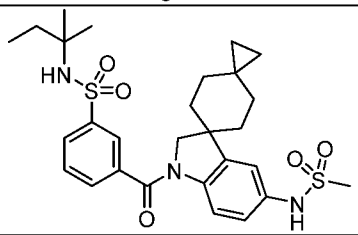
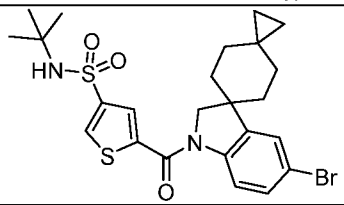
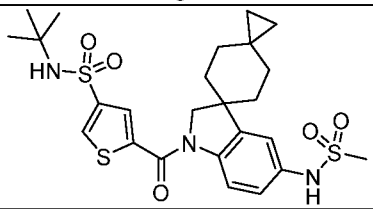
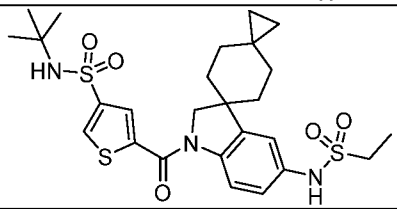
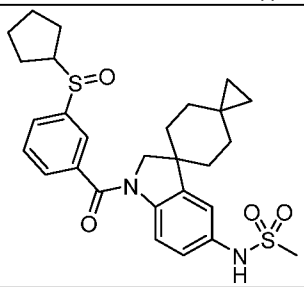
Compound No.	Structure	Name
Compound 238		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-fluoropyrrolidin-1-yl)sulfonyl)phenyl)methanone
(R)-Compound 238		(R)-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-fluoropyrrolidin-1-yl)sulfonyl)phenyl)methanone
(S)-Compound 238		(S)-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-fluoropyrrolidin-1-yl)sulfonyl)phenyl)methanone
Compound 239		N-(1"-(3-((3-fluoropyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 239		(R)-N-(1"-(3-((3-fluoropyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 239		(S)-N-(1"-(3-((3-fluoropyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

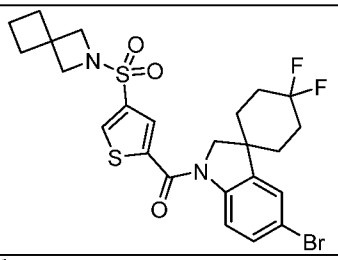
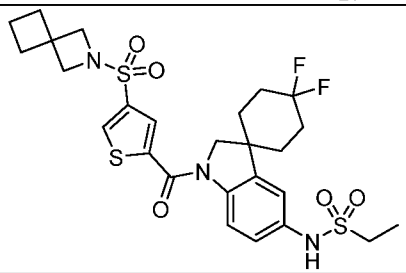
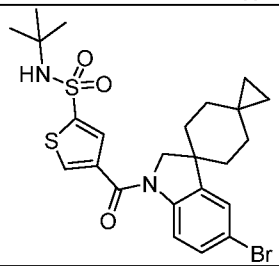
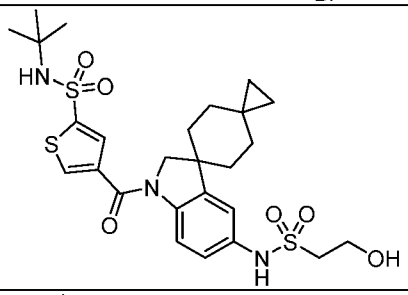
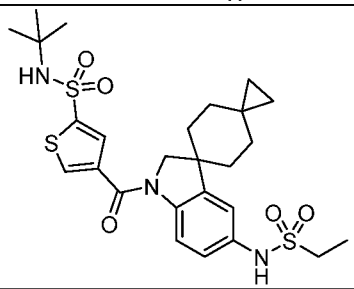
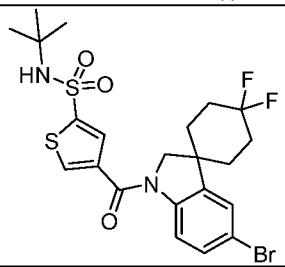
Compound No.	Structure	Name
Compound 240		N-(1'-(3-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 241		N-(1'-(3-(pyrrolidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide
Compound 242		3-(5'-bromospiro[cyclopentane-1,3'-indolin]-3-en-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 243		N-(tert-butyl)-3-(5'-(methylsulfonamido)spiro[cyclopentane-1,3'-indolin]-3-en-1'-carbonyl)benzenesulfonamide
Compound 244		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((2,2-dimethylazetidin-1-yl)sulfonyl)phenyl)methanone
Compound 245		N-(1"-(3-((2,2-dimethylazetidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 246		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-(difluoromethyl)pyrrolidin-1-yl)sulfonyl)phenyl)methanone

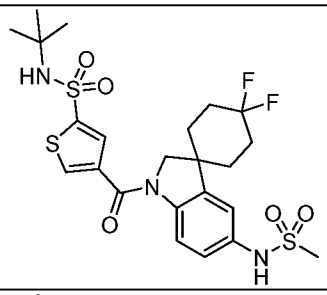
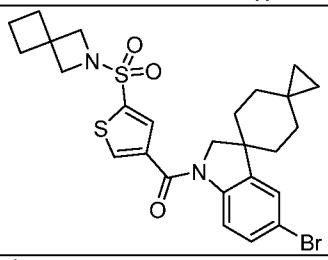
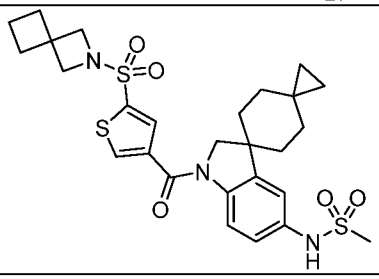
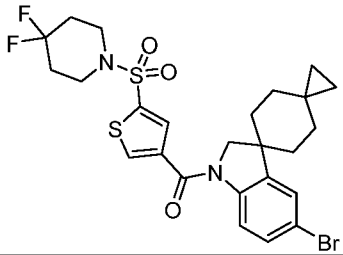
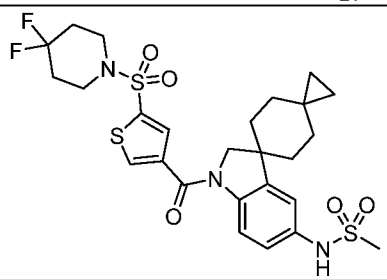
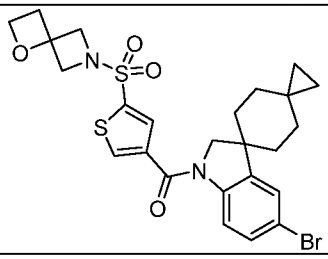
Compound No.	Structure	Name
Compound 247		N-(1"-(3-((3-(difluoromethyl)pyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 248		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-methylpyrrolidin-1-yl)sulfonyl)phenyl)methanone
(S)-Compound 248		(S)-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-methylpyrrolidin-1-yl)sulfonyl)phenyl)methanone
Compound 249		N-(1"-(3-((3-methylpyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 249		(S)-N-(1"-(3-((3-methylpyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 249		(R)-N-(1"-(3-((3-methylpyrrolidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

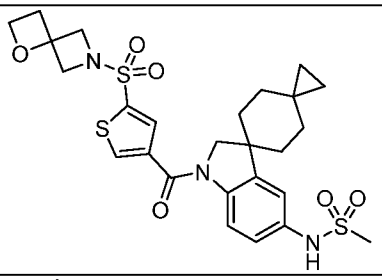
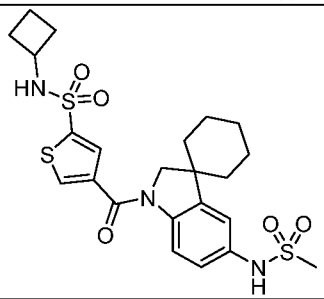
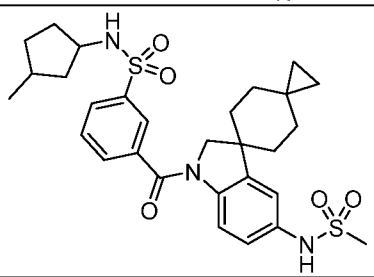
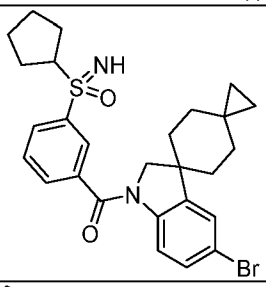
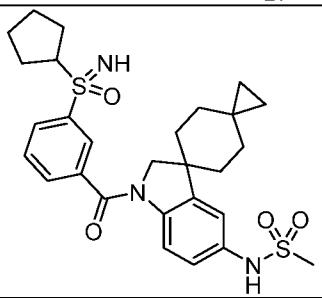
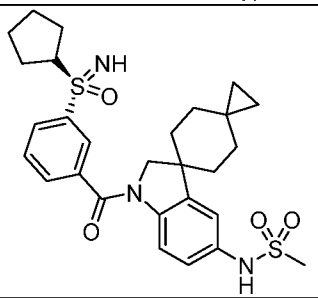
Compound No.	Structure	Name
Compound 250		(5'-(methylsulfonyl)spiro[cyclohexane-1,3'-indolin]-1'-yl)(3-(piperidin-1-ylsulfonyl)phenyl)methanone
Compound 251		3-(5'-bromo-3-methylspiro[cyclopentane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 252		N-(tert-butyl)-3-(3-methyl-5'-(methylsulfonamido)spiro[cyclopentane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 253		N-(bicyclo[3.1.0]hexan-3-yl)-3-(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 254		N-(bicyclo[3.1.0]hexan-3-yl)-3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 255		N-(1''-(3-((3-hydroxy-3-methylazetidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 256		(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)(3-((3,3-difluoroazetidin-1-yl)sulfonyl)phenyl)methanone

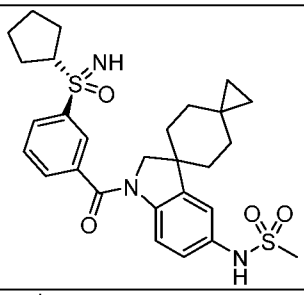
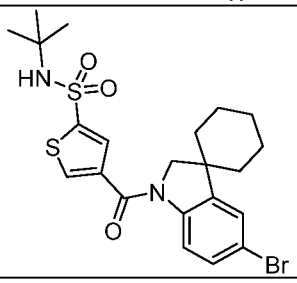
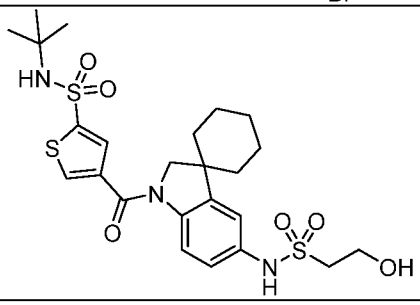
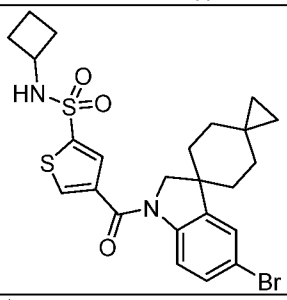
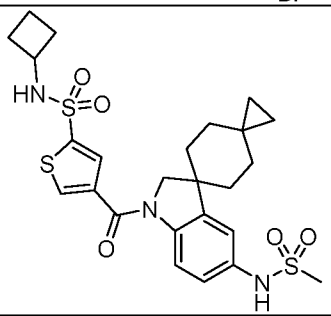
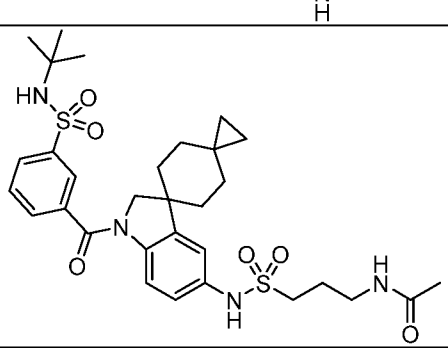
Compound No.	Structure	Name
Compound 257		N-(1"-(3-((3,3-difluoroazetidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 258		N-(1"-(3-((3-methyleneazetidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 259		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(3-((3-methylazetidin-1-yl)sulfonyl)phenyl)methanone
Compound 260		N-(1"-(3-((3-methylazetidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 261		N-cyclobutyl-3-(5"-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 262		N-(tert-butyl)-4-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)thiophene-2-sulfonamide
Compound 263		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(1-cyanocyclopropyl)benzenesulfonamide

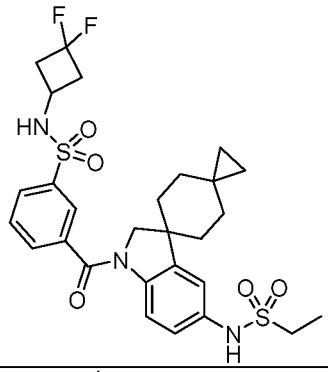
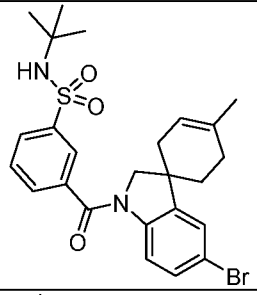
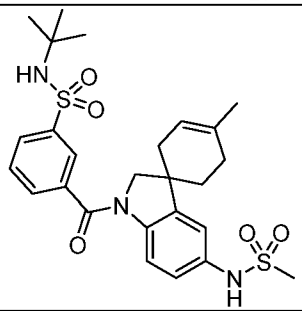
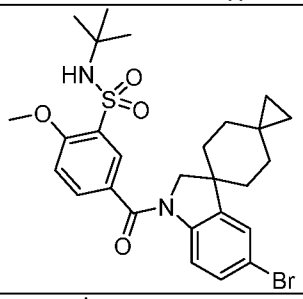
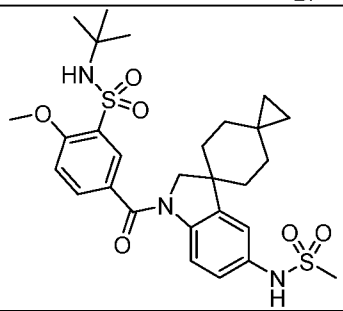
Compound No.	Structure	Name
Compound 264		N-(1-cyanocyclopropyl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 265		3-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-pentyl)benzenesulfonamide
Compound 266		3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-pentyl)benzenesulfonamide
Compound 267		5-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-butyl)thiophene-3-sulfonamide
Compound 268		N-(tert-butyl)-5-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)thiophene-3-sulfonamide
Compound 269		N-(tert-butyl)-5-(5"-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)thiophene-3-sulfonamide
Compound 270		N-(1"-(3-(cyclopentylsulfinyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

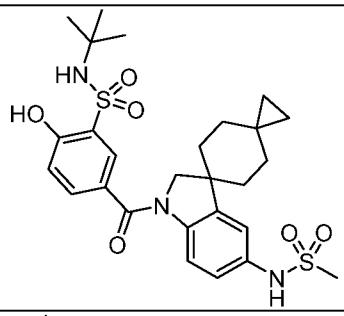
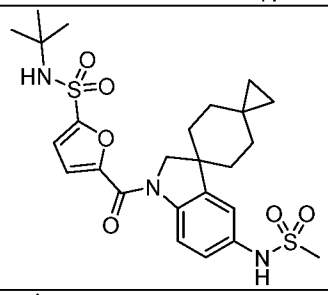
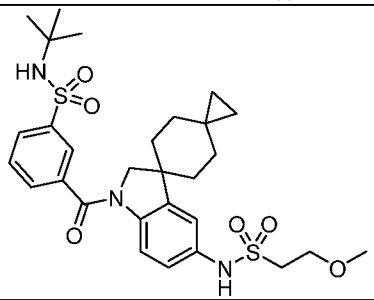
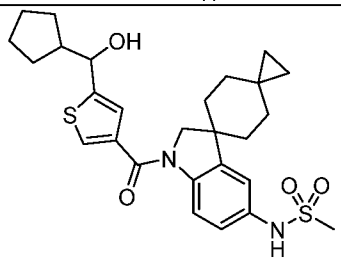
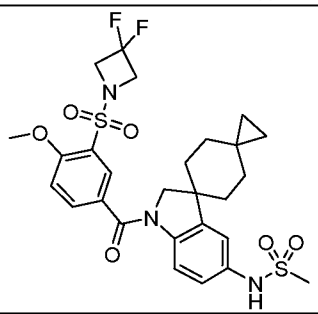
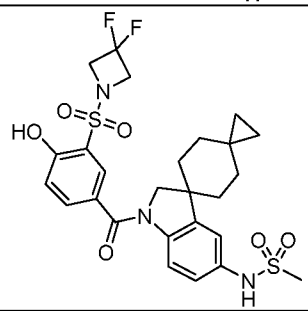
Compound No.	Structure	Name
Compound 271		(4-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)thiophen-2-yl)(5'-bromo-4,4-difluorospiro[cyclohexane-1,3'-indolin]-1'-yl)methanone
Compound 272		N-(1'-(4-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)thiophene-2-carbonyl)-4,4-difluorospiro[cyclohexane-1,3'-indolin]-5'-yl)ethanesulfonamide
Compound 273		4-(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-butyl)thiophene-2-sulfonamide
Compound 274		N-(tert-butyl)-4-(5"-((2-hydroxyethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)thiophene-2-sulfonamide
Compound 275		N-(tert-butyl)-4-(5"-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)thiophene-2-sulfonamide
Compound 276		4-(5'-bromo-4,4-difluorospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)thiophene-2-sulfonamide

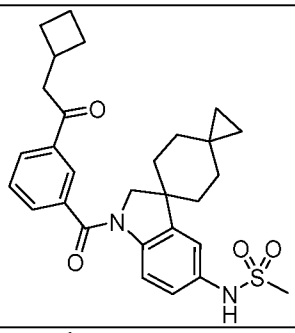
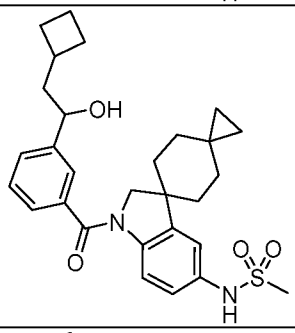
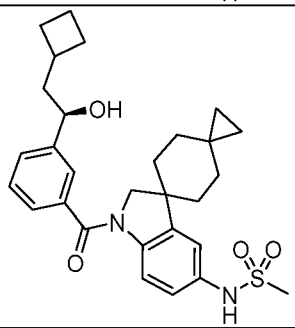
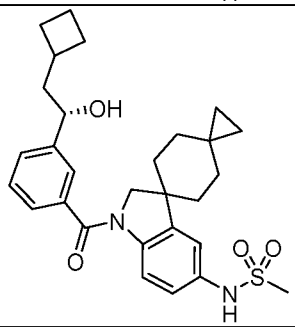
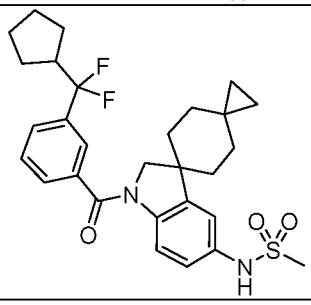
Compound No.	Structure	Name
Compound 277		N-(tert-butyl)-4-(4,4-difluoro-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)thiophene-2-sulfonamide
Compound 278		(5-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)thiophen-3-yl)(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)methanone
Compound 279		N-(1"-(5-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 280		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(5-((4,4-difluoropiperidin-1-yl)sulfonyl)thiophen-3-yl)methanone
Compound 281		N-(1"-(5-((4,4-difluoropiperidin-1-yl)sulfonyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 282		(5-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)thiophen-3-yl)(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)methanone

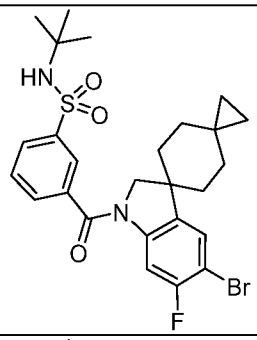
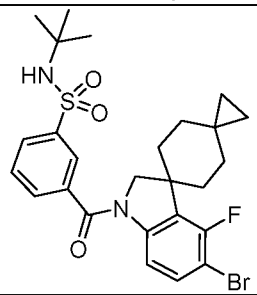
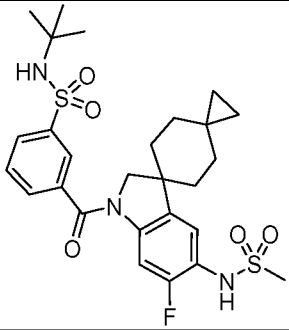
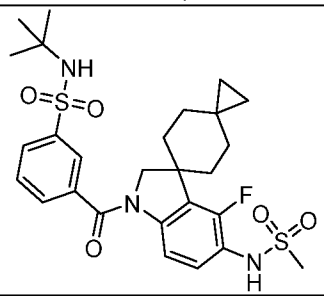
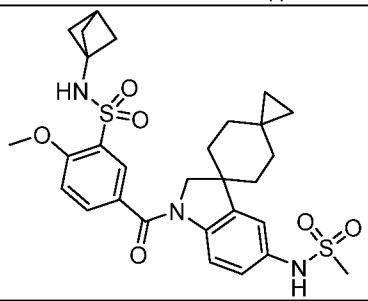
Compound No.	Structure	Name
Compound 283		N-(1''-(5-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 284		N-cyclobutyl-4-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)thiophene-2-sulfonamide
Compound 285		N-(3-methylcyclopentyl)-3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 286		(3-(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)phenyl)(cyclopentyl)(imino)-l6-sulfanone
Compound 287		N-(1''-(3-(cyclopentanesulfonimidoyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
(R)-Compound 287		(R)-N-(1''-(3-(cyclopentanesulfonimidoyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

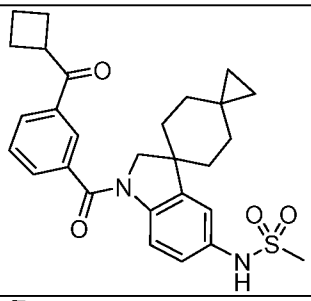
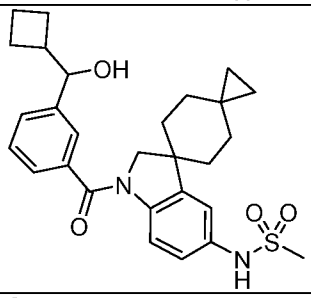
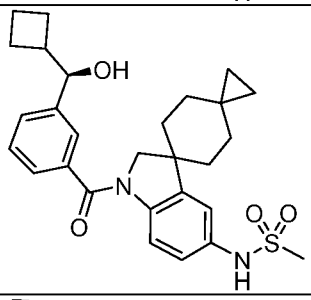
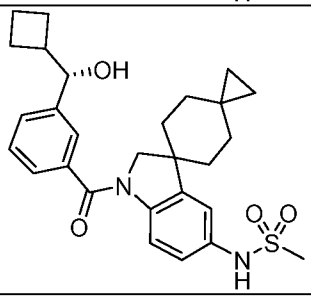
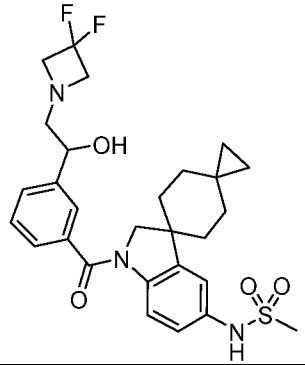
Compound No.	Structure	Name
(S)-Compound 287		(S)-N-(1''-(3-(cyclopentanesulfonimidoyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 288		4-(5'-bromospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)thiophene-2-sulfonamide
Compound 289		N-(tert-butyl)-4-(5'-((2-hydroxyethyl)sulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)thiophene-2-sulfonamide
Compound 290		4-(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)-N-cyclobutylthiophene-2-sulfonamide
Compound 291		N-cyclobutyl-4-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)thiophene-2-sulfonamide
Compound 292		N-(3-(N-(1''-(3-(N-(tert-butyl)sulfamoyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)sulfamoyl)propyl)acetamide

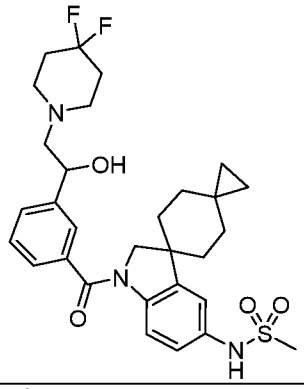
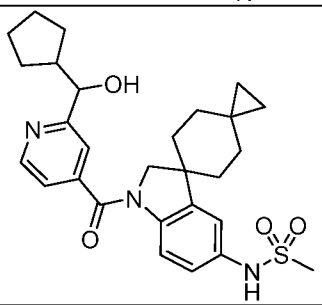
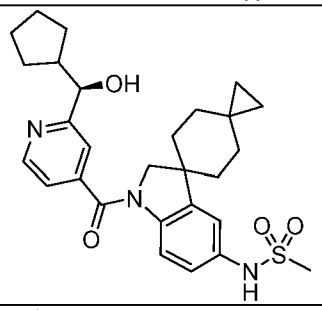
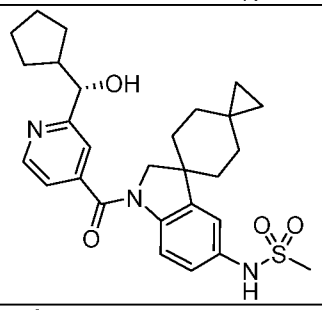
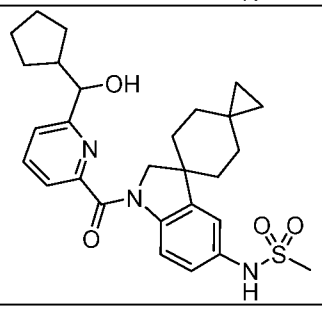
Compound No.	Structure	Name
Compound 293		N-(3,3-difluorocyclobutyl)-3-(5''-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 294		3-(5'-bromo-4-methylspiro[cyclohexane-1,3'-indolin]-3-en-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 295		N-(tert-butyl)-3-(4-methyl-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indolin]-3-en-1'-carbonyl)benzenesulfonamide
Compound 296		5-(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)-N-(tert-butyl)-2-methoxybenzenesulfonamide
Compound 297		N-(tert-butyl)-2-methoxy-5-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide

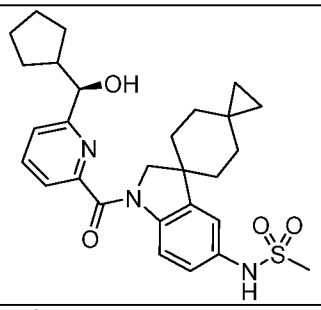
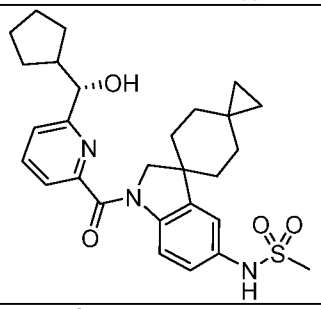
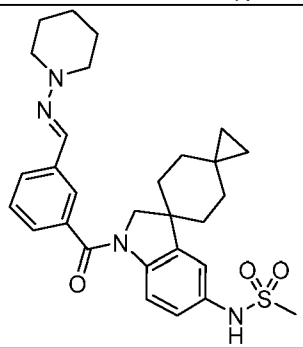
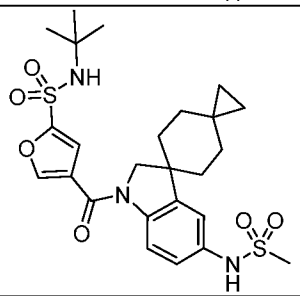
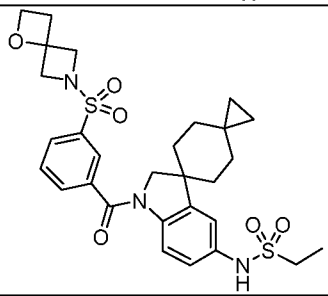
Compound No.	Structure	Name
Compound 298		N-(tert-butyl)-2-hydroxy-5-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 299		N-(tert-butyl)-5-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)furan-2-sulfonamide
Compound 300		*N*-(*tert*-butyl)-3-(5''-((2-methoxyethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide
Compound 301		N-(1''-(5-(cyclopentyl(hydroxy)methyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 302		N-(1''-(3-((3,3-difluoroazetidin-1-yl)sulfonyl)-4-methoxybenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 303		N-(1''-(3-((3,3-difluoroazetidin-1-yl)sulfonyl)-4-hydroxybenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

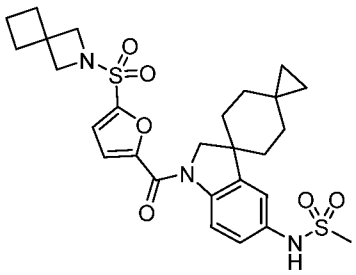
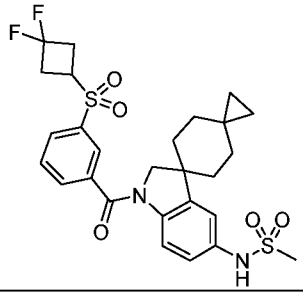
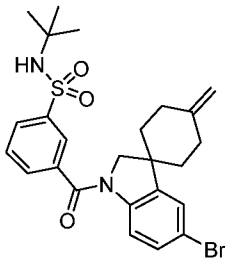
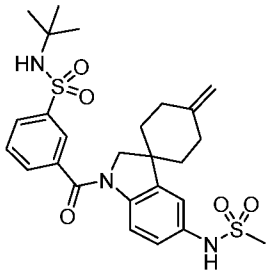
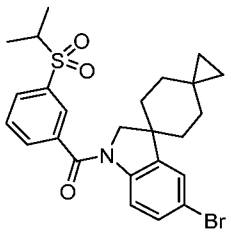
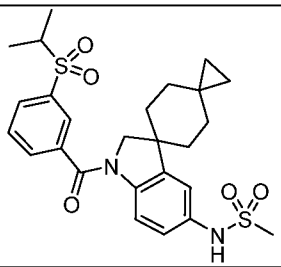
Compound No.	Structure	Name
Compound 304		N-(1"-(3-(2-cyclobutylacetyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 305		N-(1"-(3-(2-cyclobutyl-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 305		(R)-N-(1"-(3-(2-cyclobutyl-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 305		(S)-N-(1"-(3-(2-cyclobutyl-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 306		N-(1"-(3-(cyclopentyldifluoromethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

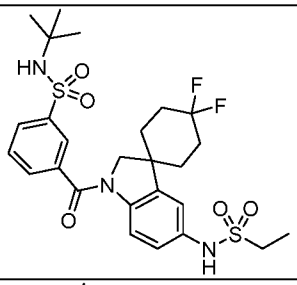
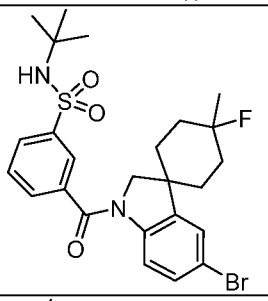
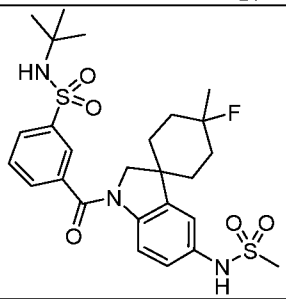
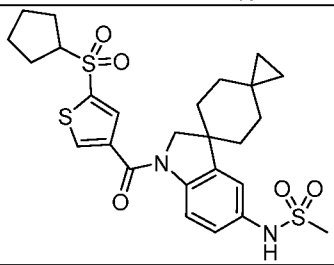
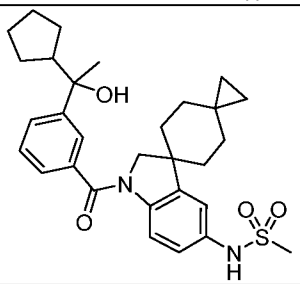
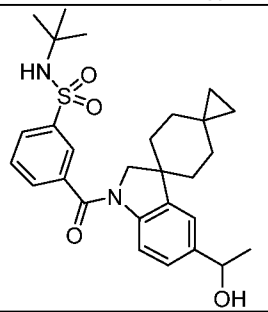
Compound No.	Structure	Name
Compound 307		3-(5"-bromo-6"-fluorodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 308		3-(5"-bromo-4"-fluorodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 309		N-(tert-butyl)-3-(6"-fluoro-5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 310		N-(tert-butyl)-3-(4"-fluoro-5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 311		N-(bicyclo[1.1.1]pentan-1-yl)-2-methoxy-5-(5"-(methylsulfonamido) dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

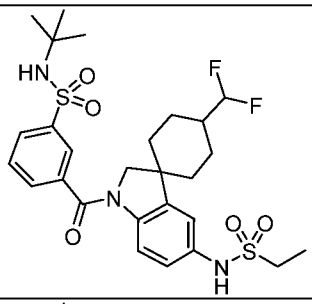
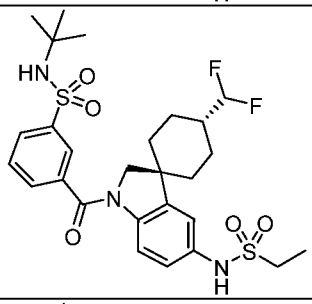
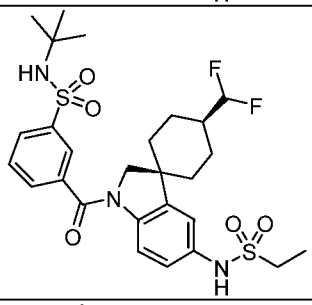
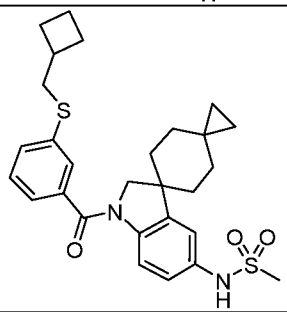
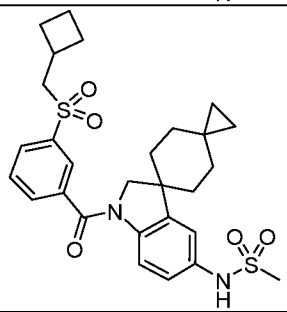
Compound No.	Structure	Name
Compound 312		N-(1"-(3-(cyclobutanecarbonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 313		N-(1"-(3-(cyclobutyl(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 313		(R)-N-(1"-(3-(cyclobutyl(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 313		(S)-N-(1"-(3-(cyclobutyl(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 314		N-(1"-(3-(2-(3,3-difluoroazetidin-1-yl)-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

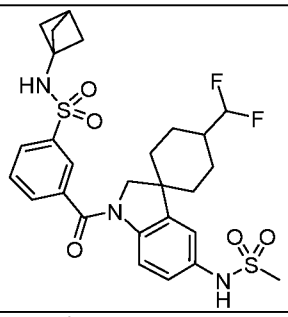
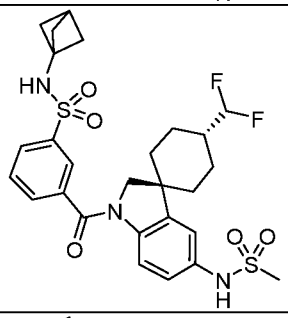
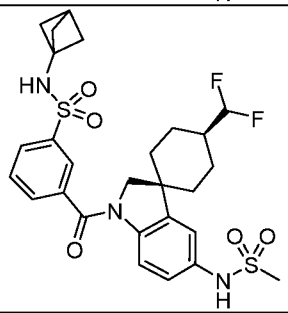
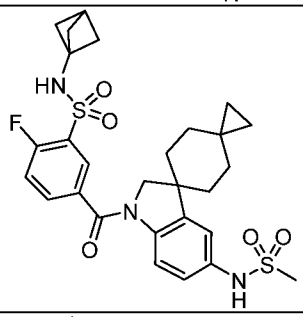
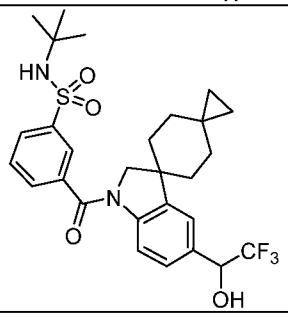
Compound No.	Structure	Name
Compound 315		N-(1"-(3-(2-(4,4-difluoropiperidin-1-yl)-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 316		N-(1"-(2-(cyclopentyl(hydroxy)methyl)isonicotinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 316		(R)- N-(1"-(2-(cyclopentyl(hydroxy)methyl)isonicotinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 316		(S)-N-(1"-(2-(cyclopentyl(hydroxy)methyl)isonicotinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 317		N-(1"-(6-(cyclopentyl(hydroxy)methyl)picolinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

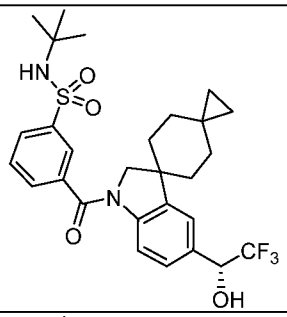
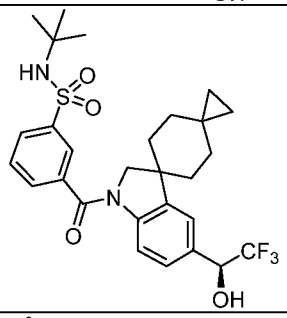
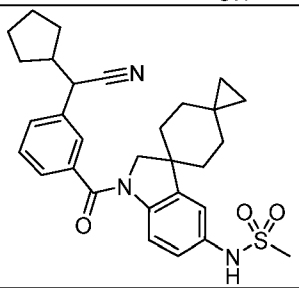
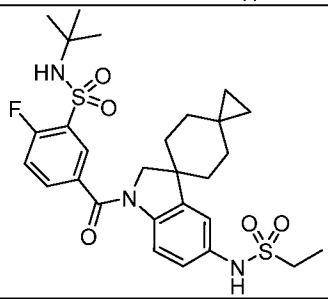
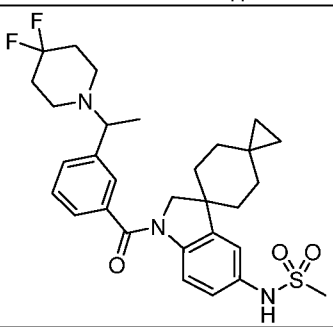
Compound No.	Structure	Name
(R)-Compound 317		(R)-N-(1''-(6-(cyclopentyl(hydroxy)methyl)picolinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
(S)-Compound 317		(S)-N-(1''-(6-(cyclopentyl(hydroxy)methyl)picolinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 318		N-(1''-(3-((piperidin-1-ylimino)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 319		N-(tert-butyl)-4-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)furan-2-sulfonamide
Compound 320		N-(1''-(3-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide

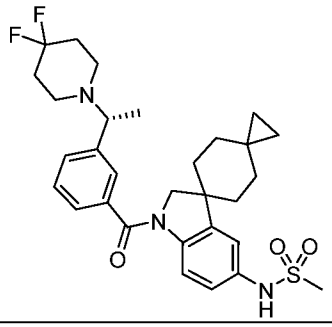
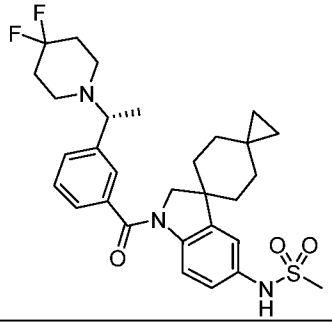
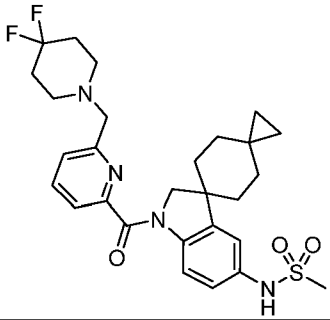
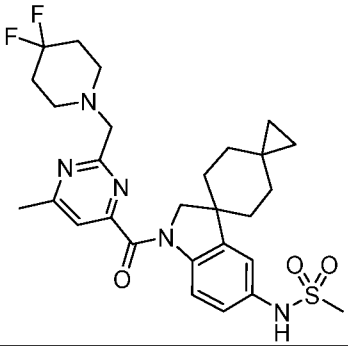
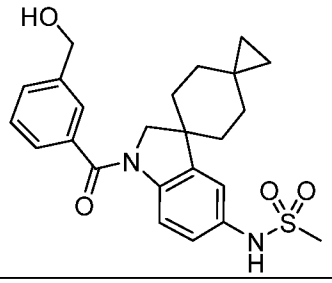
Compound No.	Structure	Name
Compound 321		N-(1''-(5-((2-azaspiro[3.3]heptan-2-yl)sulfonyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 322		N-(1''-(3-((3,3-difluorocyclobutyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 323		3-(5'-bromo-4-methylenespiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 324		N-(tert-butyl)-3-(4-methylene-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 325		(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)(3-(isopropylsulfonyl)phenyl)methanone
Compound 326		N-(1''-(3-(isopropylsulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

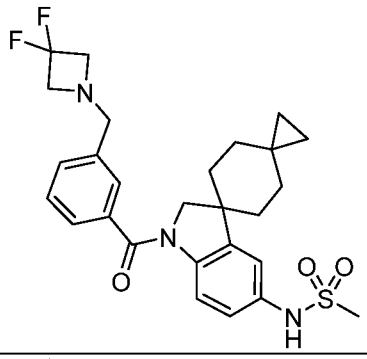
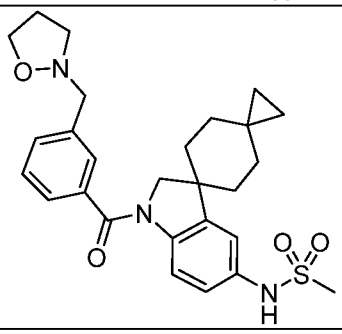
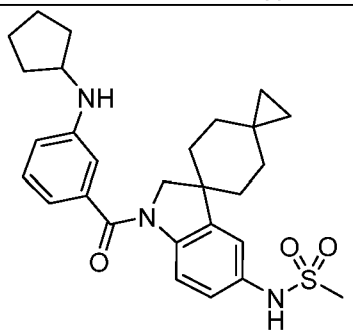
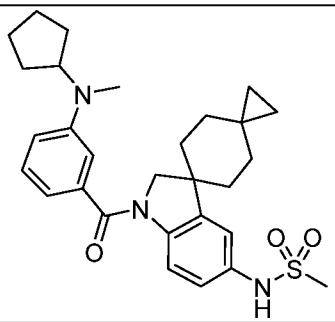
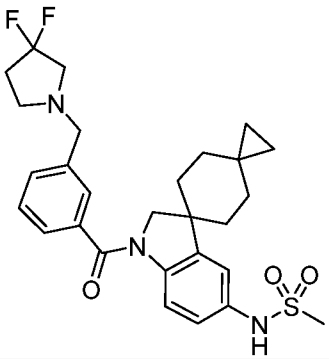
Compound No.	Structure	Name
Compound 327		N-(tert-butyl)-3-(5'-(ethylsulfonamido)-4,4-difluorospiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 328		3-(5'-bromo-4-fluoro-4-methylspiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
Compound 329		N-(tert-butyl)-3-(4-fluoro-4-methyl-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 330		N-(1''-(5-(cyclopentylsulfonyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 331		N-(1''-(3-(1-cyclopentyl-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 332		N-(tert-butyl)-3-(5''-(1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide

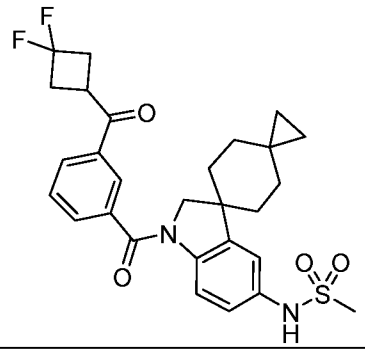
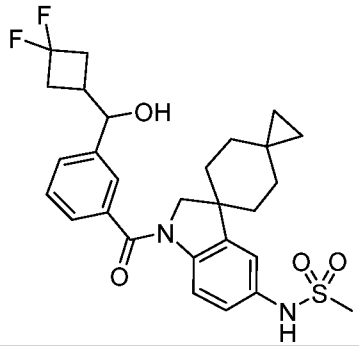
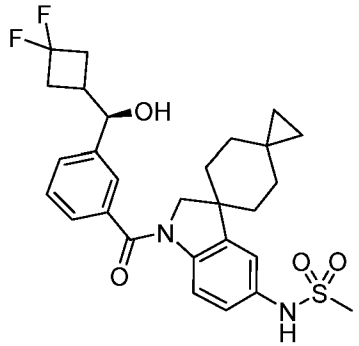
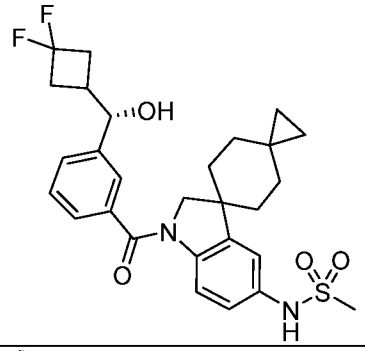
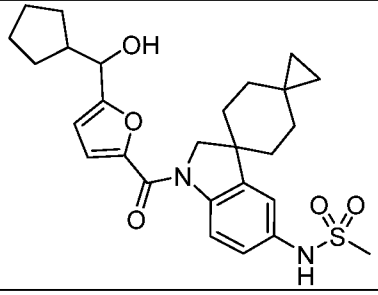
Compound No.	Structure	Name
Compound 333		N-(tert-butyl)-3-(4-(difluoromethyl)-5'-(ethylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1r,4r)-Compound 333		N-(tert-butyl)-3-((1r,4r)-4-(difluoromethyl)-5'-(ethylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1r,4r)-Compound 333		N-(tert-butyl)-3-((1s,4s)-4-(difluoromethyl)-5'-(ethylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 334		N-(1''-(3-((cyclobutylmethyl)thio)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 335		N-(1''-(3-((cyclobutylmethyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

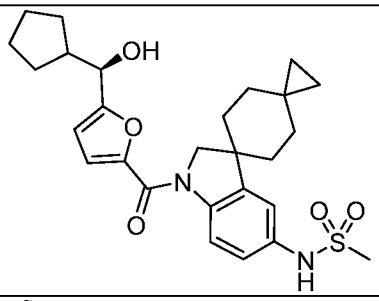
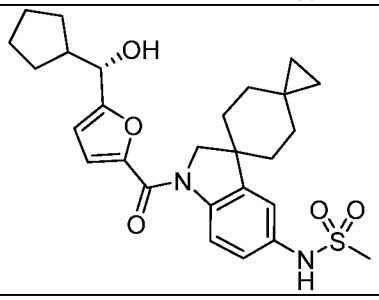
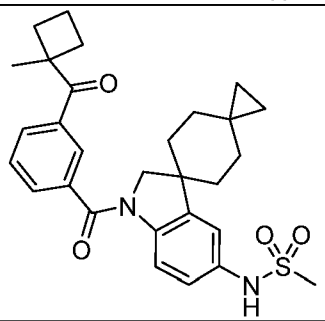
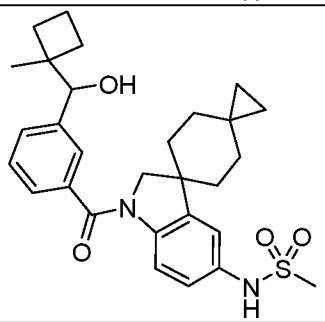
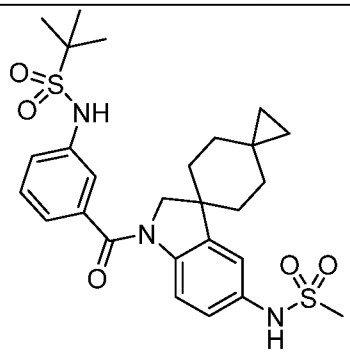
Compound No.	Structure	Name
Compound 336		N-(bicyclo[1.1.1]pentan-1-yl)-3-(4-(difluoromethyl)-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1r,4r)-Compound 336		N-(bicyclo[1.1.1]pentan-1-yl)-3-((1r,4r)-4-(difluoromethyl)-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1s,4s)-Compound 336		N-(bicyclo[1.1.1]pentan-1-yl)-3-((1s,4s)-4-(difluoromethyl)-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 337		N-(bicyclo[1.1.1]pentan-1-yl)-2-fluoro-5-(5"-(methylsulfonamido) dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 338		N-(tert-butyl)-3-(5"-(2,2,2-trifluoro-1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

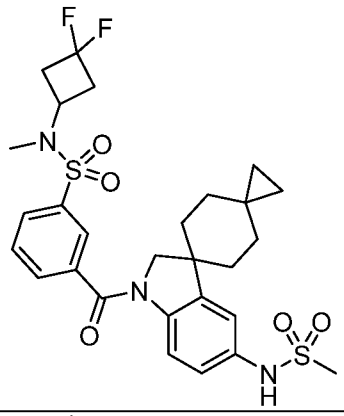
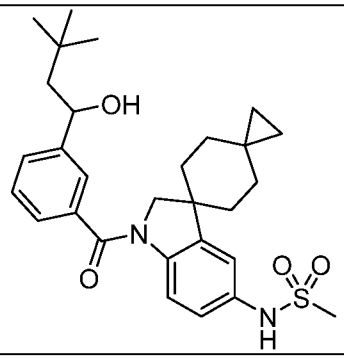
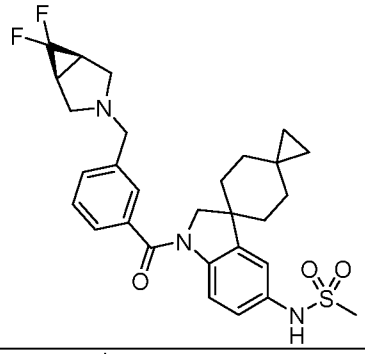
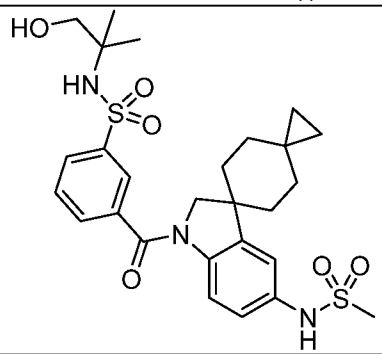
Compound No.	Structure	Name
(R)-Compound 338		(R)-N-(tert-butyl)-3-(5"-(2,2,2-trifluoro-1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
(S)-Compound 338		(S)-N-(tert-butyl)-3-(5"-(2,2,2-trifluoro-1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 339		N-(1"-(3-(cyano(cyclopentyl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 340		N-(tert-butyl)-5-(5"-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)-2-fluorobenzenesulfonamide
Compound 341		N-(1"-(3-(1-(4,4-difluoropiperidin-1-yl)ethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

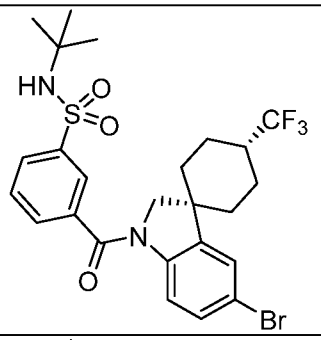
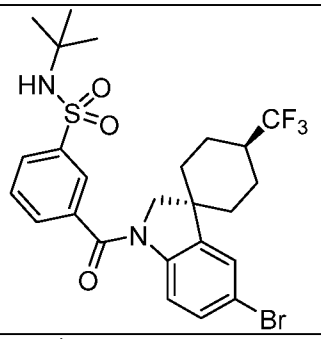
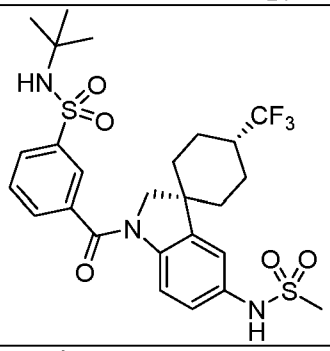
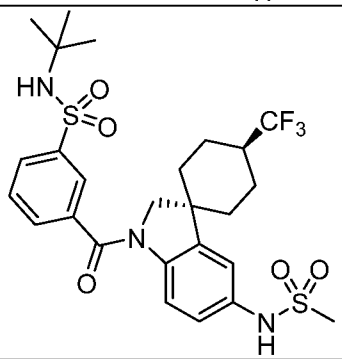
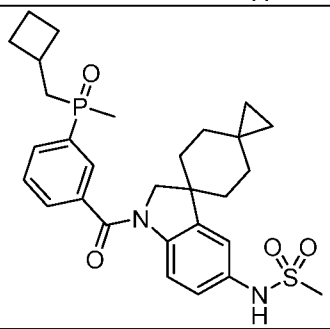
Compound No.	Structure	Name
(R)-Compound 341		(R)-N-(1"-(3-(1-(4,4-difluoropiperidin-1-yl)ethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 341		(S)-N-(1"-(3-(1-(4,4-difluoropiperidin-1-yl)ethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 342		N-(1"-(6-((4,4-difluoropiperidin-1-yl)methyl)picolinoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 343		N-(1"-(2-((4,4-difluoropiperidin-1-yl)methyl)-6-methylpyrimidine-4-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 344		N-(1"-(3-(hydroxymethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

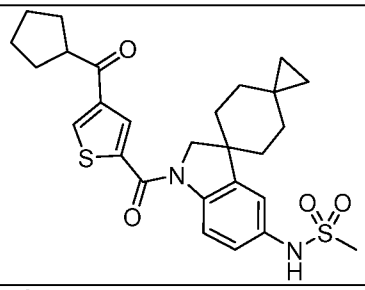
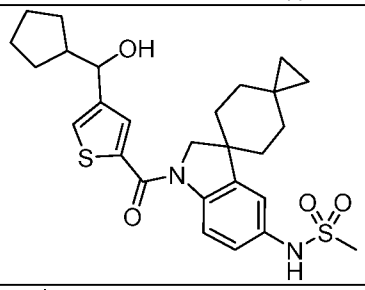
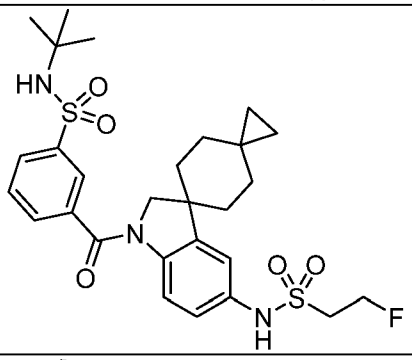
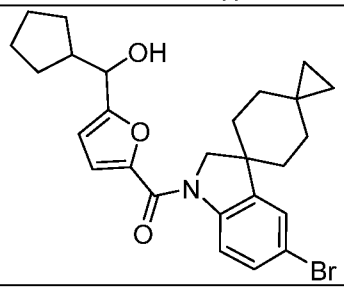
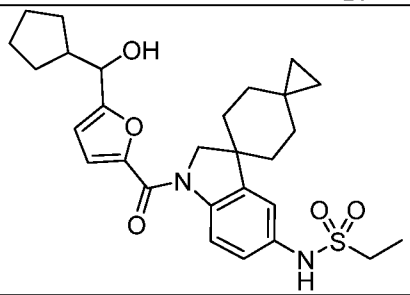
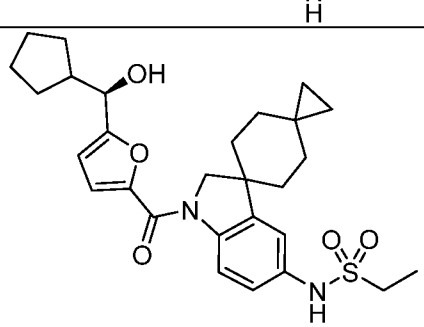
Compound No.	Structure	Name
Compound 345		N-(1"-(3-((3,3-difluoroazetidin-1-yl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 346		N-(1"-(3-(isoxazolidin-2-ylmethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 347		N-(1"-(3-(cyclopentylamino)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 348		N-(1"-(3-(cyclopentyl(methyl)amino)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 349		N-(1"-(3-((3,3-difluoropyrrolidin-1-yl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

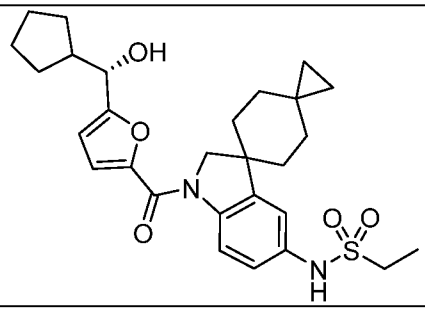
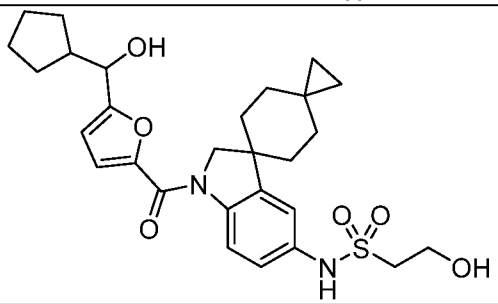
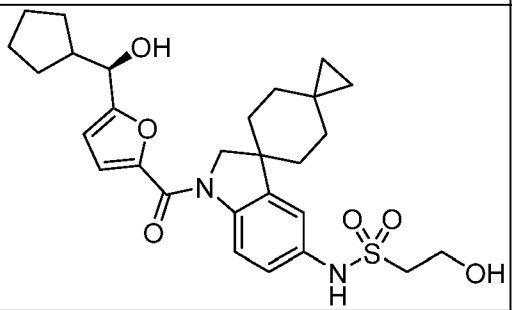
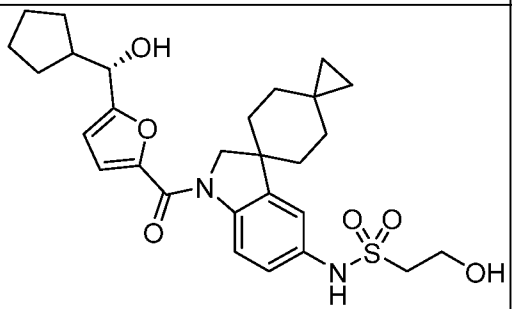
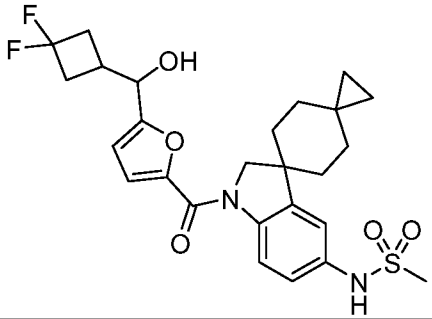
Compound No.	Structure	Name
Compound 350		N-(1"-(3-(3,3-difluorocyclobutane-1-carbonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 351		N-(1"-(3-((3,3-difluorocyclobutyl)(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 351		(R)-N-(1"-(3-((3,3-difluorocyclobutyl)(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 351		(S)-N-(1"-(3-((3,3-difluorocyclobutyl)(hydroxy)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 352		N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

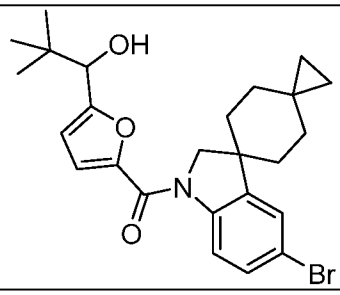
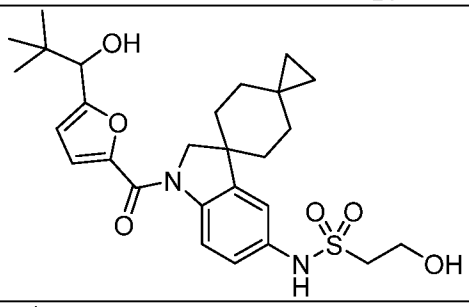
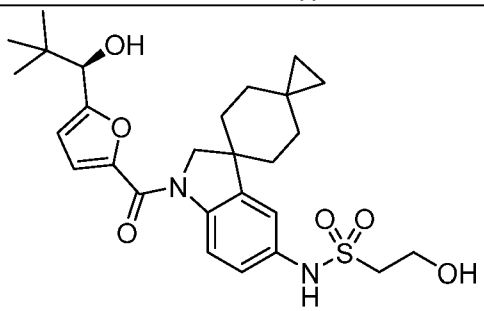
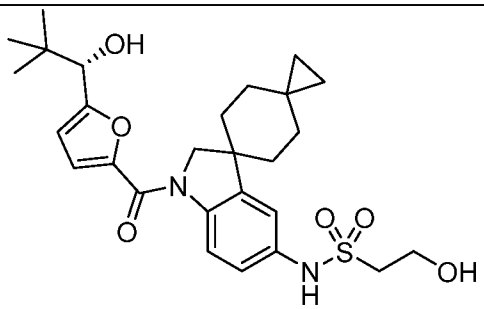
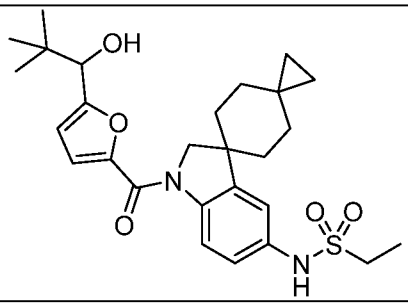
Compound No.	Structure	Name
(R)-Compound 352		(R)-N-(1''-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
(S)-Compound 352		(S)-N-(1''-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 353		N-(1''-(3-(1-methylcyclobutane-1-carbonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 354		N-(1''-(3-(hydroxy(1-methylcyclobutyl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
Compound 355		2-methyl-N-(3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)phenyl)propane-2-sulfonamide

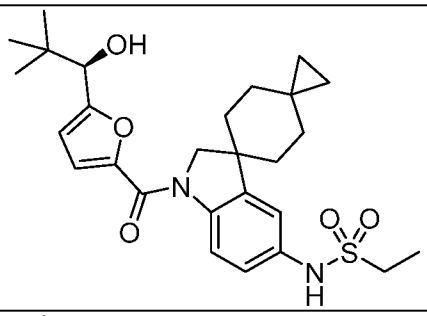
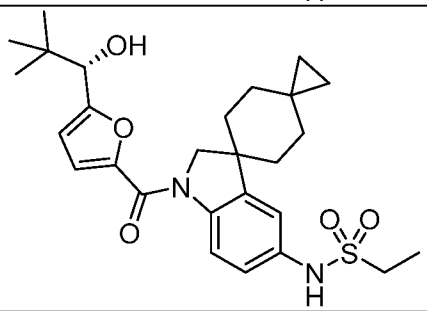
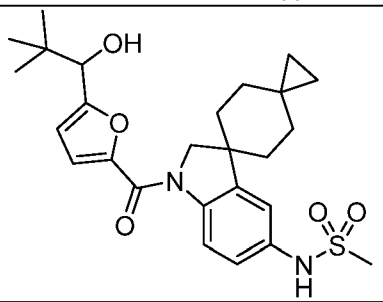
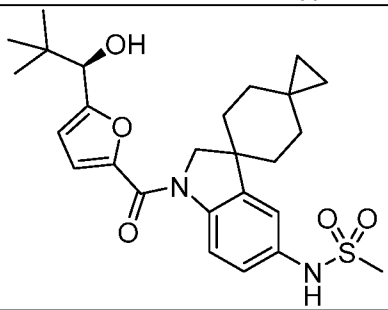
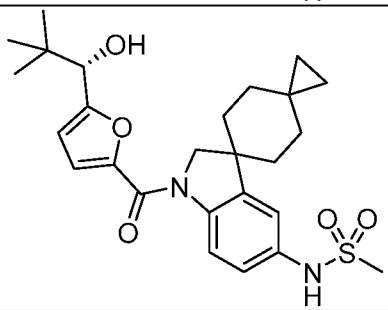
Compound No.	Structure	Name
Compound 356		N-(3,3-difluorocyclobutyl)-N-methyl-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 357		N-(1"-(3-(1-hydroxy-3,3-dimethylbutyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 358		N-(1"-(3-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 359		N-(1-hydroxy-2-methylpropan-2-yl)-3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide

Compound No.	Structure	Name
(1s,4s)-Compound 360		3-((1s,4s)-5'-bromo-4-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
(1r,4r)-Compound 360		3-((1r,4r)-5'-bromo-4-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)-N-(tert-butyl)benzenesulfonamide
(1s,4s)-Compound 361		N-(tert-butyl)-3-((1s,4s)-5'-(methylsulfonamido)-4-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
(1r,4r)-Compound 361		N-(tert-butyl)-3-((1r,4r)-5'-(methylsulfonamido)-4-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide
Compound 362		N-(1''-(3-((cyclobutylmethyl)(methyl)phosphoryl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

Compound No.	Structure	Name
Compound 363		N-(1"-(4-(cyclopentanecarbonyl)thiophene-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 364		N-(1"-(4-(cyclopentyl(hydroxy)methyl)thiophene-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
Compound 365		N-(tert-butyl)-3-(5"-((2-fluoroethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide
Compound 366		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(5-(cyclopentyl(hydroxy)methyl)furan-2-yl)methanone
Compound 367		N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide
(R)-Compound 367		(R)-N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide

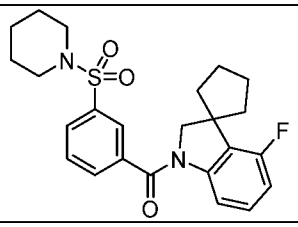
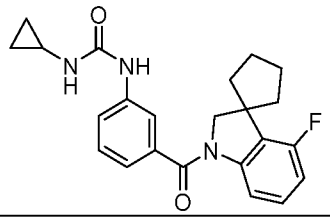
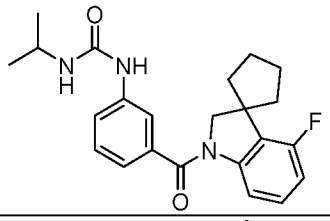
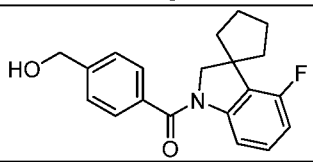
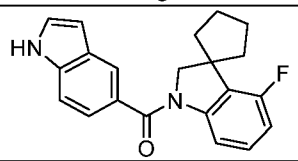
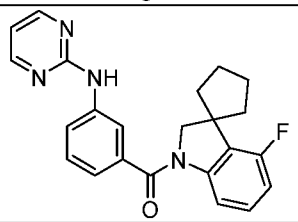
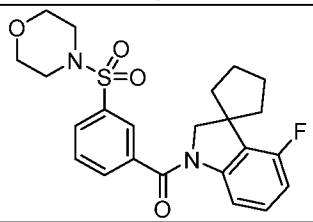
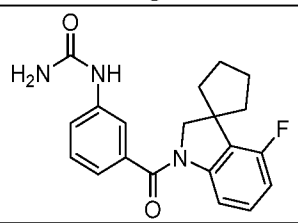
Compound No.	Structure	Name
(S)-Compound 367		(S)-N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide
Compound 368		N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)-2-hydroxyethane-1-sulfonamide
(R)-Compound 368		(R)-N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)-2-hydroxyethane-1-sulfonamide
(S)-Compound 368		(S)-N-(1"-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)-2-hydroxyethane-1-sulfonamide
Compound 369		N-(1"-(5-((3,3-difluorocyclobutyl)(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

Compound No.	Structure	Name
Compound 370		(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-yl)methanone
Compound 371		2-hydroxy-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethane-1-sulfonamide
(R)-Compound 371		(R)-2-hydroxy-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethane-1-sulfonamide
(S)-Compound 371		(S)-2-hydroxy-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethane-1-sulfonamide
Compound 372		N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide

Compound No.	Structure	Name
(R)-Compound 372		(R)-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide
(S)-Compound 372		(S)-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide
Compound 373		N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(R)-Compound 373		(R)-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide
(S)-Compound 373		(S)-N-(1"-(5-(1-hydroxy-2,2-dimethylpropyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide

[0101] In some embodiments, provided herein are compounds and salts thereof described in **Table 2**. In some embodiments, compounds described herein are not compounds of **Table 2**.

Table 2.

Compound No.	Structure	Name
Compound 1'		(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)(3-(piperidin-1-ylsulfonyl)phenyl)methanone
Compound 2'		1-cyclopropyl-3-(3-(4'-fluorospiro[cyclopentane-1,3'-indoline]-1'-carbonyl)phenyl)urea
Compound 3'		1-(3-(4'-fluorospiro[cyclopentane-1,3'-indoline]-1'-carbonyl)phenyl)-3-isopropylurea
Compound 4'		(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)(4-(hydroxymethyl)phenyl)methanone
Compound 5'		(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)(1H-indol-5-yl)methanone
Compound 6'		(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)(3-(pyrimidin-2-ylamino)phenyl)methanone
Compound 7'		(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)(3-(morpholinosulfonyl) phenyl)methanone
Compound 8'		1-(3-(4'-fluorospiro[cyclopentane-1,3'-indoline]-1'-carbonyl)phenyl)urea

[0102] In some variations, any of the compounds described herein, such as a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2), or (II), or any variation thereof, or a compound of **Table 1** or **2** may be deuterated (e.g., a hydrogen atom is replaced by a deuterium atom). In some of these variations, the compound is deuterated at a single site. In other variations, the compound is deuterated at multiple sites. Deuterated compounds can be prepared from deuterated starting materials in a manner similar to the preparation of the corresponding non-deuterated compounds. Hydrogen atoms may also be replaced with deuterium atoms using other method known in the art.

[0103] Any formula given herein, such as Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2), or (II), is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric or diastereomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof in any ratio, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof in any ratio. Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to refer also to any one of hydrates, solvates, and amorphous and polymorphic forms of such compounds, and mixtures thereof, even if such forms are not listed explicitly. In some embodiments, the solvent is water and the solvates are hydrates.

[0104] Representative examples of compounds detailed herein, including intermediates and final compounds, are depicted in the tables and elsewhere herein. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

[0105] The compounds depicted herein may be present as salts even if salts are not depicted, and it is understood that the compositions and methods provided herein embrace all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts.

[0106] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, provided are pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0107] Any variation or embodiment of ring A, ring B, ring C, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a7}, R^{a8}, R^{a9}, R^{a10}, R^{a11}, R^{a12}, R^{a13}, R^{a14}, R^{a15}, R^{a16}, R^{a17}, R^{a18}, R^{a19}, R^{a20}, R^{a21}, R^{a22}, R^{a23}, R^{a24}, R^{a25}, R^{a26}, R^{a27}, R^{a28}, R^{a29}, R^{a30}, R^{a31}, R^{a32}, R^{a33}, R^{a34}, R^{a35}, R^{a36}, R^{a37}, R^{a38}, R^{a39}, R^{a40}, R^{1a1}, R^{1a2}, R^{1a3}, R^{1a4}, R^{B}, m, X, Y^1, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{c1}, R^{c2}, R^{c3}, R^{c4}, R^{c5}, R^{c6}, R^{c7}, R^{c8}, R^{c9}, R^{c10}, R^{c11}, R^{c12}, R^{c13}, R^{c14}, R^{c15}, R^{c16}, R^{c17}, R^{c18}, R^{c19}, R^{D}, R^{E}, or R^{F} provided herein can be combined with every other variation or embodiment of ring A, ring B, ring C, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a7}, R^{a8}, R^{a9}, R^{a10}, R^{a11}, R^{a12}, R^{a13}, R^{a14}, R^{a15}, R^{a16}, R^{a17}, R^{a18}, R^{a19}, R^{a20}, R^{a21}, R^{a22}, Ra23, R^{a24}, R^{a25}, R^{a26}, R^{a27}, R^{a28}, R^{a29}, R^{a30}, R^{a31}, R^{a32}, R^{a33}, R^{a34}, R^{a35}, R^{a36}, R^{a37}, R^{a38}, R^{a39}, R^{a40}, R^{1a1}, R^{1a2}, R^{1a3}, R^{1a4}, R^{B}, m, X, Y^1, Y^2, Y^3, Y^4, Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{c1}, R^{c2}, R^{c3}, R^{c4}, R^{c5}, R^{c6}, R^{c7}, R^{c8}, R^{c9}, R^{c10}, R^{c11}, R^{c12}, R^{c13}, R^{c14}, R^{c15}, R^{c16}, R^{c17}, R^{c18}, R^{c19}, R^{D}, R^{E}, or R^{F}, the same as if each and every combination had been individually and specifically described.

[0108] As used herein, when any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence.

[0109] Compound names provided herein, including in **Table 1** and **Table 2**, are provided by Chemaxon Marvin Structure to Name 20 or ChemDraw Professional 20. One of skilled in the art would understand that the compounds may be named or identified using various commonly recognized nomenclature systems and symbols. By way of example, the compounds may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry include, for example, Chemical Abstract Service (CAS), ChemBioDraw Ultra, and International Union of Pure and Applied Chemistry (IUPAC).

Compositions

[0110] Also provided are compositions, such as pharmaceutical compositions, that include a compound disclosed and/or described herein and one or more additional medicinal agents, pharmaceutical agents, adjuvants, carriers, excipients, and the like. Suitable medicinal and pharmaceutical agents include those described herein. In some embodiments, the pharmaceutical composition includes a pharmaceutically acceptable excipient or adjuvant and at least one chemical entity as described herein. Examples of pharmaceutically acceptable excipients include, but are not limited to, mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, and magnesium carbonate. In some embodiments, provided are compositions, such as pharmaceutical compositions that contain one or more compounds described herein, or a pharmaceutically acceptable salt thereof.

[0111] In some embodiments, provided is a pharmaceutically acceptable composition comprising a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2), or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof. In some aspects, a composition may contain a synthetic intermediate that may be used in the preparation of a compound described herein. The compositions described herein may contain any other suitable active or inactive agents.

[0112] Any of the compositions described herein may be sterile or contain components that are sterile. Sterilization can be achieved by methods known in the art. Any of the compositions described herein may contain one or more compounds that are substantially pure.

[0113] Also provided are packaged pharmaceutical compositions, comprising a pharmaceutical composition as described herein and instructions for using the composition to treat a patient suffering from a disease or condition described herein.

Methods of Use

[0114] As described herein, the compounds of the present disclosure are inhibitors of KIF18A. In one aspect, the compounds and pharmaceutical compositions herein may be used to inhibit KIF18A. In another aspect, the compounds and pharmaceutical compositions herein may be used to treat or prevent a disease or condition in an individual.

[0115] The inhibitory activity of the compounds described herein against KIF18A may be determined and measured by methods known in the art including, but not limited to, inhibition of ATP hydrolysis in the presence of microtubules (Hackney D.D., Jiang W. (2001) Assays for Kinesin Microtubule-Stimulated ATPase Activity. In: Vernos I. (eds) Kinesin Protocols. Methods in Molecular Biology™, vol 164. Humana Press. https://doi.org/10.1385/1-59259-069-1:65).

[0116] In one aspect, provided herein is a method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound or a pharmaceutical composition as described herein. In some embodiments, provided herein are methods of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof. In some embodiments, provided herein are methods of inhibiting KIF18A comprising contacting a cell with an effective amount of a pharmaceutical composition comprising a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II)or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof. In one variations of the aforementioned embodiments, the cell is contacted *in vitro*. In other variations of the aforementioned embodiments, the cell is contacted *in vivo*.

[0117] In another aspect, the compounds and pharmaceutical compositions herein may be used to treat or prevent a disease or condition in an individual, comprising administering an effective amount of a compound or a pharmaceutical composition as described herein. When used in a prophylactic manner, the compounds disclosed and/or described herein may prevent a disease or disorder from developing in an individual at risk of developing the disease or disorder, or lessen the extent of a disease or disorder that may develop.

[0118] In some embodiments, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition as described herein. In some embodiments, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a compound Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof. In some embodiments, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a

pharmaceutical composition comprising a compound a compound Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof.

[0119] In some embodiments, the disease or condition is mediated by KIF18A. In some embodiments, the disease or condition is cancer. In some embodiments, the disease or condition is a cellular proliferation disorder, including uncontrolled cell growth, aberrant cell cycle regulation, centrosome abnormalities (structural and or numeric, fragmentation), a solid tumor, hematopoietic cancer and hyperproliferative disorder, such as thyroid hyperplasia (especially Grave's disease), and cyst (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome). Solid and hematologically derived tumors, such as carcinomas, may include but are not limited to cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung (including squamous cell and small cell lung cancer), pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, and skin (including squamous cell carcinoma), hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma), hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia), hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g., soft tissue and bone), tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas), tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors (including retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer, Ewing's sarcoma, Kaposi's sarcoma), and other cancer-related disorders that are a consequence of cancer presence or progression such as tumor-induced pleural or pericardial effusions, and malignant ascites.

[0120] In some embodiments, provided are methods of treating or preventing cancer in an individual, comprising administering to the individual in need thereof a compound of

Formula Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof. In some embodiments, provided are methods of treating or preventing cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of at least one chemical entity as described herein. Also provided herein is the use of a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treatment of a disease in a subject.

[0121] In some embodiments, provided herein are methods of treating cancer, comprising administering to an individual in need thereof a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof. Also provided herein is the use of a compound of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2) or (II), or a compound of **Table 1** or **2**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treatment of a cancer.

[0122] In some embodiments, provided herein are methods of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition as described herein.

[0123] In some embodiments, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition as described herein. In some embodiments, the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

Dosages

[0124] The compounds and compositions disclosed and/or described herein are administered at a therapeutically effective dosage, e.g., a dosage sufficient to provide treatment for the disease state. While human dosage levels have yet to be optimized for the chemical entities described herein, generally, a daily dose ranges from about 0.01 to 100 mg/kg of body weight; in some embodiments, from about 0.05 to 10.0 mg/kg of body weight, and in some embodiments, from about 0.10 to 1.4 mg/kg of body weight. Thus, for administration to a 70 kg person, in some embodiments, the dosage range would be about from 0.7 to 7000 mg per day; in some embodiments, about from 3.5 to 700.0 mg per day, and in some embodiments, about from 7 to 100.0 mg per day. The amount of the chemical entity administered will be dependent, for example, on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician. For example, an exemplary dosage range for oral administration is from about 5 mg to about 500 mg per day, and an exemplary intravenous administration dosage is from about 5 mg to about 500 mg per day, each depending upon the compound pharmacokinetics.

[0125] Administration of the compounds and compositions disclosed and/or described herein can be via any accepted mode of administration for therapeutic agents including, but not limited to, oral, sublingual, subcutaneous, parenteral, intravenous, intranasal, topical, transdermal, intraperitoneal, intramuscular, intrapulmonary, vaginal, rectal, or intraocular administration. In some embodiments, the compound or composition is administered orally or intravenously. In some embodiments, the compound or composition disclosed and/or described herein is administered orally.

[0126] Pharmaceutically acceptable compositions include solid, semi-solid, liquid and aerosol dosage forms, such as tablet, capsule, powder, liquid, suspension, suppository, and aerosol forms. The compounds disclosed and/or described herein can also be administered in sustained or controlled release dosage forms (e.g., controlled/sustained release pill, depot injection, osmotic pump, or transdermal (including electrotransport) patch forms) for prolonged timed, and/or pulsed administration at a predetermined rate. In some embodiments, the compositions are provided in unit dosage forms suitable for single administration of a precise dose.

[0127] The compounds disclosed and/or described herein can be administered either alone or in combination with one or more conventional pharmaceutical carriers or excipients (e.g., mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, magnesium carbonate). If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like (e.g., sodium acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate). Generally, depending on the intended mode of administration, the pharmaceutical composition will contain about 0.005% to 95%, or about 0.5% to 50%, by weight of a compound disclosed and/or described herein. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pennsylvania.

[0128] In some embodiments, the compositions will take the form of a pill or tablet and thus the composition may contain, along with a compounds disclosed and/or described herein, one or more of a diluent (e.g., lactose, sucrose, dicalcium phosphate), a lubricant (e.g., magnesium stearate), and/or a binder (e.g., starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives). Other solid dosage forms include a powder, marume, solution or suspension (e.g., in propylene carbonate, vegetable oils or triglycerides) encapsulated in a gelatin capsule.

[0129] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing or suspending etc. a compound disclosed and/or described herein and optional pharmaceutical additives in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution or suspension. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, as emulsions, or in solid forms suitable for dissolution or suspension in liquid prior to injection. The percentage of the compound contained in such parenteral compositions depends, for example, on the physical nature of the compound, the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.01% to 10% in solution are employable, and may be higher if the composition is a solid which will be subsequently diluted to another concentration. In some embodiments, the composition will comprise from about 0.2 to 2% of a compound disclosed and/or described herein in solution.

[0130] Pharmaceutical compositions of the compounds disclosed and/or described herein may also be administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the pharmaceutical composition may have diameters of less than 50 microns, or in some embodiments, less than 10 microns.

[0131] In addition, pharmaceutical compositions can include a compound disclosed and/or described herein and one or more additional medicinal agents, pharmaceutical agents, adjuvants, and the like. Suitable medicinal and pharmaceutical agents include those described herein.

Kits

[0132] Also provided are articles of manufacture and kits containing any of the compounds or pharmaceutical compositions provided herein. The article of manufacture may comprise a container with a label. Suitable containers include, for example, bottles, vials, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container may hold a pharmaceutical composition provided herein. The label on the container may indicate that the pharmaceutical composition is used for preventing, treating or suppressing a condition described herein, and may also indicate directions for either *in vivo* or *in vitro* use.

[0133] In one aspect, provided herein are kits containing a compound or composition described herein and instructions for use. The kits may contain instructions for use in the treatment of any disease or condition described herein in an individual in need thereof. A kit may additionally contain any materials or equipment that may be used in the administration of the compound or composition, such as vials, syringes, or IV bags. A kit may also contain sterile packaging.

Combinations

[0134] The compounds and compositions described and/or disclosed herein may be administered alone or in combination with other therapies and/or therapeutic agents useful in the treatment of the aforementioned disorders.

[0135] The compounds and compositions described and/or disclosed herein may be combined with one or more other therapies to treat the diseases or conditions described herein. In some embodiments, the disease or condition is cancer. In some embodiments, the disease or condition is a cellular proliferation disorder, including uncontrolled cell growth, aberrant cell cycle regulation, centrosome abnormalities (structural and or numeric, fragmentation), a solid tumor, hematopoietic cancer and hyperproliferative disorder, such as thyroid hyperplasia (especially Grave's disease), and cyst (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome). Solid and hematologically derived tumors, such as carcinomas, may include but are not limited to cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung (including squamous cell and small cell lung cancer), pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, and skin (including squamous cell carcinoma), hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma), hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia), hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g., soft tissue and bone), tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas), tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors (including retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer, Ewing's sarcoma, Kaposi's sarcoma), and other cancer-related disorders that are a consequence of cancer presence or progression such as tumor-induced pleural or pericardial effusions, and malignant ascites.

General Synthetic Methods

[0136] Compounds of Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2), or (II) will now be described by reference to illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various

compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. In addition, one of skill in the art will recognize that protecting groups may be used to protect certain functional groups (amino, carboxy, or side chain groups) from reaction conditions, and that such groups are removed under standard conditions when appropriate. Unless otherwise specified, the variables are as defined above in reference to Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2), or (II).

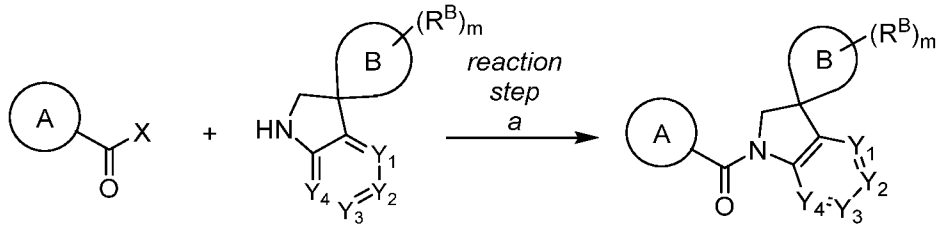
[0137] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, e.g., a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[0138] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[0139] General methods of preparing compounds described herein are depicted in exemplified methods below. Variable groups in the schemes provided herein are defined as for Formula (I), (I-1), (I-2), (I-3), (Ia1), (Ia2), or (II), or any variation thereof. Other compounds described herein may be prepared by similar methods.

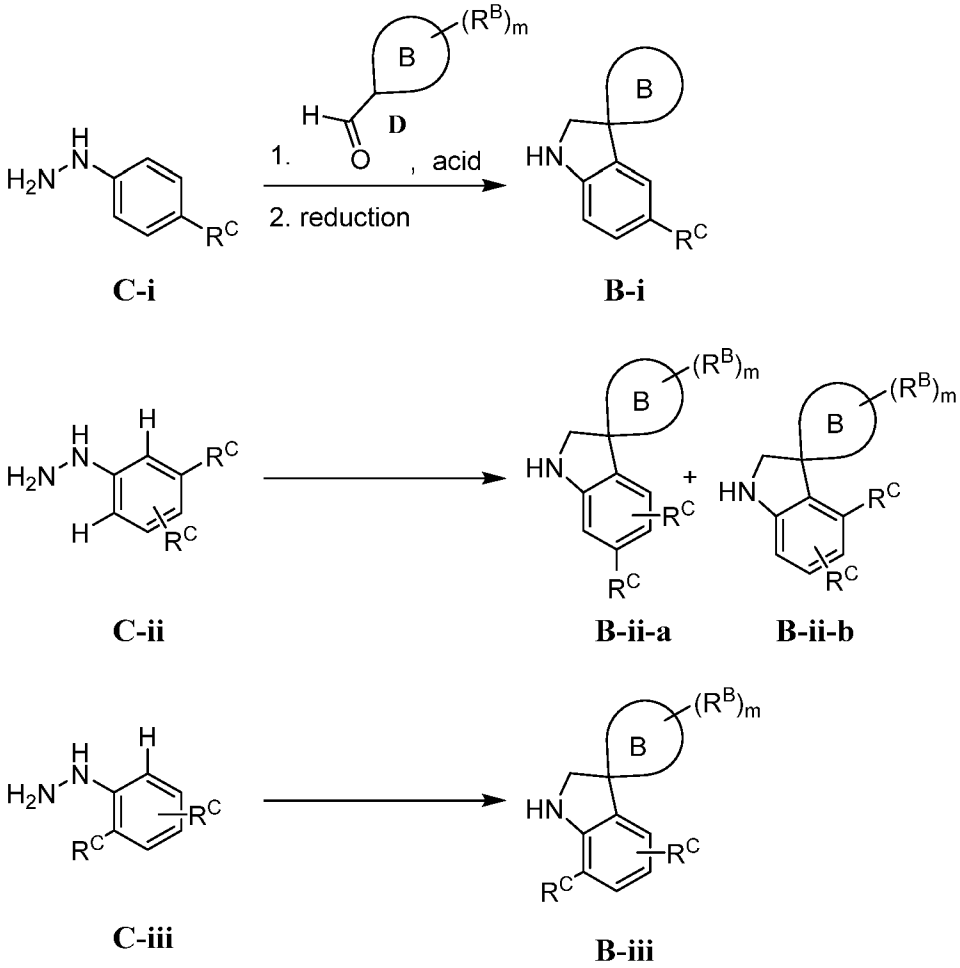
[0140] In some embodiments, compounds provided herein may be synthesized according to Scheme 1, Scheme 2, Scheme 3, and/or Scheme 4. Ring A, Ring B, Y^1, Y^2, Y^3, Y^4, m, R^B, and R^C, as shown in Schems 1-4 below, are as defined for the compounds of Formula I.

Scheme 1.



[0141] **Scheme 1** outlines an exemplary route to the synthesis of compound of general formula **I**. Compounds of formula **I** are prepared by the reaction of a carboxylic acid of formula **A** (*e.g.*, X = OH) and an indoline of formula **B** in the presence of coupling reagent, such as HATU with a base such as iPr_2NEt, or EDCI with a HOBt or DMAP. Alternatively, an acid halide of formula **A** (*e.g.*, X = Cl or F) is reacted directly with the compound of formula **B** with an acid scavenger, such as Et_3N.

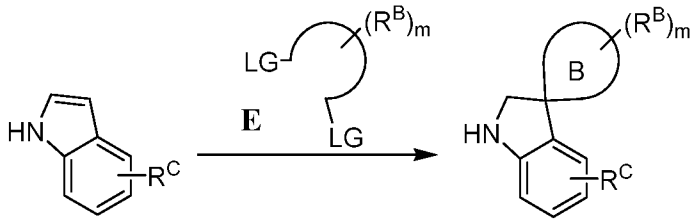
Scheme 2.



[0142] Indoline intermediates of formula **B** may be prepared *via* the Fisher Indole Synthesis as described in **Scheme 2**. Arylhydrazines of formula **C** (*e.g.*, formula **C-i**, formula

C-ii, and formula **C-iii**) are reacted with a Ring B-substituted carbaldehyde of formula **D** in the presence of acid, followed by reaction with a reducing agent such as $NaBH_4$, Pd/C and H_2 gas, or Et_3SiH. Arylhydrazines of formula **C-i**, which are para-mono-substituted, provide indolines of formula **B-i**, while hydrazines of formula **C-ii**, which contain at least one meta substituent and are not substituted in the ortho positions, provide a mixture of indolines of formulae **B-ii-a** and **B-ii-b**. Arylhydrazines of formula **C-iii**, that are substituted at one ortho position, provide indolines of formula **B-iii**.

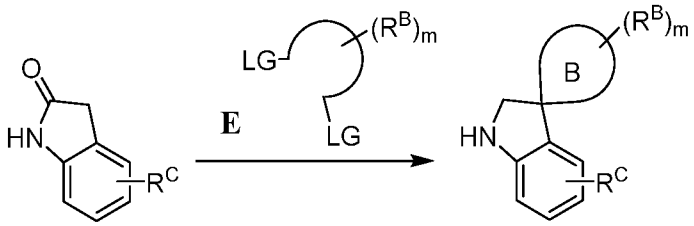
Scheme 3.



D **B**

[0143] Indolines of formula **B** may also be prepared via an 3,3-dialkylation method described in **Scheme 3**. An indole of formula **D** is reacted with an optionally substituted 3-6 atom aliphatic and heteroaliphatic linear chain with two terminal leaving groups "LG" (formula **E**). LG may be Cl, Br, I, or sulfonate ester, or another suitable group displaceable by a nucleophile. The transformation may be mediated by a trialkylboron, such as Et_3B, and base, such as potassium t-butoxide. The spiroannulation reaction is followed by a reaction with a reducing agent such as $NaBH_4$, Pd/C and H_2 gas, or Et_3SiH.

Scheme 4.



F **B**

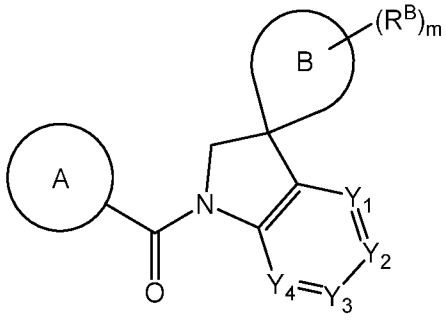
[0144] Indolines of formula **B** may also be prepared via the enolate alkylation of an indolin-2-one of formula **F**. The indolin-2-one of formula **F** is deprotonated with a strong base, such as butyllithium, sodium hexamethylsilazide, or potassium t-butoxide, and reacted with an optionally substituted 3-6 atom aliphatic and heteroaliphatic linear chain with two

terminal leaving groups "LG" (formula **E**). LG may be Cl, Br, I, or sulfonate ester, or another suitable group displaceable by a nucleophile. This reaction may be mediated by an additive such as tetramethyldiaminoethane or hexamethylphosphorous triamide. The spiroannulation reaction is followed by a reaction with a reducing agent such as $LiAlH_4$ or borane.

ENUMERATED EMBODIMENTS

[0145] The following enumerated embodiments are representative of some aspects of the invention.

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is not 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; or salt of any of the foregoing.

3. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted C_{6-14} aryl.

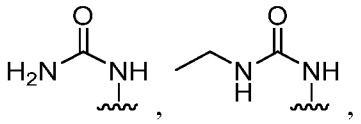
4. The compound of embodiment 3, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted phenyl.

5. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted 5- to 10-membered heteroaryl.

6. The compound of embodiment 5, or a pharmaceutically acceptable salt thereof, wherein ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted.

7. The compound of any one of embodiments 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{a1} is hydrogen or C_{1-6} alkyl; R^{a2} and R^{a3} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a4} is hydrogen or C_{1-6} alkyl; R^{a5} is hydrogen or C_{1-6} alkyl; R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl; R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a10} is C_{3-10} cycloalkyl; R^{a11} is C_{3-10} cycloalkyl; R^{a12} is hydrogen or C_{1-6} alkyl; R^{a13} is C_{3-10} cycloalkyl; R^{a16} is C_{3-10} cycloalkyl or 3- to 12-membered heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo; R^{a17} and R^{a18} are each independently hydrogen or C_{1-6} alkyl; and R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl.

8. The compound of any one of embodiments 1-7, or a pharmaceutically acceptable salt thereof, wherein R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one or more C_{1-6} alkyl.

9. The compound of any one of embodiments 1-8, or a pharmaceutically acceptable salt thereof, wherein ring A is substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, -OH, methyl, amino, 

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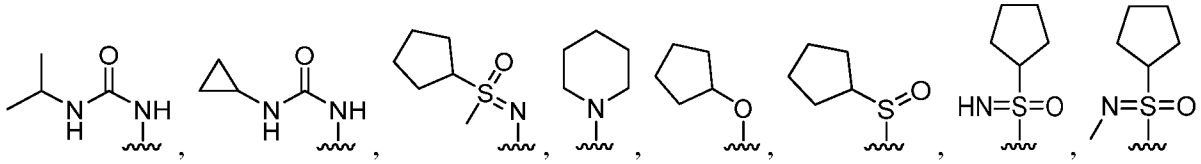
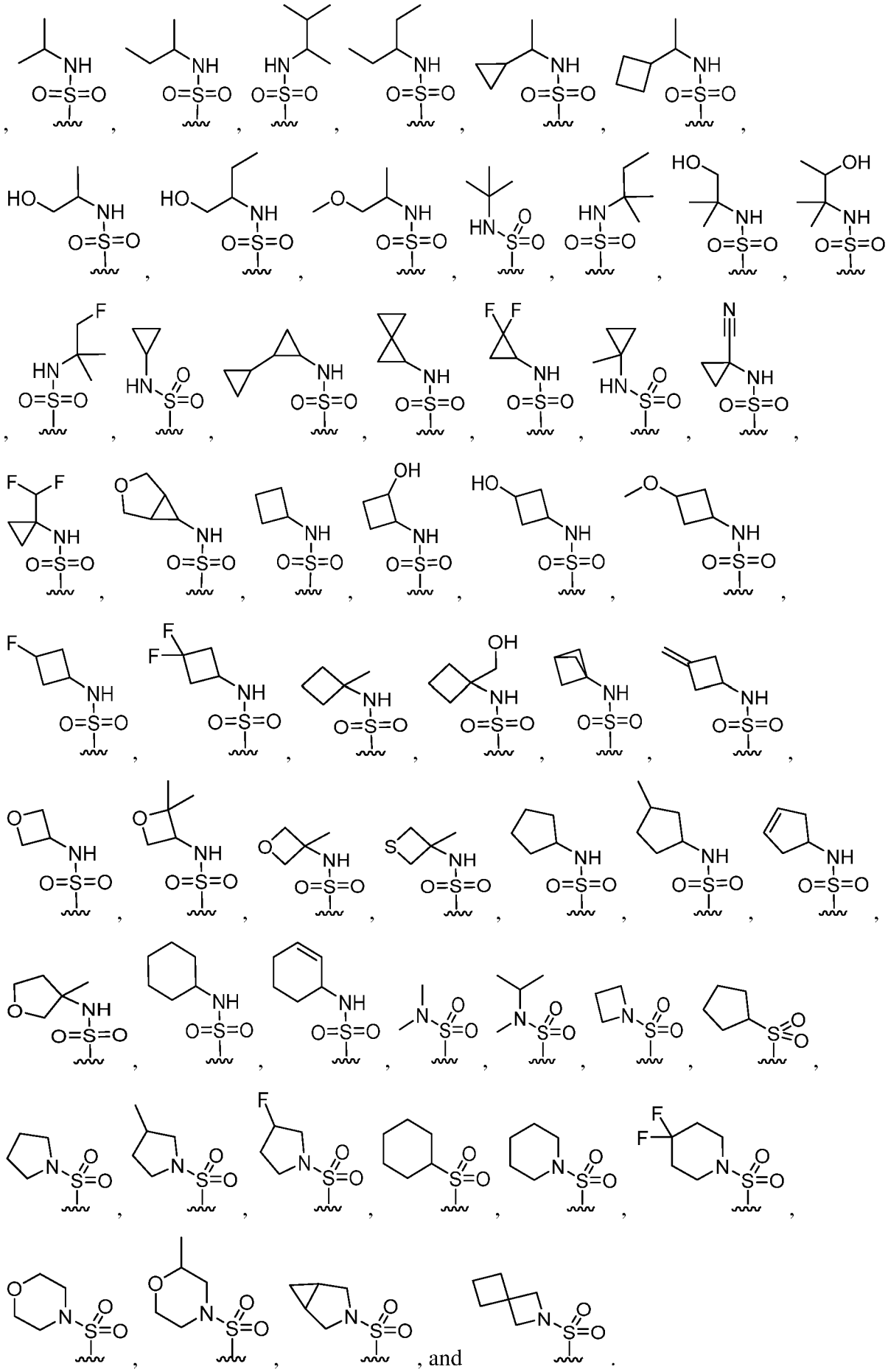
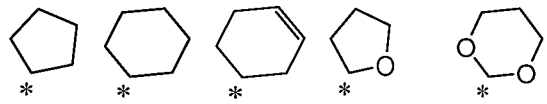


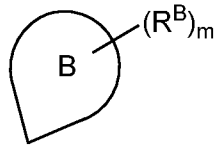
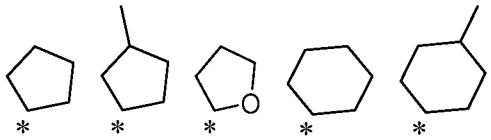
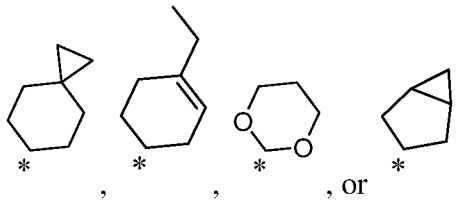


, and .

10. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

11. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

12. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein ring B is  , wherein * denotes the point of attachment to the rest of Formula (I).

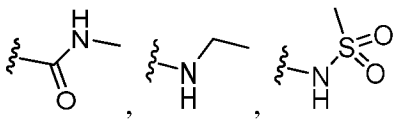
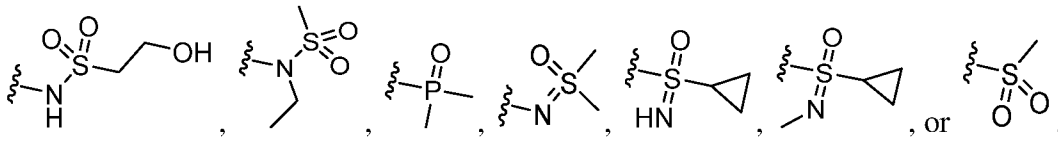
13. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is  ,  , wherein * denotes the point of attachment to the rest of Formula (I).

14. The compound of any one of embodiments 1-13, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

15. The compound of any one of embodiments 1-13, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

16. The compound of any one of embodiments 1-13, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

17. The compound of any one of embodiments 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

18. The compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, $-CH_2OH$, bromo, $-NO_2$,  ,  .

19. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of **Table 1**.

20. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of **Table 2**.

21. A pharmaceutical composition comprising a compound of any one of embodiments 1-18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

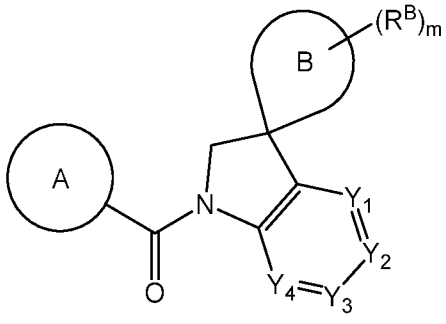
22. A method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound of any one of embodiments 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 21.

23. A method of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 21.

24. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 21.

25. The method of embodiment 24, wherein the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

26. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

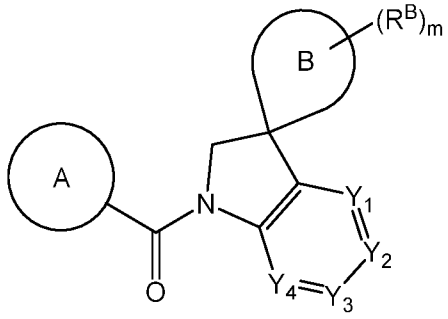
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

27. A compound of Formula (I-1)



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

28. The compound of embodiment 26 or 27, or a pharmaceutically acceptable salt thereof, wherein the compound is not 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; or salt of any of the foregoing.

29. The compound of embodiment 26 or 28, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted C_{6-14} aryl.

30. The compound of embodiment 29, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted phenyl.

31. The compound of embodiment 26 or 28, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted 5- to 10-membered heteroaryl.

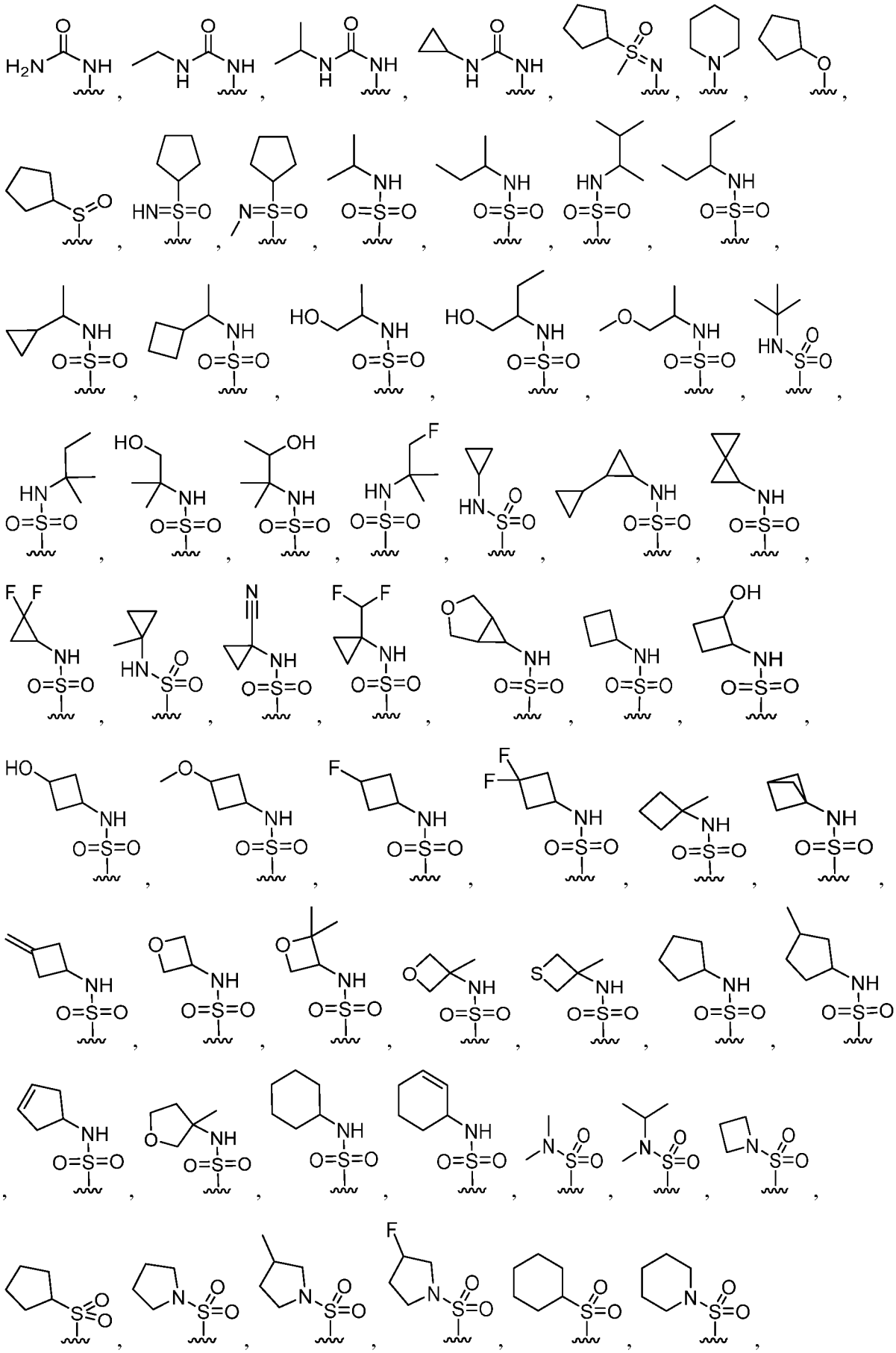
32. The compound of embodiment 31, or a pharmaceutically acceptable salt thereof, wherein ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted.

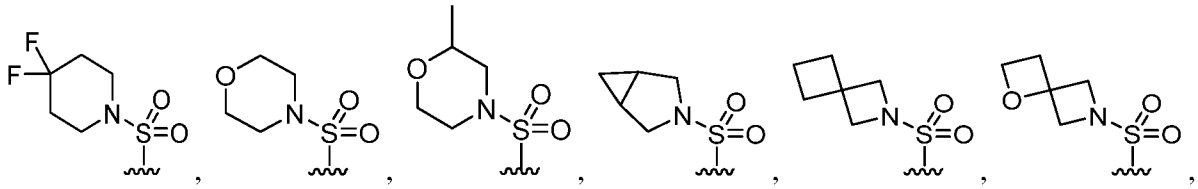
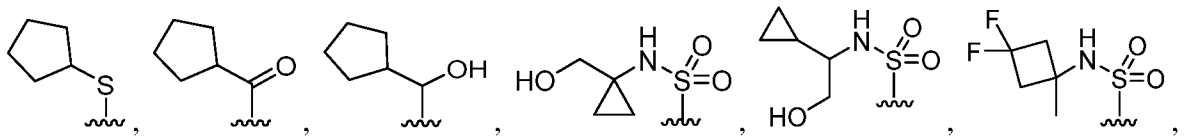
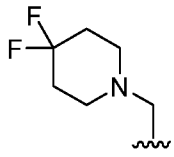
33. The compound of any one of embodiments 26 and 28-32, or a pharmaceutically acceptable salt thereof, wherein R^{a1} is hydrogen or C_{1-6} alkyl; R^{a2} and R^{a3} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a4} is hydrogen or C_{1-6} alkyl; R^{a5} is hydrogen or C_{1-6} alkyl; R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl; R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a10} is C_{3-10} cycloalkyl; R^{a11} is C_{3-10} cycloalkyl; R^{a12} is hydrogen or C_{1-6} alkyl; R^{a13} is C_{3-10} cycloalkyl; R^{a16} is C_{3-10} cycloalkyl or 3- to 12-membered heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo; R^{a17} and R^{a18} are each independently hydrogen or C_{1-6} alkyl; R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a21} is C_{3-10} cycloalkyl; and R^{a22} is C_{3-10} cycloalkyl.

34. The compound of any one of embodiments 26 and 28-33, or a pharmaceutically acceptable salt thereof, wherein R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one or more C_{1-6} alkyl.

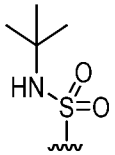
35. The compound of any one of embodiments 26 and 28-34, or a pharmaceutically acceptable salt thereof, wherein R^{a14} is hydrogen and R^{a15} is *tert*-butyl.

36. The compound of any one of embodiments 26 and 28-35, or a pharmaceutically acceptable salt thereof, wherein ring A is substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, -OH, methyl, amino,



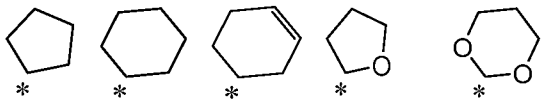




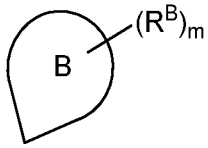
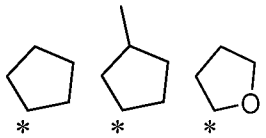
and .

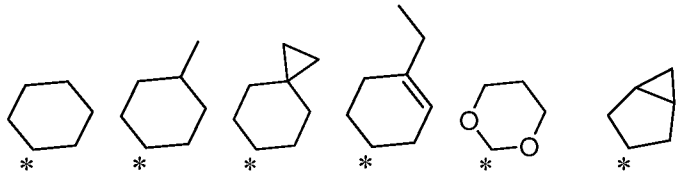
37. The compound of any one of embodiments 26 and 28-36, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl substituted with  .

38. The compound of any one of embodiments 26 and 28-37, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

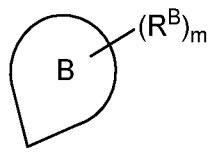
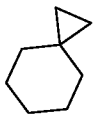
39. The compound of any one of embodiments 26 and 28-37, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

40. The compound of any one of embodiments 26 and 28-37, or a pharmaceutically acceptable salt thereof, wherein ring B is  , wherein * denotes the point of attachment to the rest of Formula (I).

41. The compound of any one of embodiments 26 and 28-37, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is  ,

 , wherein * denotes the point of attachment to the rest of Formula (I).

42. The compound of embodiment 41, or a pharmaceutically acceptable salt thereof,

wherein  of Formula (I) is  .

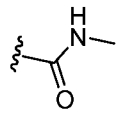
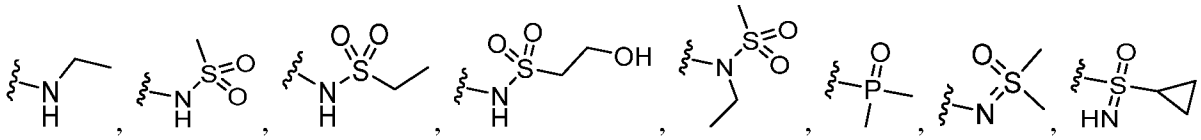
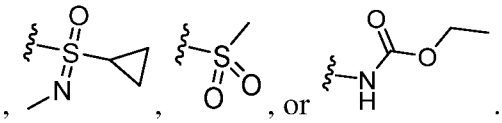
43. The compound of any one of embodiments 25 and 28-42, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

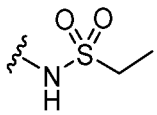
44. The compound of embodiment 43, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

45. The compound of embodiment 43 or 44, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each hydrogen.

46. The compound of any one of embodiments 25 and 28-41, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

47. The compound of any one of embodiments 25 and 28-41, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

48. The compound of any one of embodiments 25 and 28-47, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, $-CH_2OH$, bromo, $-NO_2$,  ,  ,  , or .

49. The compound of embodiment 48, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is  .

50. The compound of embodiment 26 or 28, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of **Table 1**.

51. The compound of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of **Table 2**.

52. A pharmaceutical composition comprising a compound of any one of embodiments 26-51, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

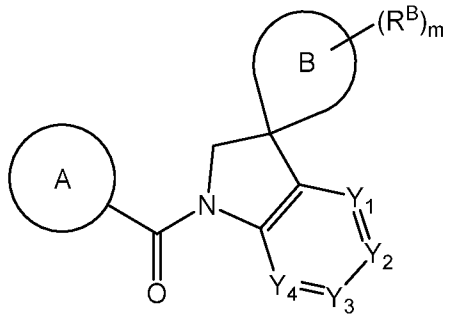
53. A method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound of any one of embodiments 26-51, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 52.

54. A method of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 26-51, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 52.

55. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 26-51, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 52.

56. The method of embodiment 55, wherein the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

57. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, -

$N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

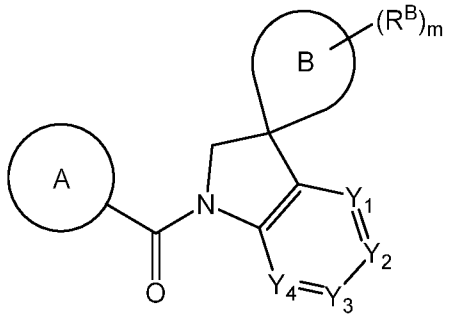
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

58. A compound of Formula (I-2)



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

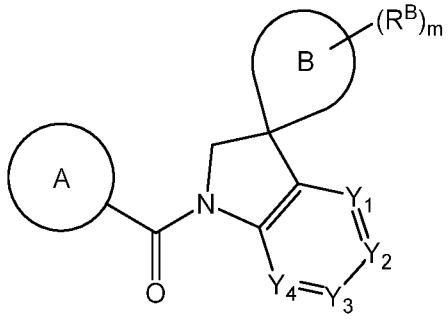
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

59. A compound of Formula (I-1)



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

60. The compound of embodiment 57 or 58, or a pharmaceutically acceptable salt thereof, wherein the compound is not 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; or salt of any of the foregoing.

61. The compound of embodiment 57 or 60, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted C6-14 aryl.

62. The compound of embodiment 61, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted phenyl.

63. The compound of embodiment 57 or 60, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted 5- to 10-membered heteroaryl.

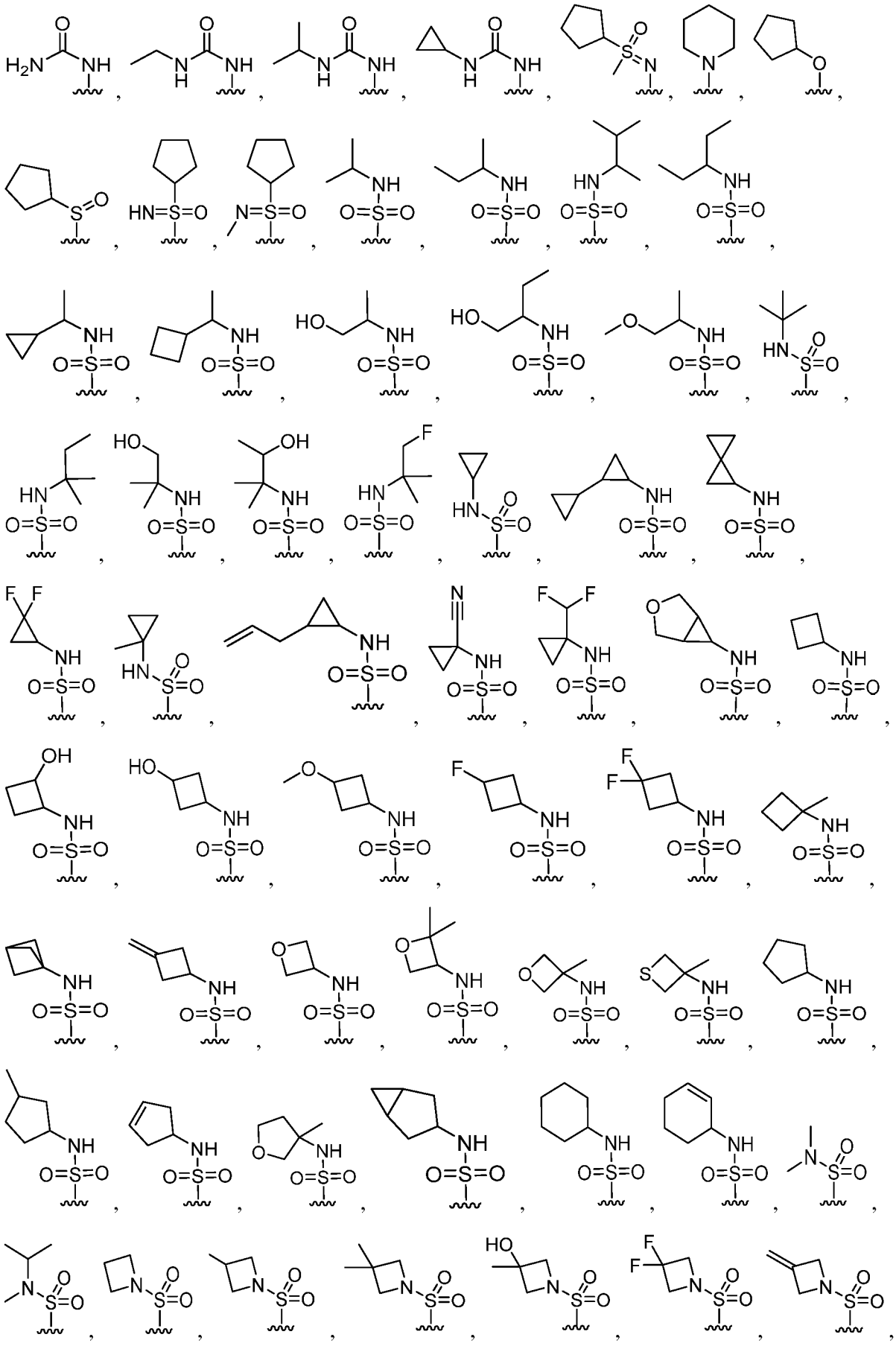
64. The compound of embodiment 63, or a pharmaceutically acceptable salt thereof, wherein ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted.

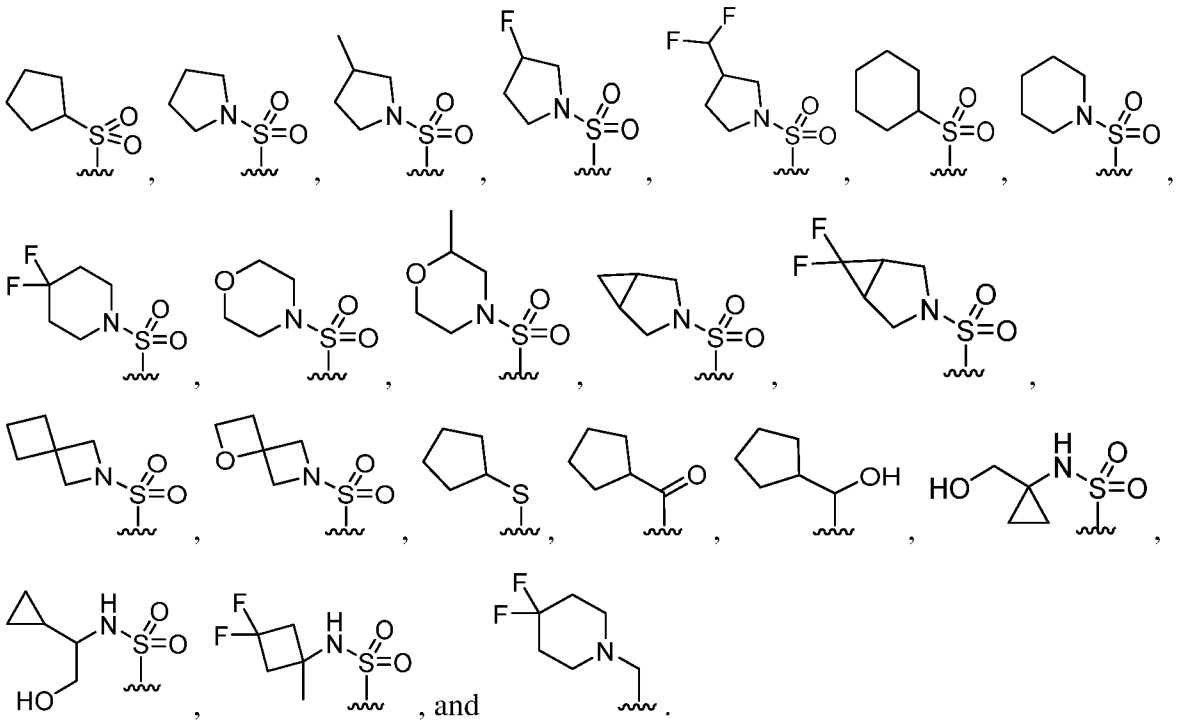
65. The compound of any one of embodiments 57 and 60-64, or a pharmaceutically acceptable salt thereof, wherein R^{a1} is hydrogen or C_{1-6} alkyl; R^{a2} and R^{a3} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a4} is hydrogen or C_{1-6} alkyl; R^{a5} is hydrogen or C_{1-6} alkyl; R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl; R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a10} is C_{3-10} cycloalkyl; R^{a11} is C_{3-10} cycloalkyl; R^{a12} is hydrogen or C_{1-6} alkyl; R^{a13} is C_{3-10} cycloalkyl; R^{a16} is C_{3-10} cycloalkyl or 3- to 12-membered heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo; R^{a17} and R^{a18} are each independently hydrogen or C_{1-6} alkyl; R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a21} is C_{3-10} cycloalkyl; and R^{a22} is C_{3-10} cycloalkyl.

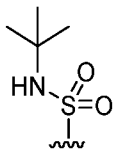
66. The compound of any one of embodiments 57 and 60-65, or a pharmaceutically acceptable salt thereof, wherein R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one or more C_{1-6} alkyl.

67. The compound of any one of embodiments 57 and 60-66, or a pharmaceutically acceptable salt thereof, wherein R^{a14} is hydrogen and R^{a15} is *tert*-butyl.

68. The compound of any one of embodiments 57 and 60-67, or a pharmaceutically acceptable salt thereof, wherein ring A is substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, -OH, methyl, amino,

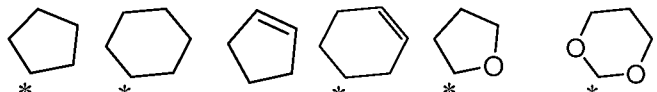


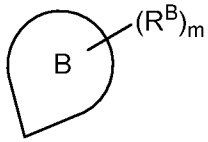
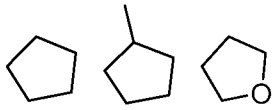


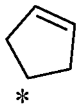
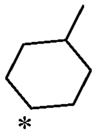
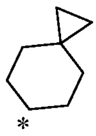
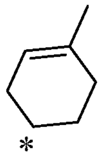
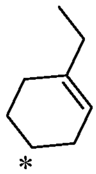
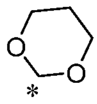
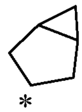
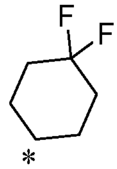
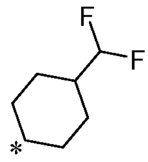
69. The compound of any one of embodiments 57 and 60-68, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl substituted with  .

70. The compound of any one of embodiments 57 and 60-69, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

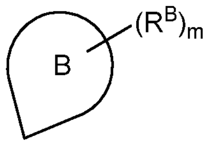
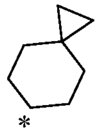
71. The compound of any one of embodiments 57 and 60-69, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

72. The compound of any one of embodiments 57 and 60-69, or a pharmaceutically acceptable salt thereof, wherein ring B is  , wherein * denotes the point of attachment to the rest of Formula (I).

73. The compound of any one of embodiments 57 and 60-69, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is  ,

 ,  ,  ,  ,  ,  ,  ,  ,  , or 

wherein * denotes the point of attachment to the rest of Formula (I).

74. The compound of embodiment 73, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is  .

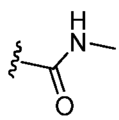
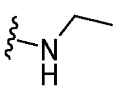
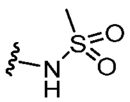
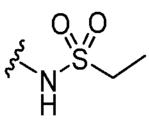
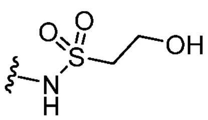
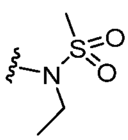
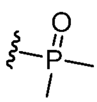
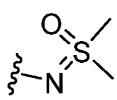
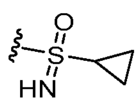
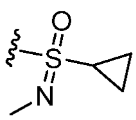
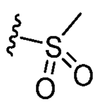
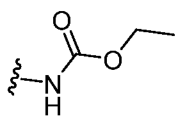
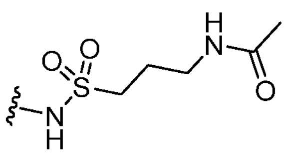
75. The compound of any one of embodiments 57 and 60-74, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

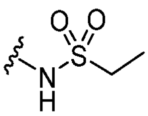
76. The compound of embodiment 75, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

77. The compound of embodiment 75 or 76, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each hydrogen.

78. The compound of any one of embodiments 57 and 60-74, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

79. The compound of any one of embodiments 57 and 60-74, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

80. The compound of any one of embodiments 57 and 60-79, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, $-CH_2OH$, bromo, $-NO_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , or  .

81. The compound of embodiment 80, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is  .

82. The compound of embodiment 57 or 60, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of **Table 1**.

83. The compound of embodiment 57, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of compounds of **Table 2**.

84. A pharmaceutical composition comprising a compound of any one of embodiments 57-83, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

85. A method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound of any one of embodiments 57-83, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 84.

86. A method of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 57-83, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 84.

87. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 57-83, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 84.

88. The method of embodiment 87, wherein the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

EXAMPLES

[0146] The following examples are offered to illustrate but not to limit the compositions, uses, and methods provided herein. The compounds are prepared using the general methods described above.

Abbreviations:

BSA: bovine serum albumin

DAST: diaminosulfur trifluoride

dba: bibenzylidene acetone

DMF: dimethylformamide

EDCI: 1-ehthyl-3-(3-dimethylaminopropyl)carbodiimide

ESI MS: electrospray mass spectrometry

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

HOBT: 1-hydroxybenzotriazole

HPLC: high-performance liquid chromatography

IC_{50}: 50% inhibitory concentration

LDA: lithium diisopropylamide

mCPBA: meta-chloroperoxybenzoic acid

MsCl: methanesulfonyl chloride

MTBE: methyl t-butyl ether

NCS: N-chlorosuccinimide

NCI: N-iodosuccinimide

NMR: nuclear magnetic resonance

PE: petroleum ether

THF: tetrahydrofuran

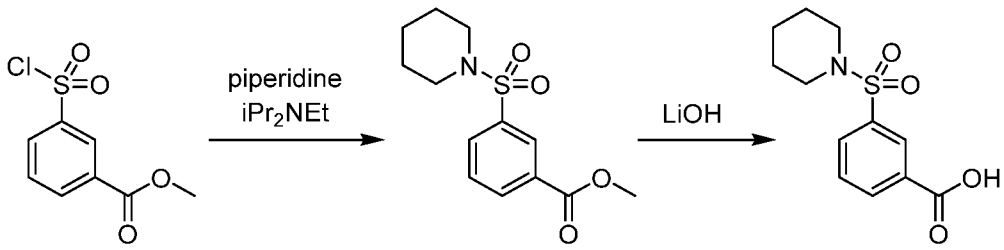
TFA: trifluoroacetic acid

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Xphos Pd G4: dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphanium; methanesulfonic acid; N-methyl-2-phenylaniline; palladium (CAS: 1599466-81-5)

Synthesis of Intermediates

Synthesis of 3-(piperidin-1-ylsulfonyl)benzoic acid (A-01)



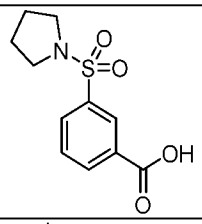
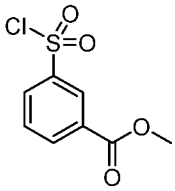
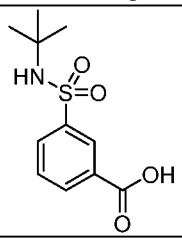
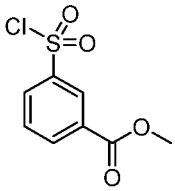
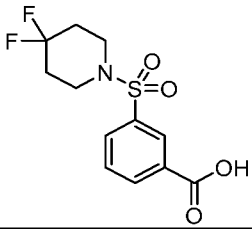
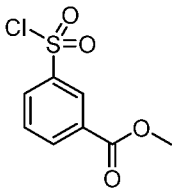
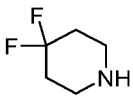
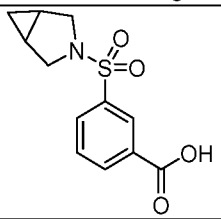
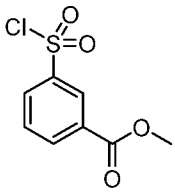
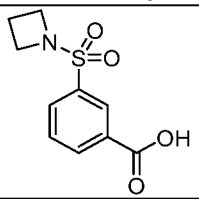
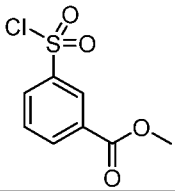
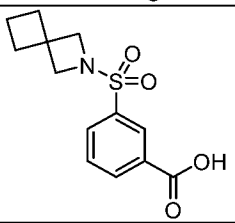
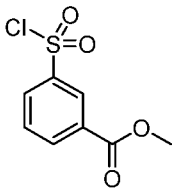
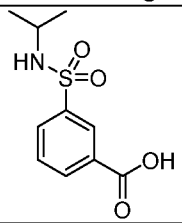
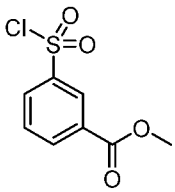
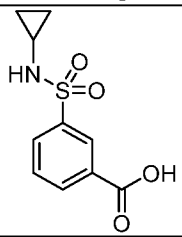
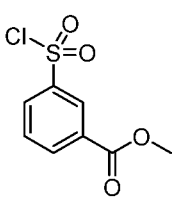
A-01

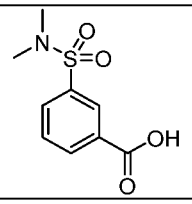
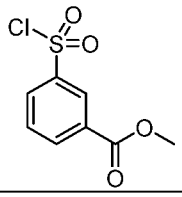
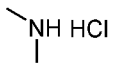
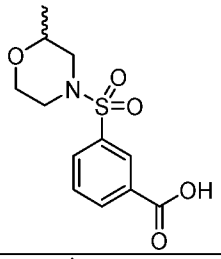
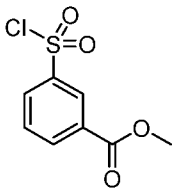
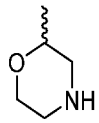
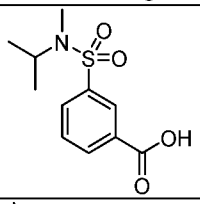
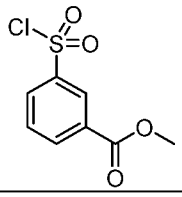
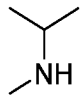
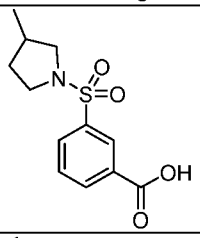
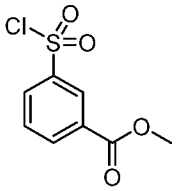
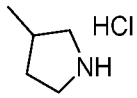
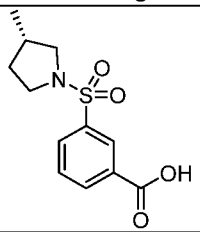
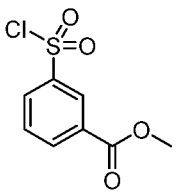
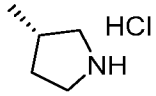
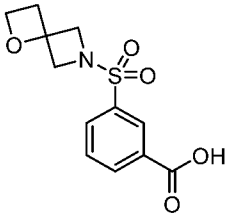
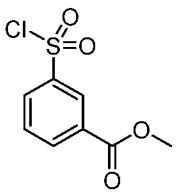
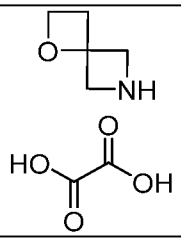
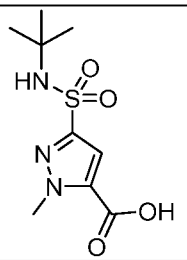
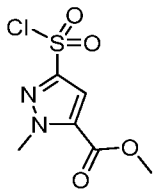
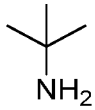
[0147] **Step 1.** A mixture of piperidine (0.25 mL, 2.6 mmol), CH_2Cl_2 (5.0 mL), iPr_2NEt (1.3 mL, 7.7 mmol) and methyl 3-chlorosulfonylbenzoate (900 mg, 3.84 mmol, 1.5 eq) was stirred for 2 h, concentrated, poured into H_2O (20 mL), and extracted with EtOAc (2 x 10 mL). The extracts were combined, washed with brine (10.0 mL), dried over Na_2SO_4, filtered, and concentrated to provide methyl 3-(1-piperidylsulfonyl) benzoate (0.95 g).

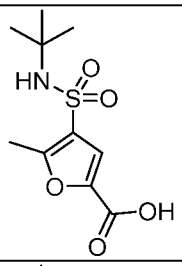
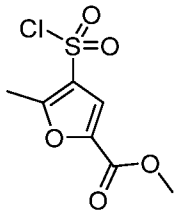
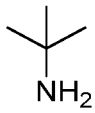
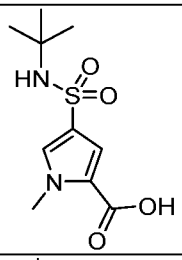
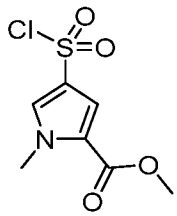
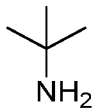
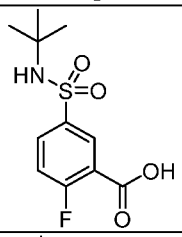
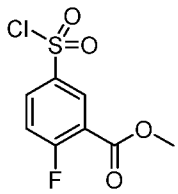
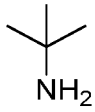
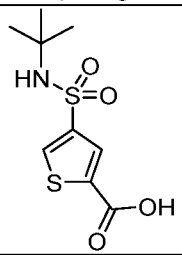
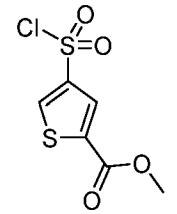
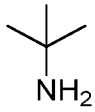
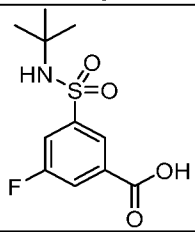
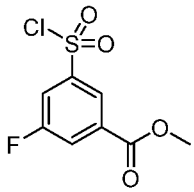
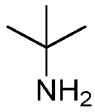
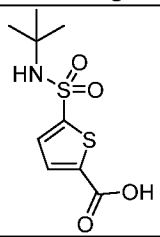
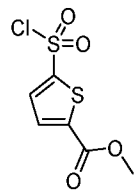
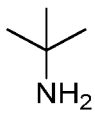
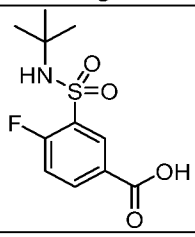
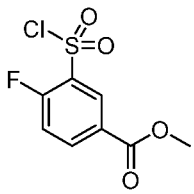
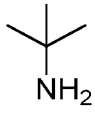
[0148] **Step 2**. A mixture of methyl 3-(1-piperidylsulfonyl) benzoate (0.90 g, 3.2 mmol), THF (6.0 mL), H_2O (2.0 mL), and $LiOH•H_2O$ (0.67 g, 16 mmol) was stirred for 2 h, then was concentrated. The mixture was treated with HCl (4N) to bring the pH to 3, poured into H_2O (10 mL), and extracted with EtOAc (2 x 10 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide 3-(1-piperidylsulfonyl) benzoic acid (**A-01**, 0.72 g). ESI MS m/z: 270.0 $(M+H)^+$.

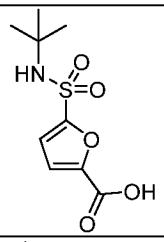
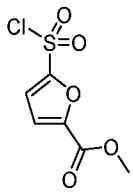
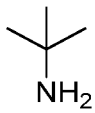
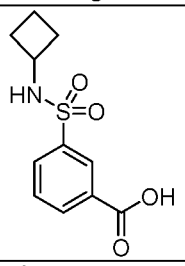
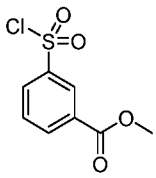
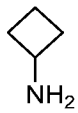
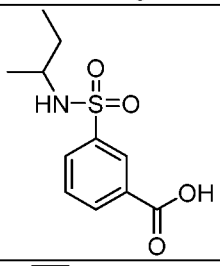
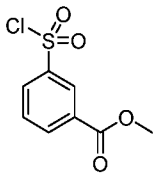
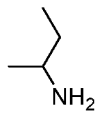
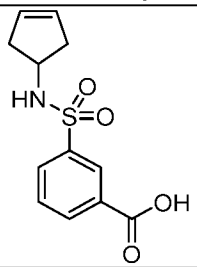
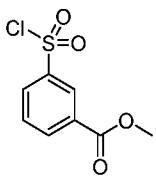
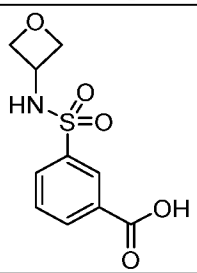
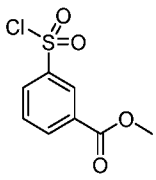
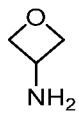
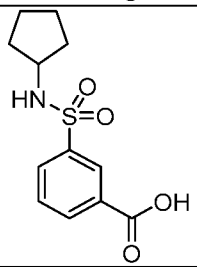
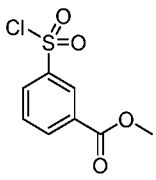
[0149] Compounds in **Table 3** were prepared in the same manner as **A-01** from the indicated sulfonyl chloride and amine.

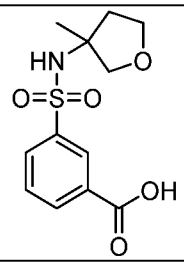
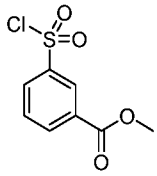
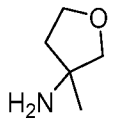
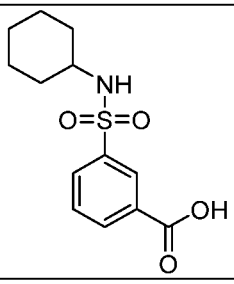
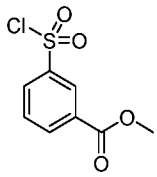
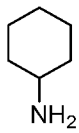
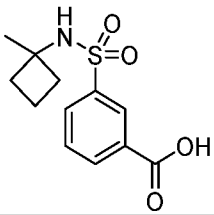
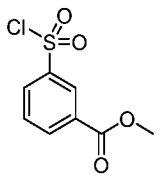
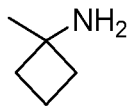
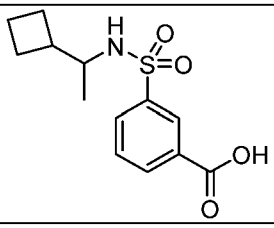
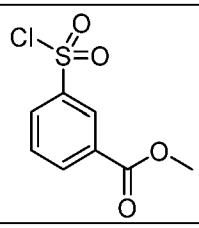
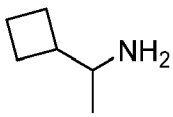
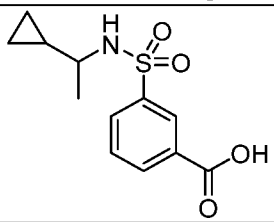
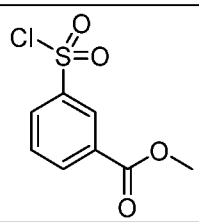
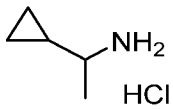
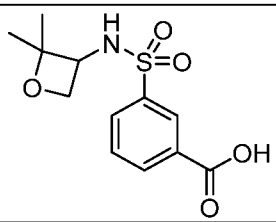
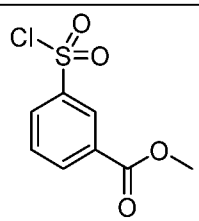
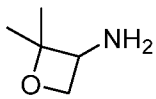
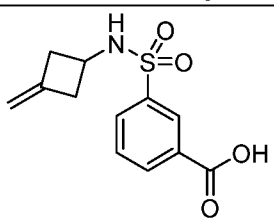
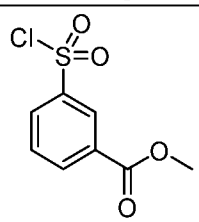
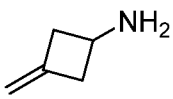
Table 3

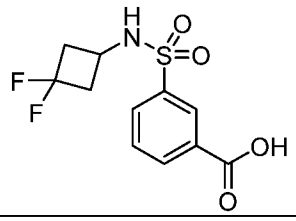
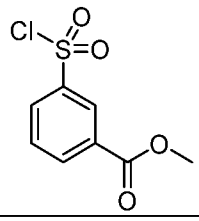
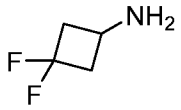
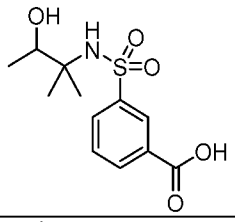
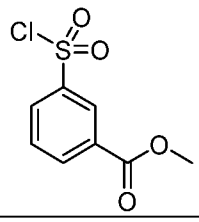
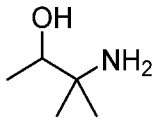
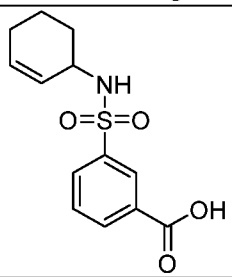
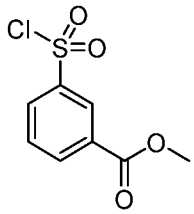
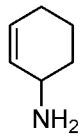
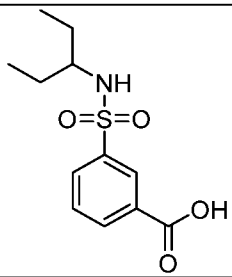
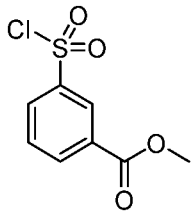
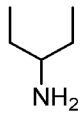
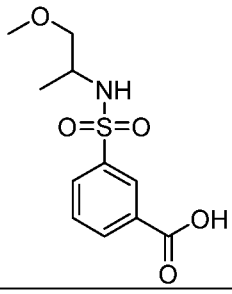
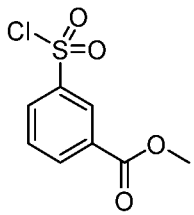
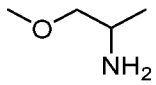
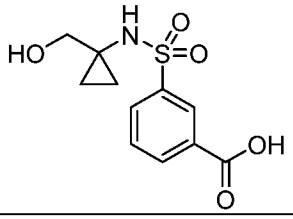
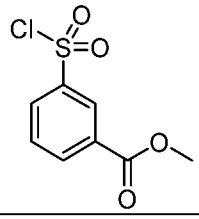
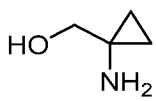
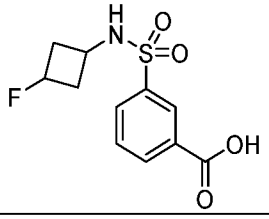
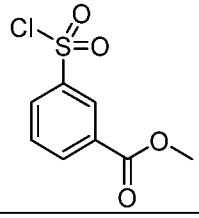
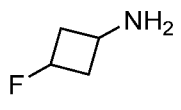
4	Structure	Sulfonyl Chloride	Amine
A-02			
A-03			
A-04			
A-05			
A-06			
A-07			
A-08			
A-09			

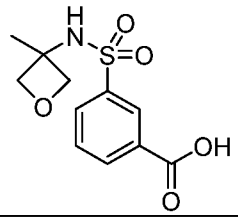
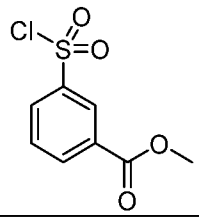
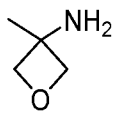
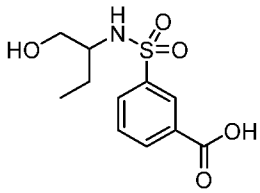
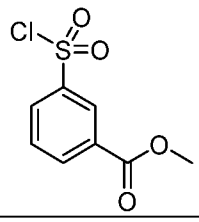
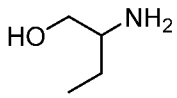
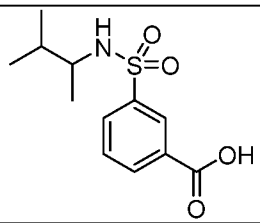
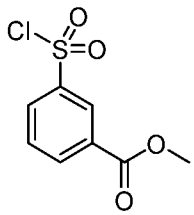
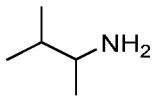
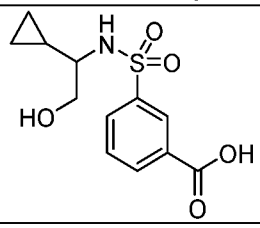
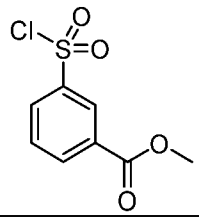
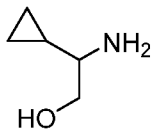
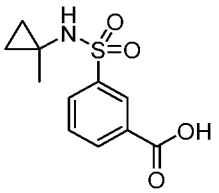
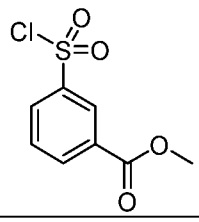
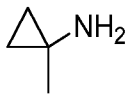
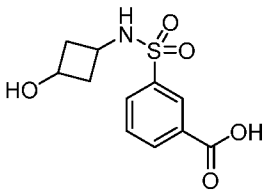
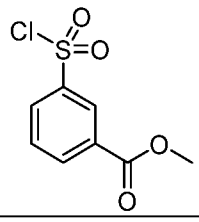
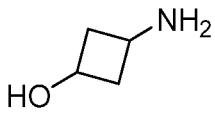
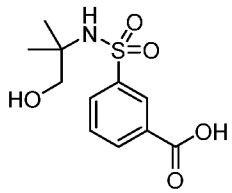
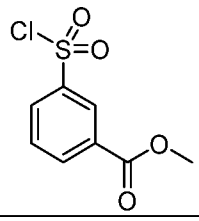
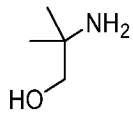
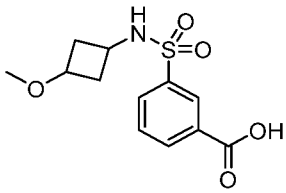
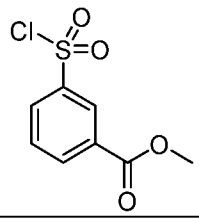
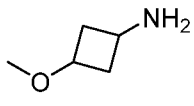
4	Structure	Sulfonyl Chloride	Amine
A-10			
A-11			
A-12			
A-13			
(S)-A-13			
A-14			
A-15			

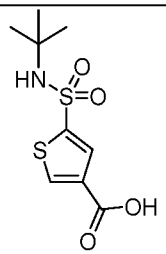
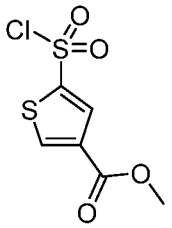
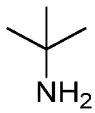
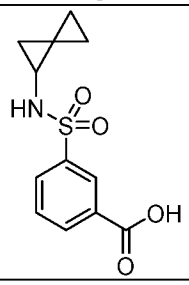
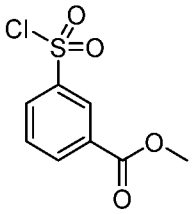
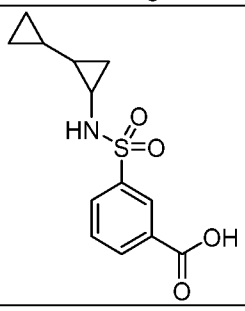
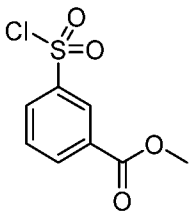
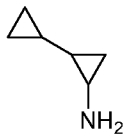
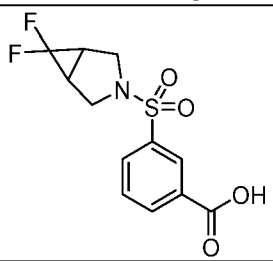
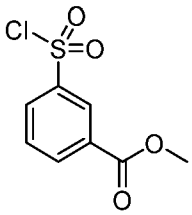
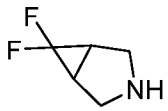
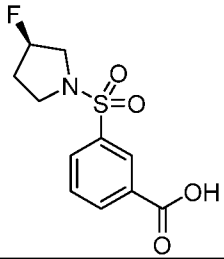
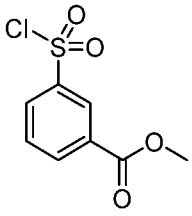
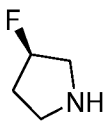
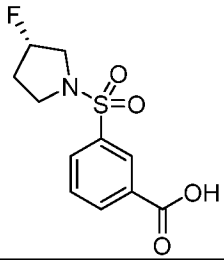
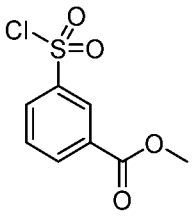
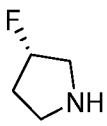
4	Structure	Sulfonyl Chloride	Amine
A-16			
A-17			
A-18			
A-19			
A-20			
A-21			
A-22			

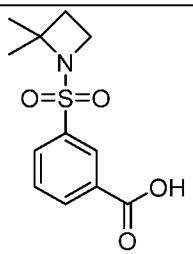
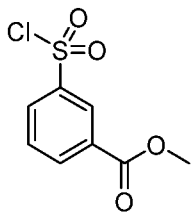
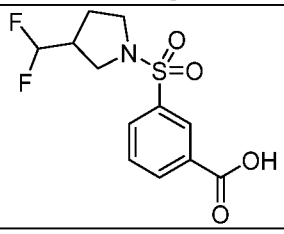
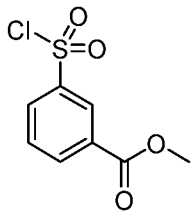
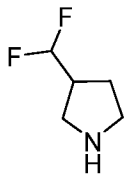
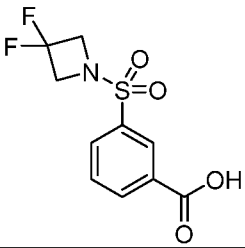
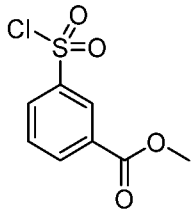
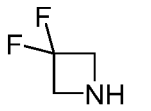
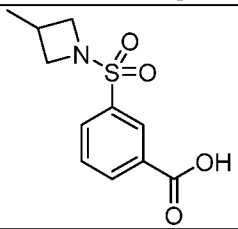
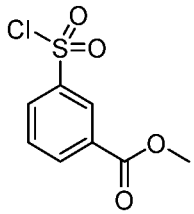
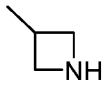
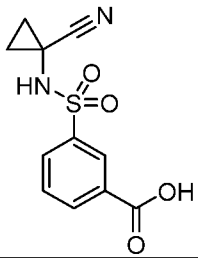
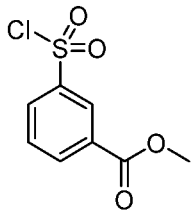
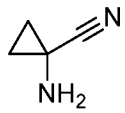
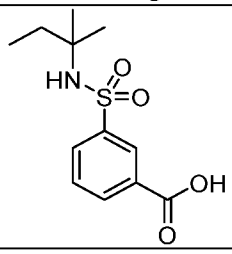
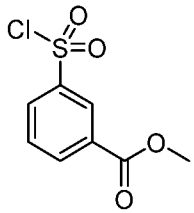
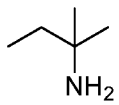
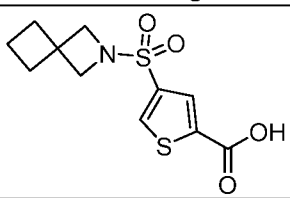
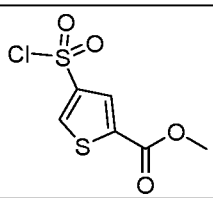
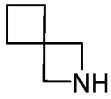
4	Structure	Sulfonyl Chloride	Amine
A-23			
A-24			
A-25			
A-26			
A-27			
A-28			

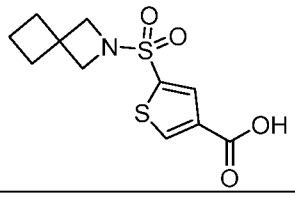
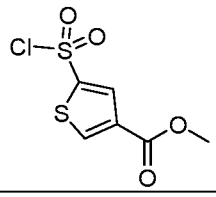
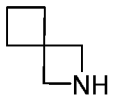
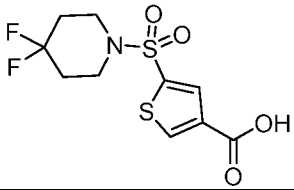
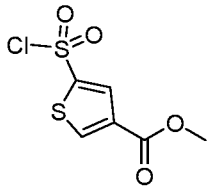
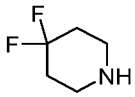
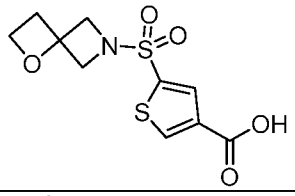
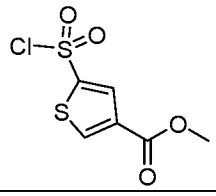
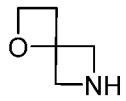
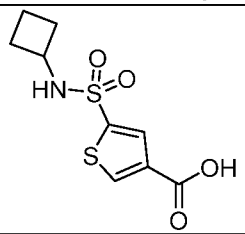
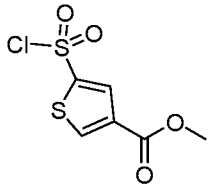
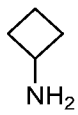
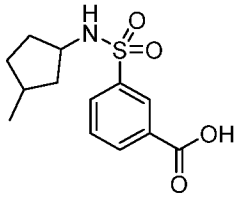
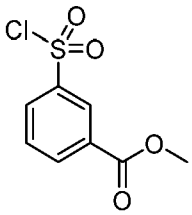
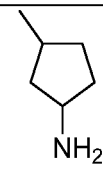
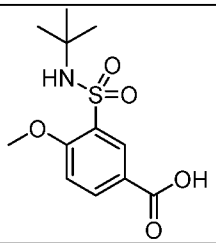
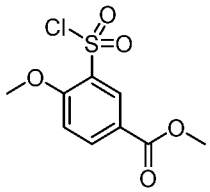
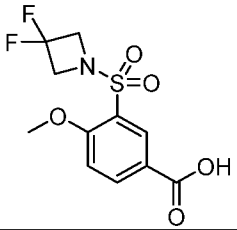
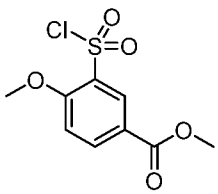
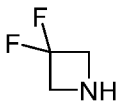
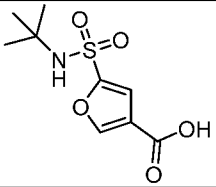
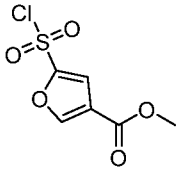
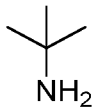
4	Structure	Sulfonyl Chloride	Amine
A-29			
A-30			
A-31			
A-32			
A-33			
A-34			
A-35			

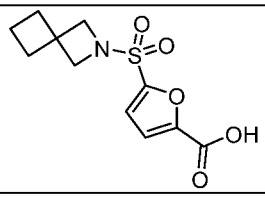
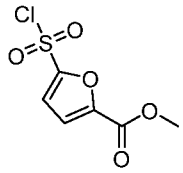
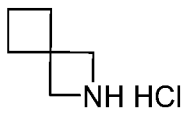
4	Structure	Sulfonyl Chloride	Amine
A-36			
A-37			
A-38			
A-39			
A-40			
A-41			
A-42			

4	Structure	Sulfonyl Chloride	Amine
A-43			
A-44			
A-45			
A-46			
A-47			
A-48			
A-49			
A-50			

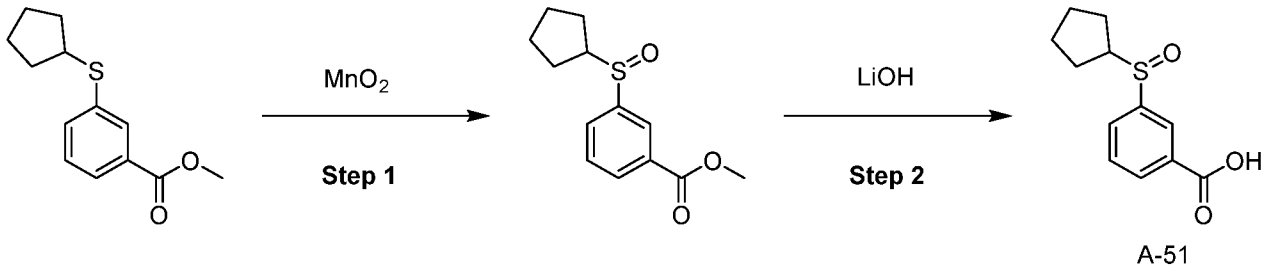
4	Structure	Sulfonyl Chloride	Amine
A-55			
A-56			
A-57			
A-58			
(R)-A-59			
(S)-A-59			

4	Structure	Sulfonyl Chloride	Amine
A-60			
A-61			
A-62			 F_3CCO_2H
A-63			
A-64			
A-65			
A-66			

4	Structure	Sulfonyl Chloride	Amine
A-67			
A-68			
A-69			
A-70			
A-71			 CF_3CO_2H
A-73			
A-74			 F_3CCO_2H
A-80			

4	Structure	Sulfonyl Chloride	Amine
A-81			

Synthesis of 3-(cyclopentylsulfinyl)benzoic acid (A-51)

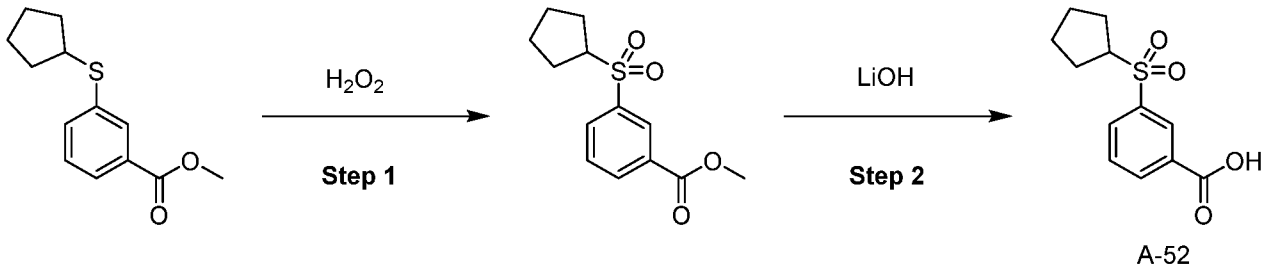


A-51

[0150] **Step 1**. A mixture of methyl 3-cyclopentylsulfanylbenzoate (0.50 g, 2.1 mmol), CH_2Cl_2 (25 mL), and MnO_2 (0.37 g, 4.2 mmol) was stirred at 20 °C for 16 h. The mixture was extracted with EtOAc (100 mL x 3), and the extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified silica gel chromatography (0-100% EtOAc/Petroleum ether) to provide methyl 3-cyclopentylsulfinylbenzoate (0.52 g).

[0151] **Step 2**. A mixture of methyl 3-cyclopentylsulfinylbenzoate (0.50 g, 2.0 mmol), THF (10 mL), H_2O (10 mL), and LiOH (95 mg, 4.0 mmol) was stirred at 25 °C for 2 h, and then was concentrated. The pH was adjusted to pH 3 with 2M HCl and the mixture was extracted with EtOAc (50 mL x 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated to provide 3-cyclopentylsulfinylbenzoic acid (**A-51**, 83 mg).

Synthesis of 3-(cyclopentylsulfonyl)benzoic acid (A-52)



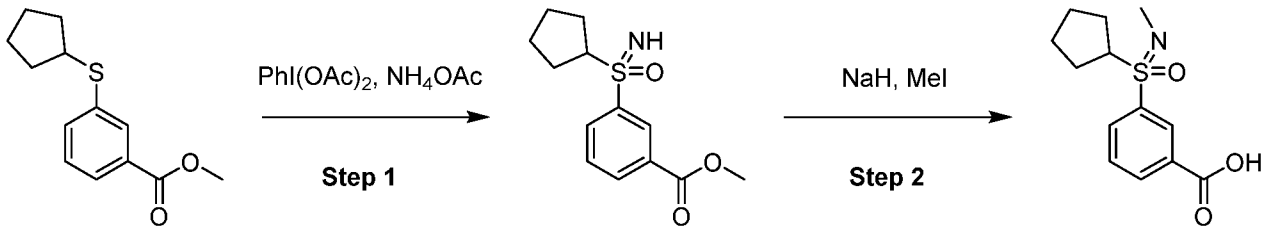
A-52

[0152] **Step 1**. To a mixture of methyl 3-cyclopentylsulfanylbenzoate (0.50 g, 2.1 mmol) in HOAc (3.0 mL) was added H_2O_2 (30%, 1.2 mL, 13 mmol). The mixture was stirred at 80 °C for 12 h, H_2O (20 mL) was added, and the mixture was extracted with EtOAc (10 mL x

3). The extracts were combined, washed saturated Na_2CO_3 (20 mL x 3), and aqueous of Na_2SO_3 (20 mL x 3), and brine (30 mL). The extracts were dried over Na_2SO_4, filtered, and concentrated to provide methyl 3-cyclopentylsulfonylbenzoate (260 mg).

[0153] **Step 2**. A mixture of methyl 3-cyclopentylsulfonylbenzoate (0.28 g, 1.0 mmol), THF (5.0 mL), H_2O (5 mL), and LiOH (50 mg, 2.1 mmol) was stirred at 25 °C for 2 h. The reaction mixture was extracted with MTBE (10 mL x 2). The pH of the aqueous phase was adjusted to 3 with HCl and it was extracted with EtOAc (3 x 20 mL). The extracts were combined, washed with 20 mL of brine, dried over Na_2SO_4, filtered, and concentrated to provide 3-cyclopentylsulfonylbenzoic acid (0.29 g).

Synthesis of 3-(N-methylcyclopentanesulfonimidoyl)benzoic acid (A-53)

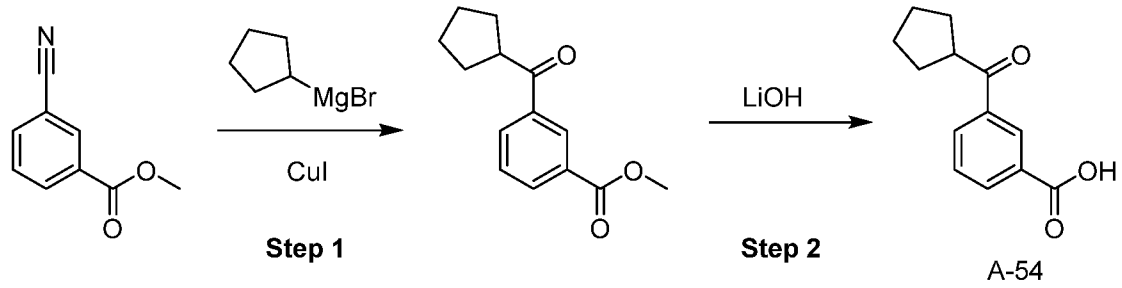


A-53

[0154] **Step 1**. To a mixture of methyl 3-cyclopentylsulfanylbenzoate (0.85 g, 3.6 mmol), EtOH (2 mL), and $PhI(OAc)_2$ (3.5 g, 11 mmol) was added NH_4OAc (1.1 g, 14 mmol). The mixture was stirred at 20 °C for 2 h, concentrated, combined with H_2O (30 mL), and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in petroleum ether) to provide methyl 3-(cyclopentylsulfonimidoyl) benzoate (0.50 g).

[0155] **Step 2**. To a 0 °C mixture of methyl 3-(cyclopentylsulfonimidoyl) benzoate (0.25 g, 0.94 mmol) and DMF (2 mL) was added NaH (60% in mineral oil, 45 mg, 1.1). The mixture was stirred at 0 °C for 0.5 h, and MeI (64 µL, 1.0 mmol) was added. The mixture was stirred at 20 °C for 12 h, poured into H_2O (30 mL) and extracted with EtOAc (2 x 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, concentrated to provide 3-(S-cyclopentyl -N-methyl-sulfonimidoyl)benzoic acid (**A-53**, 0.25 g).

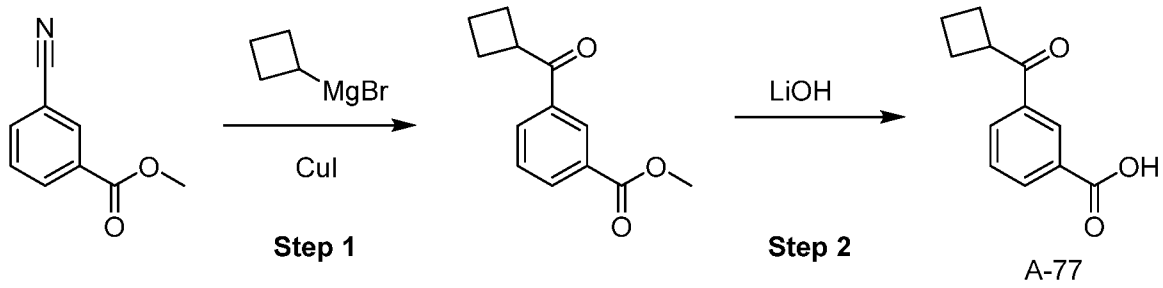
Synthesis of 3-(cyclopentanecarbonyl)benzoic acid (A-54)



[0156] **Step 1.** To a -50 °C mixture of methyl 3-cyanobenzoate (1.0 g, 6.2 mmol), CuI (0.37 g, 1.9 mmol), and THF (30 mL) was slowly added cyclopentylmagnesium bromide (1 M in THF, 24 mL, 24 mmol). The mixture was stirred at -50 °C for 5 h, then at 20 °C for 1 h, and saturated aqueous NH_4Cl (10 mL) was added at 0 °C. EtOAc (20 mL) was added, and the layers separated. The aqueous wash was extracted with EtOAc (10 mL), and extracts were combined, washed with brine (15 mL x 2), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (0-20% EtOAc / petroleum ether) to provide methyl 3-(cyclopentanecarbonyl) benzoate (0.22 g).

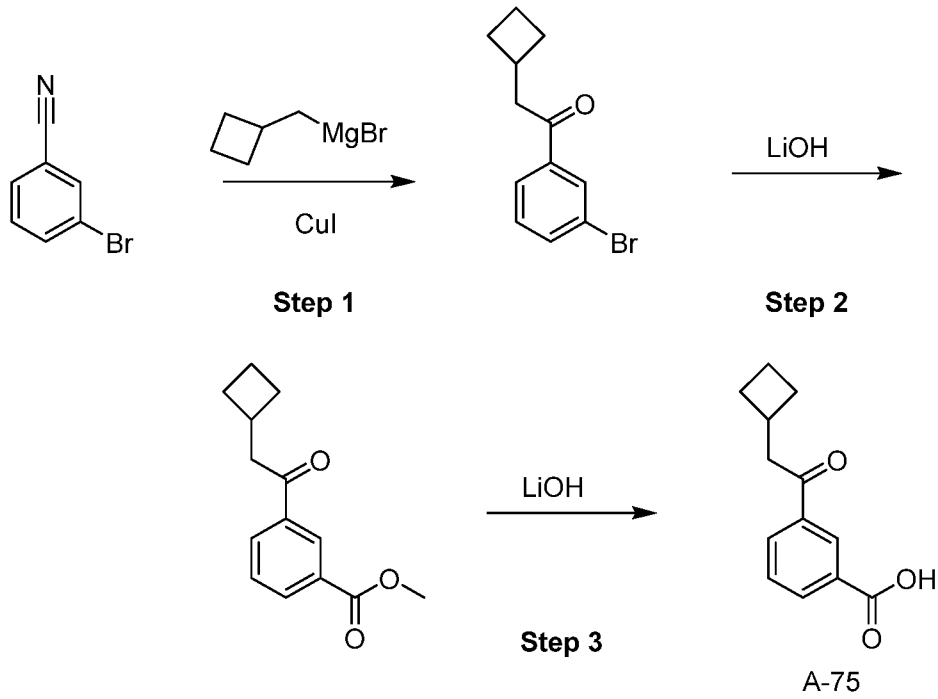
[0157] **Step 2.** A degassed mixture of methyl 3-(cyclopentanecarbonyl) benzoate (0.22 g, 0.95 mmol), LiOH (0.11 g, 4.7 mmol), THF (0.9 mL), H_2O (0.3 mL) was stirred at 25 °C for 4 h. The mixture was concentrated, combined with H_2O (10 mL), and extracted with MTBE (2 mL). The pH of the aqueous phase was adjusted to between 2 and 3 with 2N HCl. The resulting precipitate was filtered and dried under vacuum to provide 3-(cyclopentanecarbonyl)benzoic acid (**A-54**, 120 mg).

Synthesis of 3-(cyclobutanecarbonyl)benzoic acid (A-77)



[0158] 3-(Cyclobutanecarbonyl)benzoic acid was prepared from methyl 3-cyanobenzoate and cyclobutanemagnesium bromide in the same manner as **A-54**.

Synthesis of 3-(2-cyclobutylacetyl)benzoic acid (A-75)



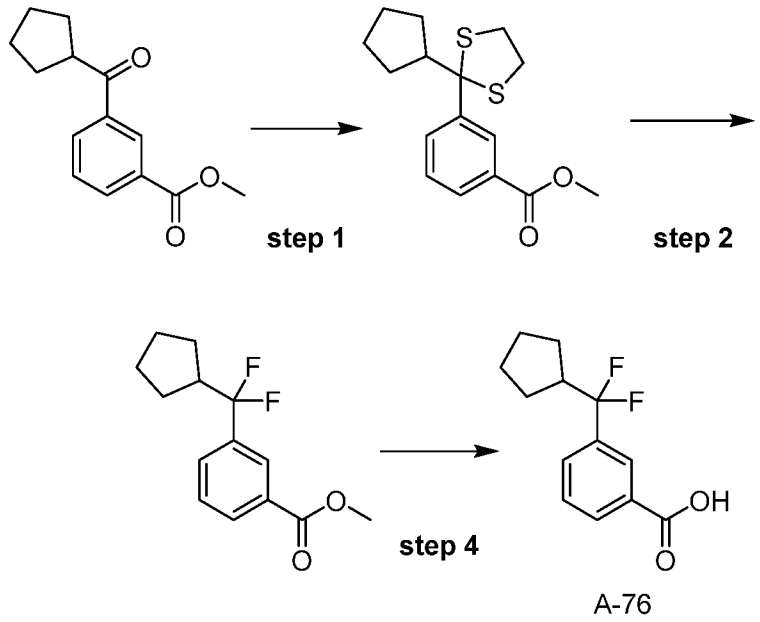
[0159] **Step 1.** To a mixture of 3-bromobenzonitrile (2.0 g, 11 mmol) and THF (10 mL) at -50 °C was added CuI (2.1 g, 11 mmol) and bromo(cyclobutylmethyl)magnesium (1 M, 13.2 mL). The mixture was stirred at -50 °C for 5 h then at 20 °C for 1 h. The mixture was poured into H_2O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (20 mL), dried over $Na2_SO_4$, concentrated, purified by silica chromatography (0-20% EtOAC in PE) to provide 1-(3-bromophenyl)-2-cyclobutylethan-1-one (1.3 g).

[0160] **Step 2.** A mixture of 1-(3-bromophenyl)-2-cyclobutylethan-1-one (1.1 g, 4.4 mmol), MeOH (4 mL), DMF (16 mL), Et_3N (1.8 mL, 13 mmol), 3-diphenylphosphanylpropyl-(diphenyl)phosphane (0.36 g, 0.87 mmol), and $Pd(OAc)_2$ (0.20 g, 0.87 mmol) was stirred at 90 °C for 12 h under CO (50 psi). The mixture was poured to water (30 mL), extracted with EtOAc (2 x 30 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-20% EtOAc in PE) provide methyl 3-(2-cyclobutylacetyl)benzoate (0.80 g).

[0161] **Step 3.** A mixture of methyl 3-(2-cyclobutylacetyl)benzoate (0.50 g, 2.2 mmol), THF (0.6 mL), H_2O (0.2 mL), and LiOH (0.16 g, 6.7 mmol) was stirred at 20 °C for 2 h. The mixture was concentrated to remove THF, and HCl (0.5 M, 5 mL) was added. The mixture was extracted with EtOAc (2 x 30 mL) and the combined extracts were washed with brine

(10 mL), dried over Na_2SO_4, and concentrated to provide 3-(2-cyclobutylacetyl)benzoic acid (0.36 g, 46% purity).

Synthesis of 3-(cyclopentyldifluoromethyl)benzoate (A-76)



A-76

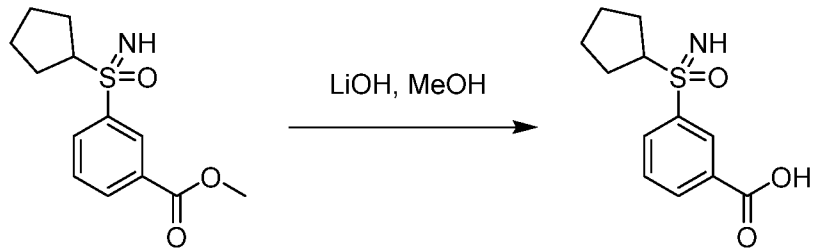
[0162] **Step 1.** To a mixture of methyl 3-(cyclopentanecarbonyl)benzoate (0.16 mg, 0.69 mmol) and CH_2Cl_2 (1 mL) was added BF_3•Et_2O (0.64 mL, 5.2 mmol) and ethane-1,2-dithiol (0.10 mL, 1.2 mmol). The mixture was stirred at 20 °C for 18 h, poured into water (20 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried Na_2SO_4, concentrated, purified by preparative TLC (10% EtOAc/PE) to provide methyl 3-(2-cyclopentyl-1,3-dithiolan-2-yl)benzoate (0.20 g).

[0163] **Step 2.** To a mixture of methyl 3-(2-cyclopentyl-1,3-dithiolan-2-yl)benzoate (0.20 g, 0.65 mmol) and CH_2Cl_2 (10 mL) was added NIS (0.29 g, 1.3 mmol) and pyridine hydrofluoride (0.33 mL, 2.6 mmol) at - 70 °C. The mixture was stirred at -70 °C for 0.5 h, poured into H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative TLC (10% EtOAc in PE) to provide methyl 3-[cyclopentyl(difluoro)methyl]benzoate (80 mg).

[0164] **Step 3.** A mixture of methyl 3-[cyclopentyl(difluoro)methyl]benzoate (80 mg, 0.32 mmol), THF (3 mL), H_2O (1 mL), and LiOH (23 mg, 0.94 mmol) was stirred at 20 °C for 2 h. The mixture was concentrated, combined with HCl (0.5 M, 5 mL), and extracted with

EtOAc (2 x 30 mL). The combined extract was washed with brine (10 mL), dried Na_2SO_4, concentrated, to provide 3-[cyclopentyl(difluoro)methyl]benzoic acid (A-76, 91 mg).

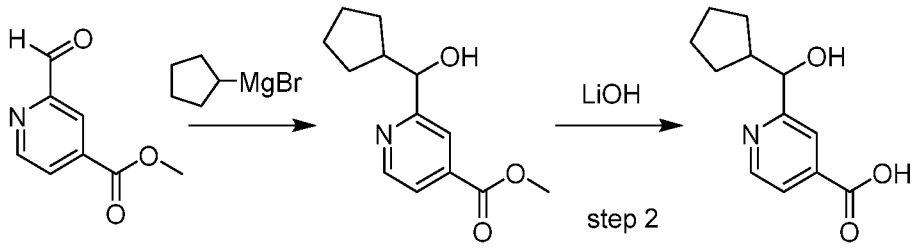
Synthesis of 3-(cyclopentanesulfonimidoyl)benzoic acid (A-72)



A-72

[0165] A mixture of methyl 3-(cyclopentylsulfonimidoyl)benzoate (0.80 g, 3.0 mmol), THF (18 mL), H_2O (6 mL), and $LiOH•H_2O$ (0.38 g, 9.0 mmol) was stirred at 25 °C for 12 h, then was poured into water (20 mL) and =extracted with EtOAc (2 x 10 mL). The organic phase was washed with brine (20 mL), dried over Na_2SO_4, and concentrated to provide 3-(cyclopentanesulfonimidoyl)benzoic acid (A-72, 0.3 g). ^1H NMR (DMSO-d^6, 400 MHz) δ ppm 13.72 - 13.06 (m, 1 H), 8.40 - 8.38 (s, 1 H), 8.20 - 8.17 (m, 1 H), 8.13 - 8.09 (m, 1 H), 7.76 - 7.72 (m, 1 H), 3.68 - 3.60 (m, 1 H), 1.91 - 1.70 (m, 4 H), 1.62 - 1.47 (m, 4 H).

Synthesis of 2-(cyclopentyl(hydroxy)methyl)isonicotinic acid (A-78)



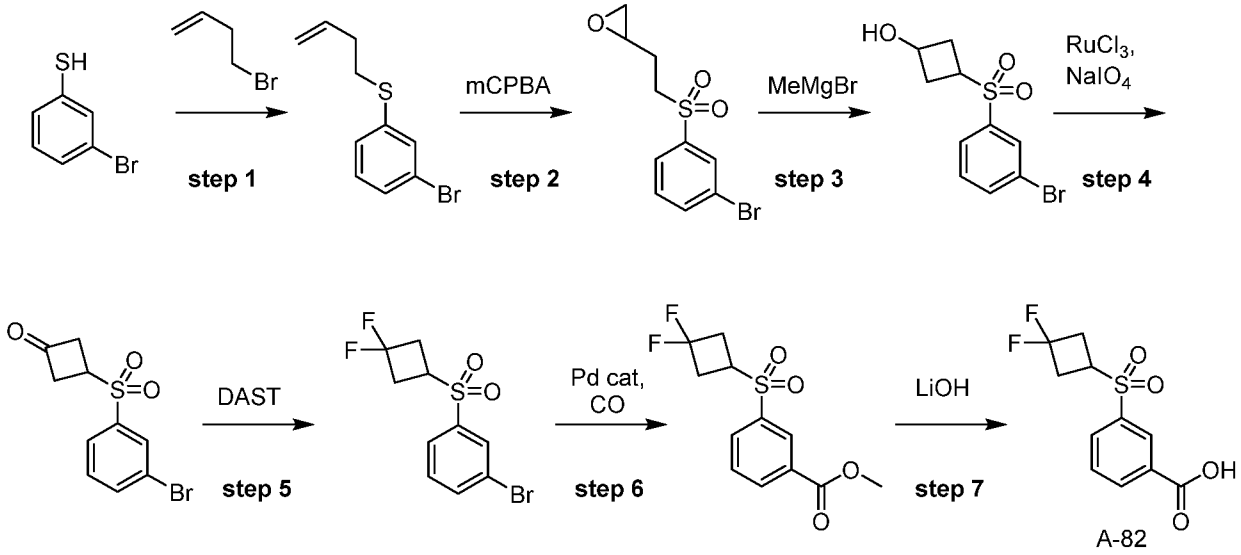
A-78

[0166] **Step 1**. To a -60 °C mixture of methyl 2-formylisonicotinate (1.0 g, 6.0 mmol) and THF (25 mL) was added cyclopentylmagnesium bromide (1 M, 7.3 mL) over 15 min. The resulting mixture was stirred at -60 °C for 1.75 h, poured into water (50 mL), and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide methyl 2-(cyclopentyl(hydroxy)methyl)isonicotinate (0.20 g).

[0167] **Step 2**. A mixture of methyl 2-(cyclopentyl(hydroxy)methyl)isonicotinate (0.18 g, 0.77 mmol), THF (2 mL), and H_2O (1 mL), and $LiOH•H_2O$ (96 mg, 2.0 mmol) was stirred at

25 °C for 2 h, poured into water (30 mL), and extracted with MTBE (2 x 20 mL). The aqueous layer was collected, and the pH was adjusted to 5 by the careful addition of 2N HCl. The mixture was concentrated to provide 2-(cyclopentyl(hydroxy)methyl)isonicotinic acid (**A-78**).

Synthesis of 3-((3,3-difluorocyclobutyl)sulfonyl)benzoic acid (A-82)



[0168] **Step 1**. To mixture of 3-bromobenzenethiol (3.4 mL, 33 mmol), 4-bromobut-1-ene (4.4 mL, 43 mmol), DMF (50 mL), and K_2CO_3 (6.8 g, 49 mmol) was stirred at 60 °C for 4 h, combined with 1M aq. $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide 1-bromo-3-but-3-enylsulfanyl-benzene (6.50 g).

[0169] **Step 2**. To a mixture of 1-bromo-3-but-3-enylsulfanyl-benzene (6.5 g, 27 mmol) and CH_2Cl_2 (50 mL) was added mCPBA (27 g, 0.13 mol, 85% purity). The mixture was stirred at 20 °C for 12 h, combined with 1M aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (2 x 30 mL), washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide 2-[2-(3-bromophenyl)sulfonylethyl]oxirane (5.1 g).

[0170] **Step 3**. To a mixture of 2-[2-(3-bromophenyl)sulfonylethyl]oxirane (5.1 g, 18 mmol) and THF (50 mL) was added MeMgBr (3 M, 23 mL, 69 mmol) at -70°C. The mixture was stirred at 20°C for 12 h, poured into saturated aqueous NH_4Cl (20 mL), and extracted

with EtOAc (2 x 20 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide 3-(3-bromophenyl)sulfonylcyclobutanol (4.3 g).

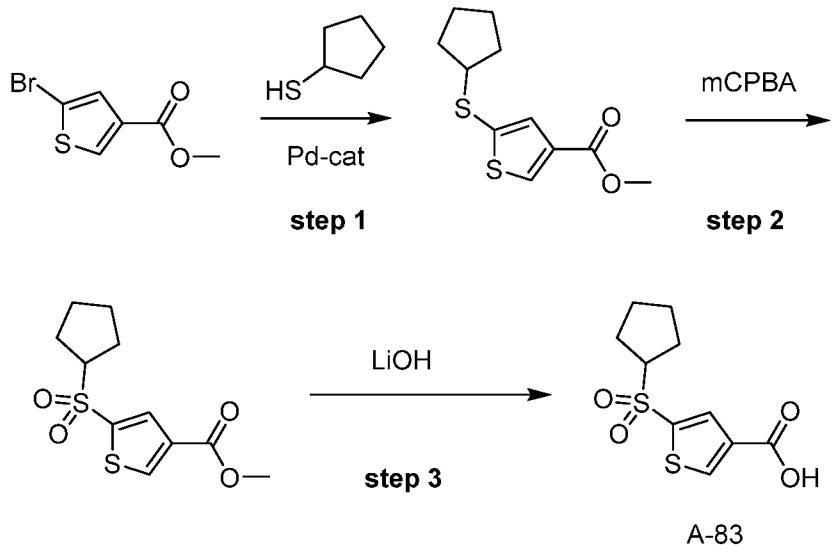
[0171] **Step 4**. To a mixture of 3-(3-bromophenyl)sulfonylcyclobutanol (1.00 g, 3.4 mmol), H_2O (10 mL), MeCN (5 mL), and CH_2Cl_2 (5 mL) at 40 °C were added $RuCl_3•H_2O$ (8 mg, 34 μmol) and $NaIO_4$ (3.7 g, 17 mmol). The mixture was stirred at 40 °C for 12 h, cold water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide 3-(3-bromophenyl)sulfonylcyclobutanone (0.64 g).

[0172] **Step 5**. To a mixture of 3-(3-bromophenyl)sulfonylcyclobutanone (0.64 g, 2.2 mmol) and CH_2Cl_2 (6 mL) was added DAST (0.88 mL, 6.6 mmol) over 0.5 h at -70 °C. The mixture was stirred for 1 h, and then allowed to warm 20 °C and stirred for 16 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and the extracted with CH_2Cl_2 (2 x 10 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide 1-bromo-3-(3,3-difluorocyclobutyl)sulfonyl-benzene (0.60 g).

[0173] **Step 6**. CO gas was bubbled through a stirring mixture of 1-bromo-3-(3,3-difluorocyclobutyl)sulfonyl-benzene (0.55 g, 1.8 mmol), Et_3N (0.49 mL, 3.5 mmol) , DMF (6 mL), MeOH (3 mL), bis(diphenylphosphino)propane (73 mg, 0.18 mmol), and $Pd(OAc)_2$ (40 mg, 0.18 mmol) for 5 mins and the mixture was then heated at 80 °C under a CO atmosphere at 15 psi for 12 h. The mixture was poured into water (30 mL), extracted with EtOAc (2 x 30 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide methyl 3-(3,3-difluorocyclobutyl)sulfonylbenzoate (0.44 g).

[0174] **Step 7**. A mixture of methyl 3-(3,3-difluorocyclobutyl) sulfonylbenzoate (0.44 g, 1.5 mmol), THF (5 mL), H_2O (1.5 mL), and $LiOH•H_2O$ (0.25 g, 6.1 mmol) was stirred at 40 °C for 2 h, concentrated, combined with H_2O (30 mL), 2N HCl was added until the pH was between 3 and 4, and the resulting mixture was extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to provide 3-((3,3-difluorocyclobutyl)sulfonyl)benzoic acid (**A-82**, 0.33 g).

Synthesis of 5-(cyclopentylsulfonyl)thiophene-3-carboxylic acid (A-83)



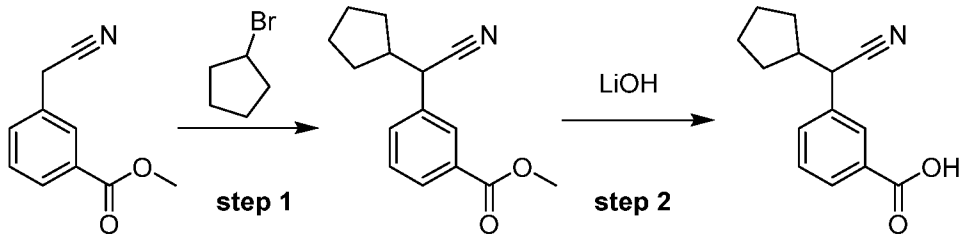
[0175] **Step 1.** A mixture of methyl 5-bromothiophene-3-carboxylate (1.0 g, 4.5 mmol), 1,4-dioxane (25 mL), iPr_2NEt (2.0 mL, 11 mmol), $Pd_2(dba)_3$ (0.41 g, 0.45 mmol), cyclopentanethiol (0.73 mL, 6.8 mmol), and Xantphos (0.26 g, 0.45 mmol) was stirred at 110 °C for 12 h. The mixture was poured into H_2O (20 mL), extracted with EtOAc (2 x 10 mL), and the combined extracts were washed with brine (20 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provide methyl 5-cyclopentylsulfanylthiophene-3-carboxylate (1.0 g).

[0176] **Step 2.** To a mixture of methyl 5-cyclopentylsulfanylthiophene-3-carboxylate (0.70 g, 2.9 mmol) and CH_2Cl_2 (20 mL) was added mCPBA (2.4 g, 12 mmol, 85% purity). The mixture was stirred at 20 °C for 12 h, poured into saturated Na_2SO_3 (10 mL), and extracted with EtOAc (2 x 5 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provide methyl 5-cyclopentylsulfonylthiophene-3-carboxylate (0.70 g).

[0177] **Step 3.** A mixture methyl 5-cyclopentylsulfonylthiophene-3-carboxylate (0.71 g, 2.6 mmol), THF (9 mL), H_2O (3 mL), and $LiOH•H_2O$ (0.32 g, 7.7 mmol) was stirred at 20 °C for 12 h, poured into H_2O (10 mL), and the pH was adjusted to

3-4 with HCl (2 N). The resulting mixture was extracted with EtOAc (2 x 5 mL). The extracts were combined, washed with brine (5 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provide 5-(cyclopentylsulfonyl)thiophene-3-carboxylic acid (A-83, 0.40 g).

Synthesis of 3-(cyano(cyclopentyl)methyl)benzoic acid (A-85)

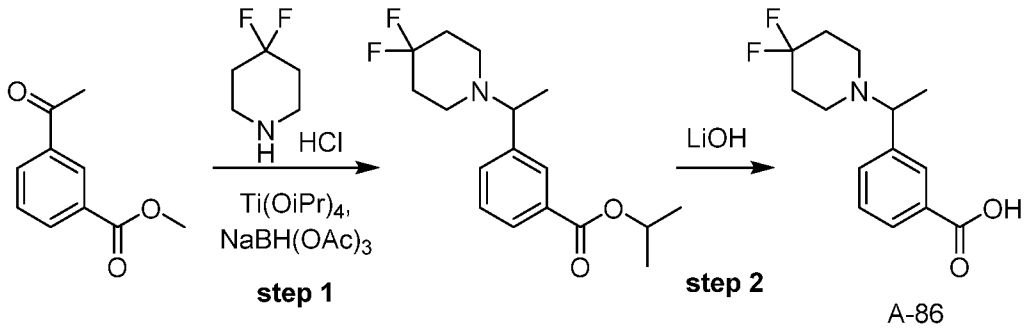


A-85

[0178] **Step 1**. To a mixture of methyl 3-(cyanomethyl)benzoate (0.10 g, 0.58 mmol) and DMF (2 mL) was added NaH (27 mg, 0.69 mmol, 285 uL, 60% purity, 1.2 eq) at 0 °C. After stirring for 0.5 h, bromocyclopentane (0.12 mL, 1.1 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 2 h, and saturated aqueous NH_4Cl (2 mL) and H_2O (10 mL) were added at 0 °C. The mixture was extracted with EtOAc (10 mL x 3), and the combined extracts were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered, concentrated, purified by silica chromatography (0-15% EtOAc in PE) to provide methyl 3-(cyano(cyclopentyl)methyl)benzoate (0.10 g).

[0179] **Step 2**. A mixture of methyl 3-(cyano(cyclopentyl)methyl)benzoate (0.10 g, 0.41 mmol), THF (3 mL), H_2O (3 mL), and $LiOH•H_2O$ (35 mg, 0.82 mmol) was stirred at 20 °C for 4 h, concentrated, and the pH adjusted to 4 by the dropwise addition of 2M HCl. The mixture was extracted with EtOAc (20 mL x 3), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated to provide 3-(cyano(cyclopentyl)methyl)benzoic acid (**A-85**, 0.11 g).

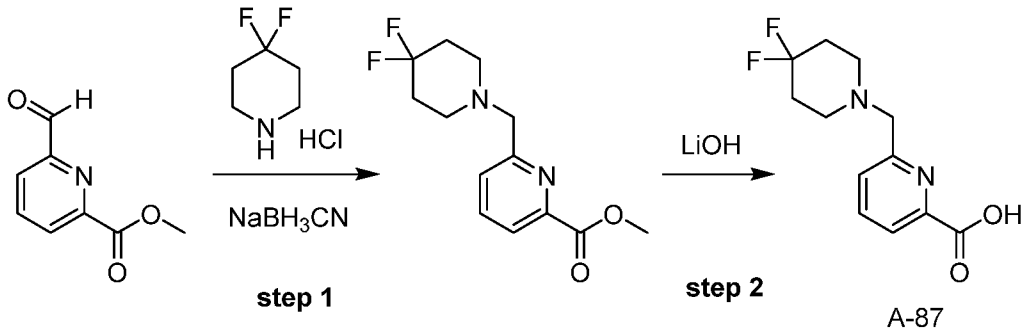
[0180] **Synthesis of 3-(1-(4,4-difluoropiperidin-1-yl)ethyl)benzoic acid (A-86)**



[0181] **Step 1**. A mixture of methyl 3-acetylbenzoate (1.0 g, 5.6 mmol) and 4,4-difluoropiperidine hydrochloride (0.88 g, 5.6 mmol), 1,2-dichloroethane (20 mL), $Ti(OiPr)_4$ (6.6 mL, 23 mmol) and then was stirred at 80 °C for 12 h. $NaBH(OAc)_3$ (3.6 g, 17 mmol) was added and the mixture was stirred at 80 °C for 2 h, poured into water (20 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to provide isopropyl 3-[1-(4,4-difluoro-1-piperidyl)ethyl]benzoate (1.5 g).

[0182] **Step 2**. A mixture of isopropyl 3-[1-(4,4-difluoro-1-piperidyl)ethyl]benzoate (1.4 g, 4.6 mmol) in THF (14 mL), MeOH (3.3 mL), and H_2O (3.3 mL), and LiOH (0.33 g, 14 mmol) was stirred at 25 °C for 2 h. The mixture was concentrated, combined with H_2O (28 mL) and washed with EtOAc (2 x 28 mL). The aqueous solution was treated with 2M HCl until a pH of 2, and the resulting mixture was concentrated to provide 3-[1-(4,4-difluoro-1-piperidyl)ethyl]benzoic acid (**A-86**, 0.91 g).

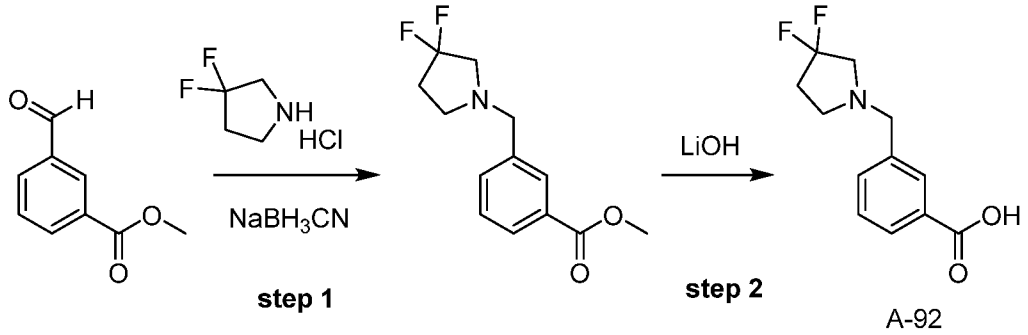
[0183] **Synthesis of 6-((4,4-difluoropiperidin-1-yl)methyl)picolinic acid (A-87)**



[0184] **Step 1.** A mixture of methyl 6-formylpyridine-2-carboxylate (0.50 g, 3.0 mmol) and 4,4-difluoropiperidine (477 mg, 3.0 mmol, 1.0 eq, HCl) in MeOH (10 mL) was added HOAc (545 mg, 9.1 mmol, 519 uL, 3.0 eq), NaOAc (745 mg, 9.1 mmol, 3.0 eq) and then was stirred at 25 °C for 1 hour. Then added NaBH3CN (761 mg, 12.1 mmol, 4.0 eq), the mixture

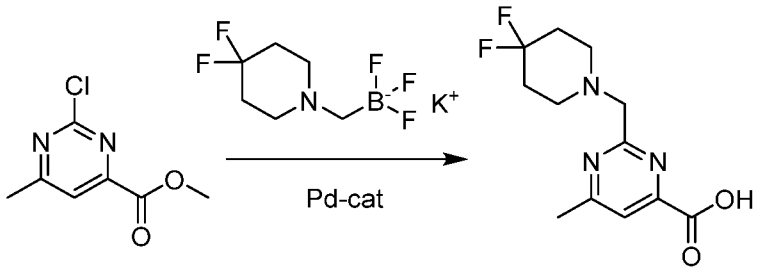
was stirred at 25 °C for 1 hour. The reaction was poured into water (10 mL) and the resulting mixture was extracted with EtOAc (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to afford the compound methyl 6-[(4,4-difluoro-1-piperidyl)methyl]pyridine-2-carboxylate (500 mg, crude) as a yellow solid.

Synthesis of 3-((3,3-difluoropyrrolidin-1-yl)methyl)benzoic acid (A-92)



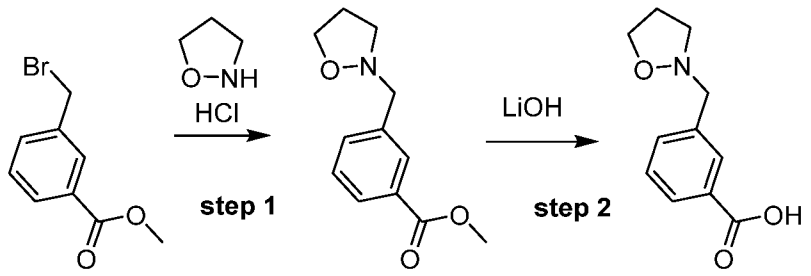
[0185] 3-((3,3-difluoropyrrolidin-1-yl)methyl)benzoic acid (**A-92**) was prepared from methyl 3-formylbenzoate in the mannet described for the synthesis of **A-87**.

Synthesis of 2-((4,4-difluoropiperidin-1-yl)methyl)-6-methylpyrimidine-4-carboxylic acid (A-88)



[0186] A mixture of potassium ((4,4-difluoropiperidin-1-yl)methyl)trifluoroborate (CAS: 1708960-44-4, 1.1 g, 4.6 mmol), methyl 2-chloro-6-methyl-pyrimidine-4-carboxylate (0.28 g, 1.5 mmol), H_2O (2 mL), THF (8 mL) Cs_2CO_3 (1.5 g, 4.6 mmol), and Xphos Pd G4 (65 mg, 76 µmol). The mixture was stirred at 80 °C for 12 h, diluted with water (10 mL), and extracted with EtOAc (10 mL × 3). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and purified by preparative HPLC (C18, 1-10% MeCN in H_2O [formic acid]) to provide 2-((4,4-difluoropiperidin-1-yl)methyl)-6-methylpyrimidine-4-carboxylic acid (**A-88**, 50 mg).

Synthesis of 3-(isoxazolidin-2-ylmethyl)benzoic acid (A-89)

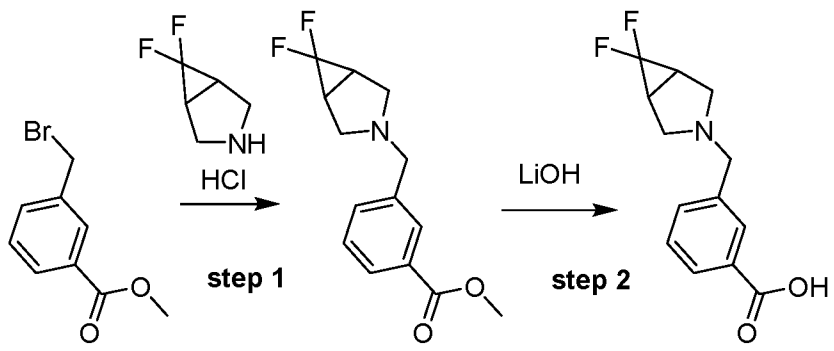


A-89

[0187] **Step 1**. A mixture of methyl 3-(bromomethyl)benzoate (0.30 g, 1.3 mmol), DMF (3 mL), isoxazolidine hydrochloride (0.14 g, 1.3), and iPr_2NEt (0.68 mL, 3.9 mmol) was stirred at 60 °C for 12 h. The mixture was combined with 0 °C H_2O (10 mL) and extracted with EtOAc (10 mL x 2). The combined extracts were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide methyl 3-(isoxazolidin-2-ylmethyl)benzoate (0.17 g).

[0188] **Step 2**. A mixture of methyl 3-(isoxazolidin-3-ylmethyl)benzoate (0.17 g, 0.77 mmol), 1,4-dioxane (1.5 mL), H_2O (0.5 mL) and $LiOH•H_2O$ (32 mg, 0.77 mmol) was stirred at 20 °C for 12 h, and H_2O (5 mL) and MTBE (10 mL). The aqueous phase was collected and the pH adjusted to 6.0 by addition of HCl (2 N). The aqueous phase was concentrated to provide 3-(isoxazolidin-3-ylmethyl)benzoic acid (**A-89**, 0.17 g, crude).

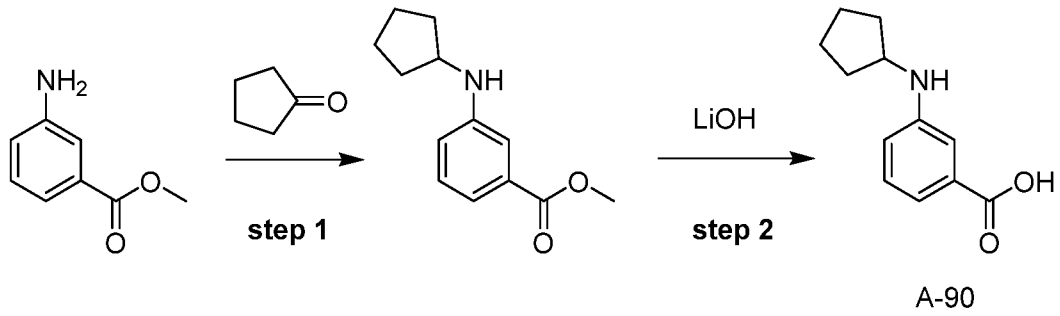
Synthesis of 3-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)benzoic acid (A-96)



A-96

[0189] Synthesis of 3-((6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)methyl)benzoic acid (**A-96**) was prepared in the same manner as **A-89** by substituting 6,6-difluoro-3-azabicyclo[3.1.0]hexane hydrochloride for isoxazolidine hydrochloride

Synthesis of 3-(cyclopentylamino)benzoic acid (A-90)

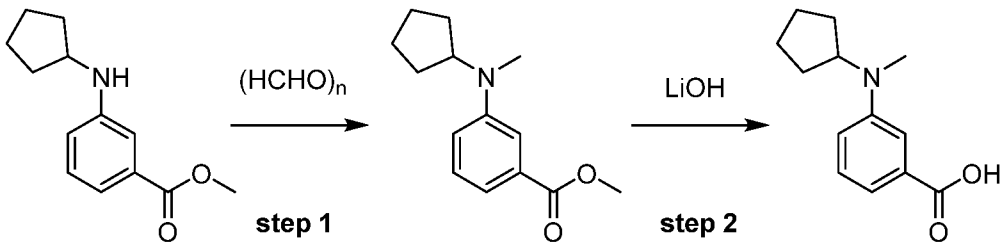


A-90

[0190] **Step 1.** A mixture of methyl 3-aminobenzoate (1.0 g, 6.6 mmol). cyclopentanone (2.9 mL, 33 mmol), MeOH (10 mL), and HOAc (0.38 mL, 6.6 mmol) was stirred for 3 hours, and $NaBH_3CN$ (0.62 g, 9.9 mmol) was added in portions. The resulting mixture was stirred for 11 h, poured into water (50 mL), and extracted with EtOAc (2 x 25 mL). The extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provide methyl 3-(cyclopentylamino)benzoatee (1.33 g, 91.68% yield) as a white solid.

[0191] **Step 2.** A mixture of methyl 3-(cyclopentylamino)benzoate (0.10 g, 0.46 mmol), THF (0.9 mL), H_2O (0.3 mL), and $LiOH•H_2O$ (96 mg, 2.3 mmol) was stirred at 60 °C for 6 h, poured into H_2O (10 mL), and the pH adjusted to 5-6 with HCl (2 N). The resulting mixture was extracted with EtOAc (2 x 5 mL), the extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to provide 3-(cyclopentylamino)benzoic acid (**A-90**, 53 mg).

Synthesis of 3-(cyclopentyl(methyl)amino)benzoic acid (A-91)

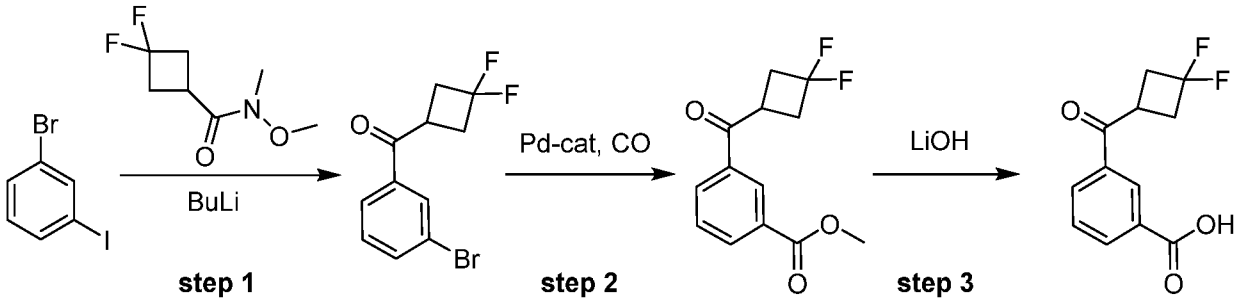


[0192] **Step 1**. To a mixture of methyl 3-(cyclopentylamino)benzoate (0.50 g, 2.0 mmol), paraformaldehyde (0.41 mg, 5 mmol), and dichloroethane (5 mL) was added HOAc (0.16 mL, 3.0 mmol) dropwise at 20 °C. After stirring for 1 h, and $NaBH(OAc)_3$ (0.97 g, 5 mmol) and the mixture was stirred at 60 °C for 11 h. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was

washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provvide methyl 3-[cyclopentyl(methyl)amino]benzoate (0.42 g).

[0193] **Step 2**. A mixture of methyl 3-[cyclopentyl(methyl)amino]benzoate (0.23 g, 0.98 mmol), THF (3 mL), and H_2O (1 mL), and $LiOH•H_2O$ (0.12 g, 3.0 mmol) was stirred at 60 °C for 2 h. The mixture was poured into water (10 mL), the pH adjusted to 3-4 with HCl (2 N), and was extracted with EtOAc (2 x 5 mL). The extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to provide 3-(cyclopentyl(methyl)amino)benzoic acid (**A-91**, 0.30 g).

Synthesis of 3-(3,3-difluorocyclobutane-1-carbonyl)benzoic acid (A-93)



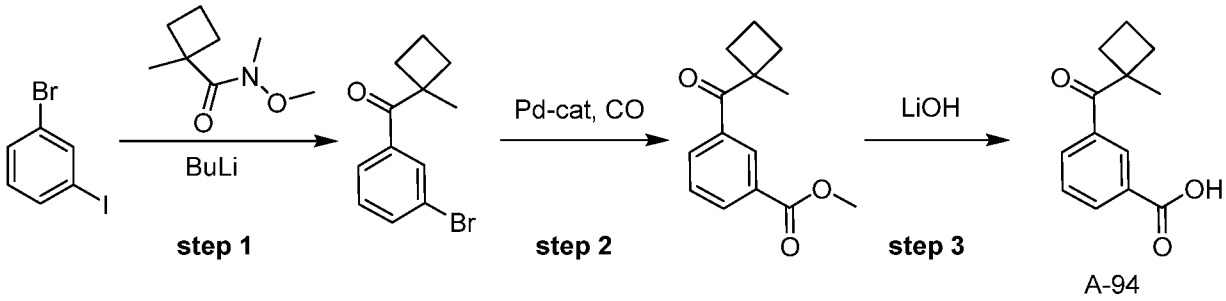
[0194] **Step 1**. To a -70 °C mixture of 1-bromo-3-iodo-benzene (1.3 mL, 10 mmol) and THF (20 mL), was added dropwise BuLi (1 M, 10 mL). The mixture was stirred for 30 min. and 3,3- difluoro-N-methoxy-N-methyl-cyclobutanecarboxamide (1.5 g, 8.4 mmol) in THF (10 mL) was added dropwise at -70 °C. The resulting mixture was stirred at 20 °C for 1.5 h, poured into saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-100% EtOAc in PE) to provide (3-bromophenyl)-(3,3-difluorocyclobutyl) methanone (1.1 g).

[0195] **Step 2**. A mixture of (3-bromophenyl)-(3,3-difluorocyclobutyl)methanone (1.0 g, 3.6 mmol), MeOH (5 mL), DMF (10 mL), Et_3N (1.5 mL, 11 mmol), 3-diphenylphosphanylpropyl (diphenyl)phosphane (0.30 g, 0.73 mmol), $Pd(OAc)_2$ (0.16 g, 0.73 mmol) was stirred at 80 °C for 12 h under CO (50 psi). The mixture was concentrated, poured into H_2O (10 mL), and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative

TLC (10% EtOAc in PE) to provide methyl 3-(3,3-difluorocyclobutanecarbonyl)benzoate (0.80 g).

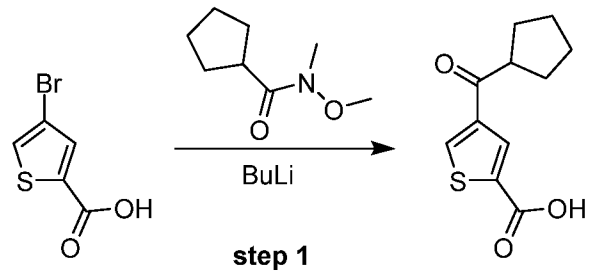
[0196] **Step 3**. A mixture methyl 3-(3,3-difluorocyclobutanecarbonyl)benzoate (0.80 g, 3.2 mmol), THF (0.6 mL), H_2O (0.2 mL), and $LiOH•H_2O$ (226 mg, 9.4 mmol, 3.0 eq) The mixture was stirred at 20 °C for 2 h, concentrated, and HCl (0.5 M, 5 mL) was added. The mixture was extracted with EtOAc (10 mL), and the extract was concentrated to provide 3-(3,3-difluorocyclobutane-1-carbonyl)benzoic acid (**A-93**, 0.50 g).

Synthesis of 3-(1-methylcyclobutane-1-carbonyl)benzoic acid (A-94)



[0197] 3-(1-methylcyclobutane-1-carbonyl)benzoic acid (**A-94**) was prepared in the same manner as **A-93**.

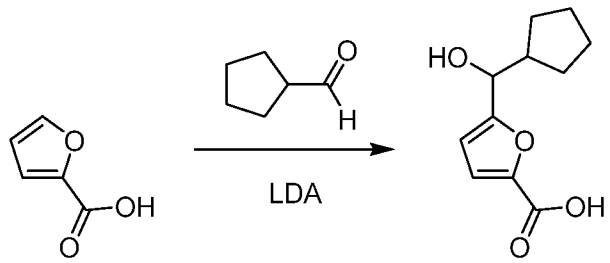
Synthesis of 4-(cyclopentanecarbonyl)thiophene-2-carboxylic acid (A-98)



[0198] nBuLi (2.5 M, 3.9 mL, 2.5 eq) was added dropwise to 4-bromothiophene-2-carboxylic acid (0.80 g, 3.9 mmol) in THF (15 mL) over 5 min at -78 °C. The mixture was stirred for 25 min, and N-methoxy-N-methyl-cyclopentanecarboxamide (0.91 g, 5.8 mmol) was added at -78 °C. The resulting mixture was stirred at 20 °C for 12 h, combined with saturated NH_4Cl 1 mL at -78 °C and H_2O (5 mL) and extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine (10 mL), dried Na_2SO_4, filtered, concentrated, and

purified by preparative HPLC (C18, 20-50% MeCN in H_2O [HCl]) to provide 4-(cyclopentanecarbonyl) thiophene-2-carboxylic acid (**A-98**, 10%).

Synthesis of 5-(cyclopentyl(hydroxy)methyl)furan-2-carboxylic acid (A-99)

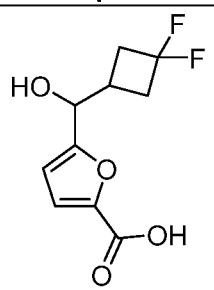
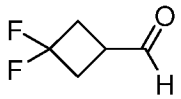
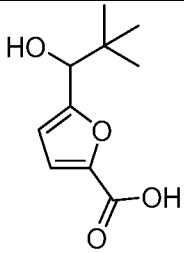


A-99

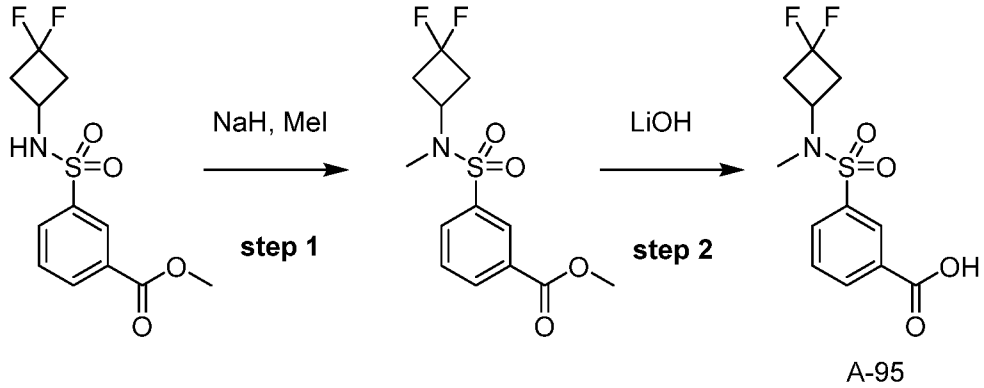
[0199] To a mixture of furan-2-carboxylic acid (2.0 g, 18 mmol) and THF (20 mL) was added dropwise LDA (2 M, 13 mL) at -70 °C. The mixture was stirred 0.5 h, and cyclopentanecarbaldehyde (2.6 g, 27 mmol) in THF (20 mL) was added dropwise at -70 °C. The resulting mixture was stirred at 20 °C for 1.5 h, poured into saturated NH_4Cl (10 mL), and the extracted with EtOAc (2 x 10 mL). The aqueous phase purified by preparative HPLC (0.1% FA condition) to provide 5-(cyclopentyl(hydroxy)methyl)furan-2-carboxylic acid (**A-99**, 0.38 g).

[0200] Compounds in **Table 3.1** were prepared from furan-2-carboxylic acid and the indicated aldehyde in the manner described for the synthesis of **A-99**

Table 3.1.

Code	Compound	Aldehyde
A-100		
A-101		pivalaldehyde

Synthesis of 3-(N-(3,3-difluorocyclobutyl)-N-methylsulfamoyl)benzoic acid (A-95)

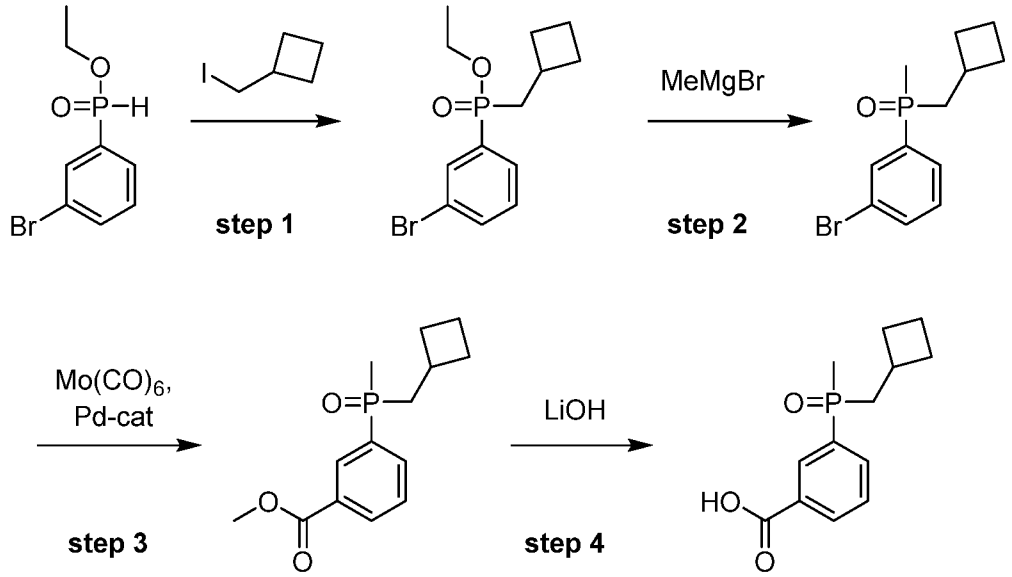


A-95

[0201] **Step 1**. To two mixtures of methyl 3-[(3,3-difluorocyclobutyl)sulfamoyl]benzoate (intermediate from synthesis of **A-36**, 0.30 & 0.10 g, 0.98 & 0.33 mmol) and DMF (4.0 & 1.3 mL) was added NaH (59 & 20 mg, 1.5 & 0.5 mmol, 60% purity) at 0 °C. The mixtures were stirred for 30 min, MeI (73 & 24 µL, 1.2 & 0.4 mmol) was added, and the mixtures were stirred at 20 °C for 30 min. The mixtures were combined and poured into water (10 mL), extracted with EtOAc (10 mL x 2), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (10-100% EtOAc in PE) to provide methyl 3-[(3,3-difluorocyclobutyl)-methyl-sulfamoyl]benzoate (0.28 g).

[0202] **Step 2**. Two mixtures of methyl 3-[(3,3-difluorocyclobutyl)-methyl-sulfamoyl]benzoate (0.23 & 0.050 g, 0.72 & 0.16 mmol), THF (1.8 & 0.4 mL), H_2O (0.6 & 0.13 mL) was added LiOH • H2O (91 & 20 mg, 2.2 & 0.48 mmol) were stirred at 20 °C for 4 h. The mixtures were combined, partially concentrated, and the pH adjusted to 3 by the addition of 2N HCl. The mixture was extracted with EtOAc (2 x 10 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to provide 3-(N-(3,3-difluorocyclobutyl)-N-methylsulfamoyl)benzoic acid (**A-95**, 0.29 g).

Synthesis of 3-((cyclobutylmethyl)(methyl)phosphoryl)benzoic acid (A-97)



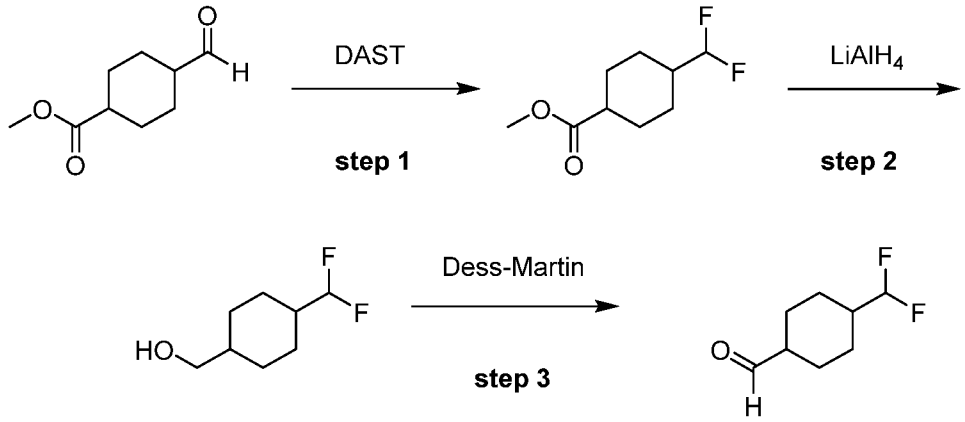
[0203] **Step 1.** To a mixture of 1-bromo-3-ethoxyphosphonoyl-benzene (1.8 g, 7.2 mmol) and DMF (20 mL) was added NaH (0.87 g, 22 mmol, 60% purity) at 0 °C. The mixture was stirred for 30 min and iodomethylcyclobutane (1.6 mL, 14 mmol) was added. The mixture was stirred at 0-20 °C for 60 min, poured into saturated NH_4Cl (20 mL), and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provide 1-bromo-3-[cyclobutylmethyl(ethoxy)phosphoryl]benzene (0.85 g).

[0204] **Step 2.** To a 0 °C mixture of 1-bromo-3-[cyclobutylmethyl(ethoxy)phosphoryl] benzene (0.68 g, 2.1 mmol) and THF (6 mL) was added MeMgBr (3 M, 6.4 mL) was stirred at 20 °C for 4 h, poured into saturated NH_4Cl (20 mL), and extracted with EtOAc (2 x 15 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-50% EtOAc in PE) to provide 1-bromo-3-[cyclobutylmethyl(methyl)phosphoryl]benzene (0.56 g).

[0205] **Step 3.** A mixture of 1-bromo-3-[cyclobutylmethyl(methyl)phosphoryl]benzene (0.49 g, 1.7 mmol), MeOH (4 mL), 1,4-dioxane (4 mL), $Mo(CO)_6$ (0.11 g, 0.43 mmol), K_3PO_4 (0.36 g, 1.7 mmol), DMAP (0.10 g, 0.85 mmol), Xantphos (99 mg, 0.17 mmol), and $Pd(OAc)_2$ (19 mg, 85 µmol) was stirred at 120 °C for 3 h. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-10% MeOH in CH_2Cl_2) to provide methyl 3-[cyclobutylmethyl(methyl)phosphoryl]benzoate (0.34 g).

[0206] **Step 4.** A mixture of methyl 3-[cyclobutylmethyl(methyl)phosphoryl]benzoate (0.32 g, 1.2 mmol), THF (3 mL), H_2O (1 mL), and LiOH • H_2O (0.15 g, 3.6 mmol) was stirred for 12 h, poured into H_2O (10 mL), and HCl (2 N) added to adjust the pH to 3-4, and extracted with EtOAc (2 x 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to provide 3-((cyclobutylmethyl)(methyl)phosphoryl)benzoic acid (**A-97**, 0.17 g).

Synthesis of 4-(difluoromethyl)cyclohexane-1-carbaldehyde



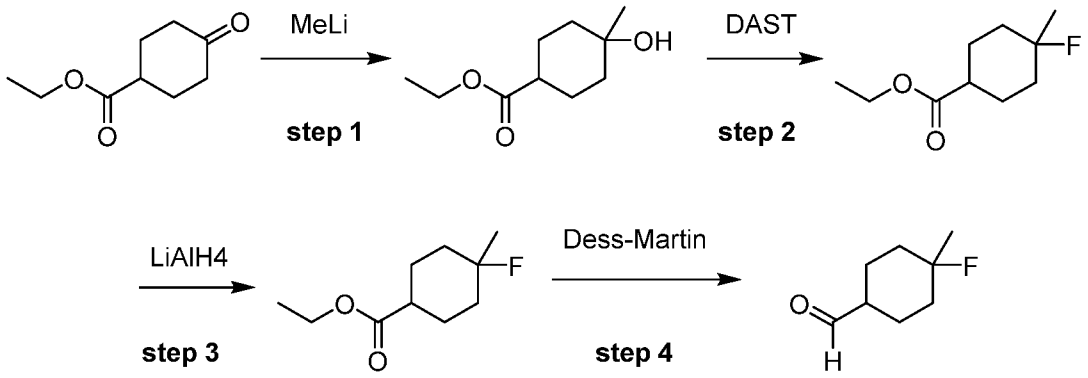
[0207] **Step 1.** To a 0 °C mixture of methyl 4-formylcyclohexanecarboxylate (5.0 g, 29 mmol) and CH_2Cl_2 (50 mL) was added slowly DAST (12 mL, 88 mmol). The mixture was stirred at 20 °C for 12 h, poured into saturated aqueous of $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (2 x 80 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, concentrated, purified by silica chromatography (5-17% EtOAc in petroleum ether) to provide methyl 4-(difluoromethyl)cyclohexanecarboxylate (3.2 g).

[0208] **Step 2.** A solution of 4-(difluoromethyl)cyclohexanecarboxylate (3.2 g, 17 mmol) in THF (10 mL) was slowly added to $LiAlH_4$ (1.3 g, 33 mmol) in THF (20 mL)and then stirred at 25 °C for 2 h. H_2O (1.3 mL), aqueous NaOH (85%, 1.3 mL), and additional H_2O (1.3 mL) were added and the mixture was filtered. The filtrate was concentration to provide [4-(difluoromethyl) cyclohexyl] methanol (1.80 g).

[0209] **Step 3.** To a mixture of [4-(difluoromethyl)cyclohexyl]methanol (1.6 g, 9.7 mmol), $NaHCO_3$ (6.6 g, 78 mmol), and CH_2Cl_2 (50 mL) was added Dess-Martin periodinane (8.3 g, 20 mmol). The mixture was stirred at 25 °C for 2, then was poured into a mixture of saturated aqueous of $NaHCO_3$ (15 mL) and saturated aqueous of Na_2SO_3 (15 mL). The resulting mixture was filtered and extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts

were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (5-17% EtOAc in petroleum ether) to provide 4-(difluoromethyl)cyclohexanecarbaldehyde (1.4 g).

Synthesis of 4-fluoro-4-methylcyclohexane-1-carbaldehyde



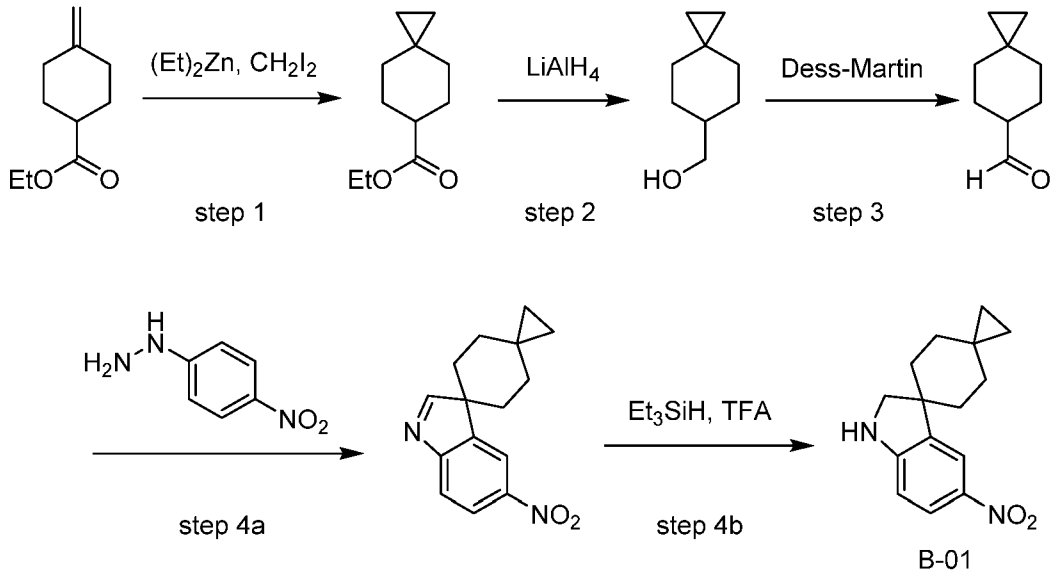
[0210] **Step 1**. To a mixture of ethyl 4-oxocyclohexanecarboxylate (4.7 mL, 29 mmol) in THF (30 mL) was slowly added MeLi (1 M, 41 mL) at - 60 °C. The mixture was stirred at -60 °C for 1 h, poured into NH_4Cl (20 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (13-50% EtOAc in PE) to ethyl 4-hydroxy-4-methyl-cyclohexanecarboxylate (2.20 g).

[0211] **Step 2**. To a solution of ethyl 4-hydroxy-4-methyl-cyclohexanecarboxylate (2.4 g, 13 mmol) and CH_2Cl_2 (1 mL) was added DAST (1.7 mL, 13 mmol). The mixture was stirred at -40 °C for 1 h, poured into 1M Na_2HCO_3 (20 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (15-50% EtOAc in PE) to provide ethyl 4-fluoro-4-methyl-cyclohexanecarboxylate (1.60 g).

[0212] **Step 3**. To a 0 °C mixture of ethyl 4-fluoro-4-methyl-cyclohexanecarboxylate (1.4 g, 7.4 mmol) and THF (30 mL) was added $LiAlH_4$ (0.57 g, 15 mmol). The mixture was stirred at 0 °C for 2 h, and 0.56 mL of H_2O, 0.56 mL of 15% aqueous NaOH, and an additional 1.7 mL of H_2O. The mixture was filtered, the filtrate was concentrated, added to H_2O (10 mL), and extracted with EtOAc (2 x15 mL). The combined extracts were washed with brine (15 mL), dried over Na2SO4, and concentrated to provide (4-fluoro-4-methyl-cyclohexyl)methanol (0.80 g).

[0213] **Step 4**. A mixture of (4-fluoro-4-methyl-cyclohexyl)methanol (0.70 mg, 4.8 mmol), CH_2Cl_2 (20 mL), $NaHCO_3$ (3.2 g, 38 mmol), and Dess-Martin periodinane (4.1 g, 9.6 mmol) was stirred at 25 °C for 2 hours. The mixture was poured into saturated $NaHCO_3$ (5 mL) and saturated Na_2SO_3 (5 mL) and the resulting mixture was filtered and extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to provide 4-fluoro-4-methyl-cyclohexanecarbaldehyde (0.60 mg).

Synthesis of 5''-nitrodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline] (B-01)



[0214] **Step 1**. To a mixture of $ZnEt_2$ (1 M in hexanes, 180 mL), CH_2Cl_2 (200 mL) at 0 °C under N_2 was added slowly CH_2I_2 (26 mL, 320 mmol), in CH_2Cl_2 (60 mL). The mixture was stirred at 0 °C for 30 min and ethyl 4-methylenecyclohexanecarboxylate (12 g, 71 mmol) in CH_2Cl_2 (50 mL) was slowly added. The mixture was stirred at 20 °C for 12 h, cooled to 0 °C, and saturated NH_4Cl (100 mL) was added. The organic phase separated, washed with water (50 mL x 2), brine (50 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (1-10% CH_2Cl_2 in petroleum ether) to afford the compound ethyl spiro[2.5]octane-6-carboxylate (10 g).

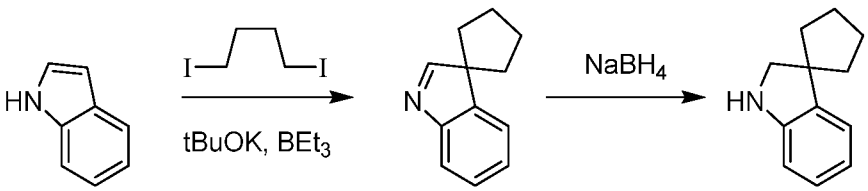
[0215] **Step 2**. To a mixture of ethyl spiro[2.5]octane-6-carboxylate (10 g, 55 mmol), THF (300 mL) at 0 °C under N_2 was added $LiAlH_4$ (3.1 g, 81 mmol) in portions. The mixture was stirred at 0 °C for 1 h, then at 22 °C for another 1 h. Aqueous 2M NaOH (3.0 mL) was slowly added to the stirring mixture, followed by Na_2SO_4 (30 g). The suspension was filtered, and the filtrate was concentrated to provide spiro[2.5]octan-6-ylmethanol (7.5 g). ^1H NMR (DMSO-d^6, 400 MHz) δ 3.51 (d, J = 6.38 Hz, 2H), 1.82-1.68 (m, 4H), 1.53 (tdt, J = 14.71,

6.38, 3.24 Hz, 1H), 1.40-1.29 (m, 1H), 1.12-1.07 (m, 2H), 0.96-0.84 (m, 2H), 0.35-0.24 (m, 2H), 0.23-0.12 (m, 2H).

[0216] **Step 3**. To a mixture of spiro [2.5]octan-6-ylmethanol (7.5 g, 54 mmol) and CH_2Cl_2 (250 mL) was added Dess-Martin periodinane (28 g, 66 mmol) at 0 °C. The mixture was stirred for 5 h as the temperature was allowed to rise to 25 °C. The mixture was filtered through celite and the filter solid was washed with CH_2Cl_2 (50 mL x 3). The filtrate was concentrated and purified by silica chromatography (0-10% EtOAc in petroleum ether) to provide spiro [2.5]octane-6-carbaldehyde (7.30 g). ^{1}H NMR (DMSO-d^6, 400 MHz) δ 9.68 (d, J = 1.25 Hz, 1H), 2.35-2.23 (m, 1H), 1.97-1.85 (m, 2H), 1.70-1.51 (m, 4H), 1.12-1.03 (m, 2H), 0.35-0.27 (m, 2H), 0.26-0.18 (m, 2H).

[0217] **Step 4**. a) A mixture of (4-nitrophenyl)hydrazine (1.8 g, 12 mmol), TFA (4.5 mL, 61 mmol), CH_2Cl_2 (40 mL), and spiro[2.5]octane-6-carbaldehyde (2.0 g, 15 mmol) was stirred at 40 °C for 15 h. b) Additional TFA (6.3 mL, 85 mmol), CH_2Cl_2, and Et_3SiH (6.3 mL, 4.6 mmol) were added at 0 °C and the mixture stirred at 25 °C for 2 h, then was concentrated and purified by silica chromatography (0-15% [1:1 Me-THF in EtOAc] in petroleum ether) to provide 5''-nitrodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline] (**B-01**, 0.88 g).

Synthesis of spiro[cyclopentane-1,3'-indoline] (B-02)



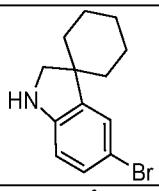
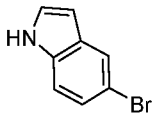
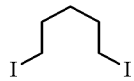
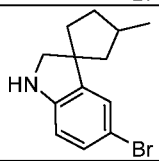
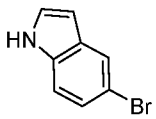
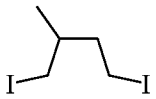
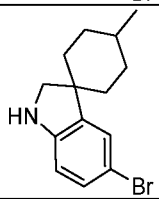
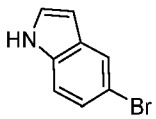
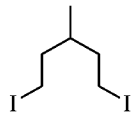
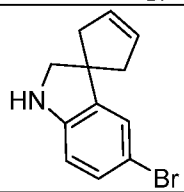
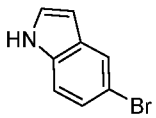
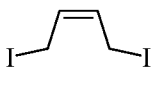
B-02

[0218] To a mixture of 1H-indole (1.0 g, 8.5 mmol) and THF (25 mL) was added dropwise t-BuOK (1 M in THF, 20 mL) and the mixture was stirred at 20 °C for 0.5 h. Et_3B (1 M in THF, 17 mL) was added and the mixture was stirred for 0.5 h. 1,4-diiodobutane (1.2 mL, 9.4 mmol) was added and the mixture was stirred at 70 °C for 13 h. MeOH (10 mL) and $NaBH_4$ (0.97 g, 26 mmol) were added and the mixture stirred at 20 °C for 12 h. The mixture was concentrated, combined with EtOAc (20 mL) and 2 N HCl (20 mL). The pH was adjusted to 9 by the slow addition of saturated aqueous $NaHCO_3$. The phases were separated, and the aqueous wash was extracted with EtOAc (2 x 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO4, filtered, and concentrated to provide

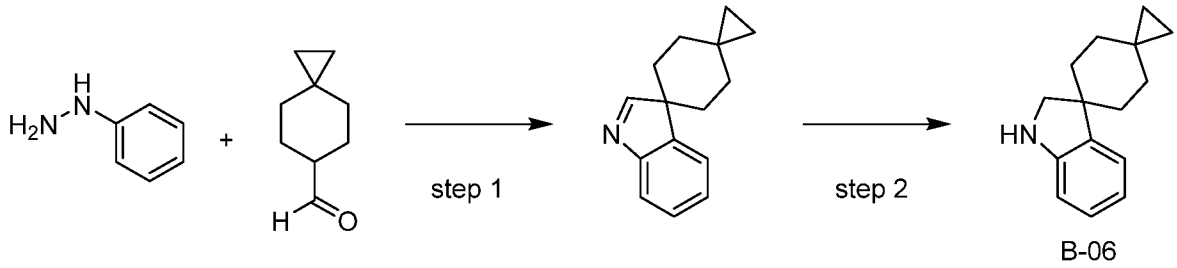
spiro[cyclopentane-1,3'-indoline] (**B-02**). ^{1}H NMR: (DMSO-d6, 400 MHz) δ 6.98 (dd, J = 7.32, 0.81 Hz, 1H), 6.90 (td, J = 7.57, 1.25 Hz, 1H), 6.55 (td, J = 7.35, 0.94 Hz, 1H), 6.49 (d, J = 7.75 Hz, 1H), 5.43 (s, 1H), 3.22 (s, 2H), 1.84-1.62 (m, 8H).

[0219] Compounds in **Table 4** were prepared from the indole and dihalide in the manner described for **B-02**.

Table 4.

Code	Structure	indole	Amine
B-03			
B-04			
B-05			
B-16			

Synthesis of dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline] (B-06)

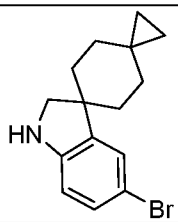
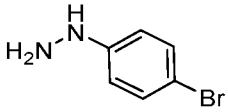
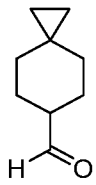
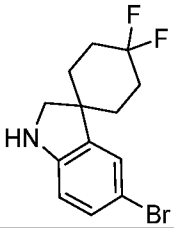
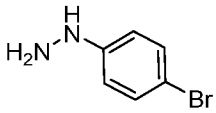
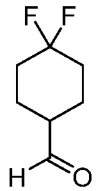
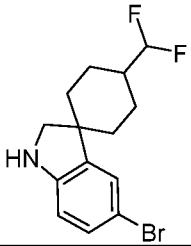
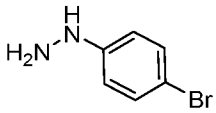
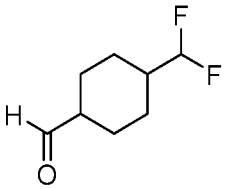
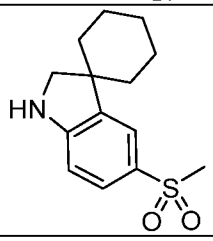
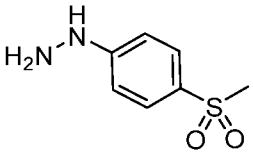
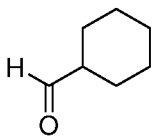
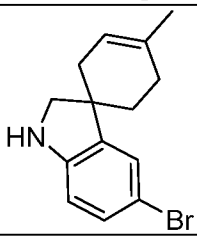
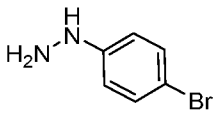
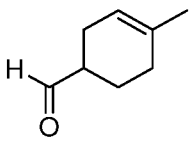


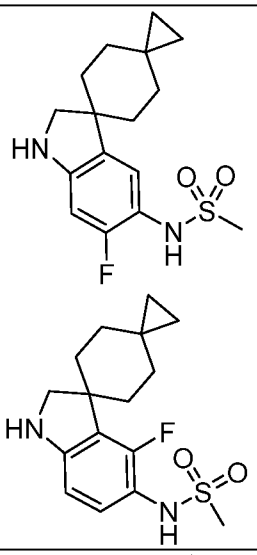
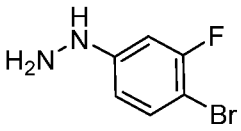
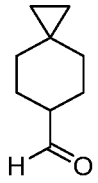
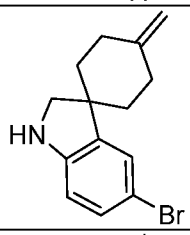
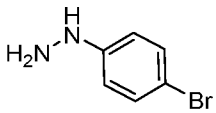
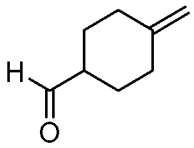
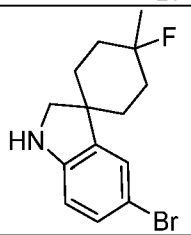
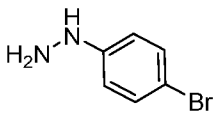
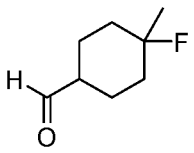
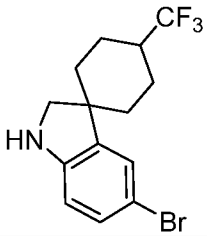
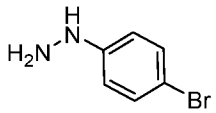
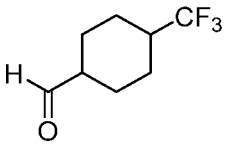
[0220] **Step 1.** Dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indole] was prepared from phenylhydrazine and spiro[2.5]octane-6-carbaldehyde in the manner described in Step 4a of the synthesis of **B-01**.

[0221] **Step 2**. To a mixture of dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indole] (1.0 g, 4.7 mmol) in MeOH (15 mL) and THF (15 mL) at 0 °C was added $NaBH_3CN$ (0.90 g, 14 mmol) in portions. The mixture was stirred at 20 °C for 12 h and $NaBH_3CN$ (0.50 g) and THF (15 mL) was added, and the mixture was stirred at 40 °C for 2 h. The reaction mixture was concentrated and purified by chromatography (silica, 0-15 % [1:1 THF/EtOAc] in petroleum ether) to afford dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline] (**B-06**, 0.64 g).

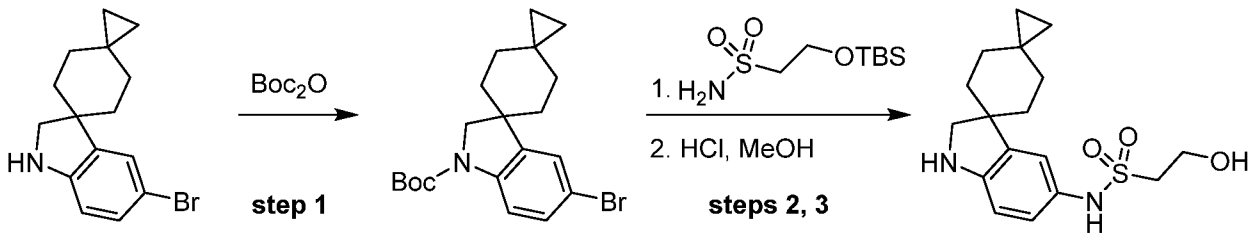
[0222] Compounds in **Table 5** were prepared from the hydrazine and the aldehyde indicated by the method described for the synthesis of **B-06**.

Table 5.

Code	Structure	Hydrazine	Aldehyde
B-07			
B-08			
B-09			
B-17			
B-18			

B-19/B-20			
B-21			
B-22			
B-24			

Synthesis of tert-butyl 5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carboxylate (B-10) and N-(dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)-2-hydroxyethane-1-sulfonamide (B-11)



[0223] **Step 1**. A mixture of **B-07** (0.2 M, 3.4 mL) and Boc_2O (0.30 g, 1.4 mmol), MeCN (10 mL), and Et_3N (0.40 mL, 2.9 mmol) was stirred at 25 °C for 12 h. The mixture was concentrated and purified by silica chromatography (0-20% MTBE in petroleum ether) to provide *tert*-butyl 5"-bromo-1",2"-dihydrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indole]-1"-carboxylate (B-10, 0.23 g).

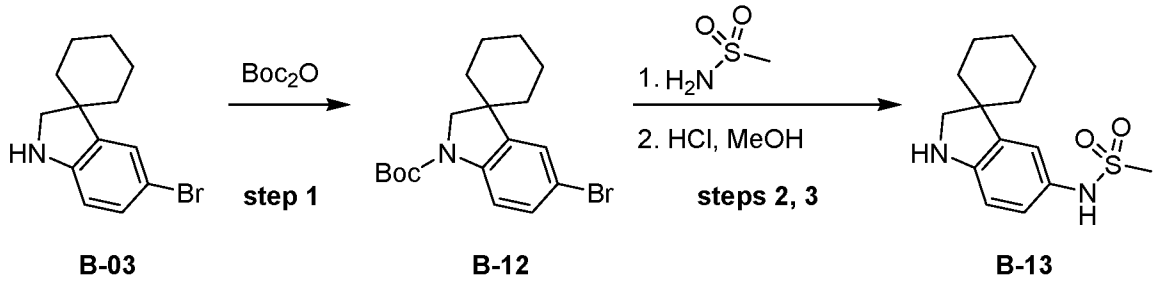
[0224] **Step 2**. a) To a mixture of *tert*-butyl 5"-bromo-1",2"-dihydrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indole]-1"-carboxylate (0.11 g, 0.27 mmol) and 2-[(tert-butyldimethylsilyl)oxy]ethane-1-sulfonamide (0.21 g, 0.88 mmol), and DMF (8.0 mL) was added CuI (57 mg, 0.30 mmol), K_3PO_4 (0.21 g, 0.99 mmol), and N^1,N^2-dimethylcyclohexane-1,2-diamine (48 mg, 0.34 mmol). The reaction mixture was stirred at 140 °C in a microwave reactor for 3 h. The reaction mixture was diluted with water 30 mL and extracted with 1:1 EtOAc / THF (15 mL x 2). The extracts were combined, washed with H_2O (10 mL x 3) and brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (0-10% [1:1 THF/EtOAc] in petroleum ether) to provide 2-[(*tert*-butyldimethylsilyl)oxy]-N-{1",2"-dihydrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indol]-5"-yl}ethane-1-sulfonamide (70 mg).

[0225] **Step 3**. A mixture of 2-[(*tert*-butyldimethylsilyl)oxy]-N-{1",2"-dihydrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indol]-5"-yl}ethane-1-sulfonamide (60 mg, 0.11 mmol), MeOH (1.0 mL), and HCl (4 M in MeOH, 1.0 mL) was stirred at 25 °C for 5 h. The mixture was concentrated to provide N-{1",2"-dihydrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indol]-5"-yl}-2-hydroxyethane-1-sulfonamide hydrochloride (B-11, 47 mg).

Separation of B-24 into diastereomers

[0226] Indoline B-24 was separated into the (1s,4s) and (1r,4r) isomers by silica chromatography (0-100% EtOAc in PE). The configurations were not determined, and the first eluting isomer is **B-24a** and the second eluting isomer is **B-24b**.

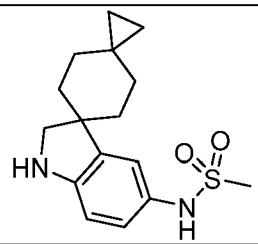
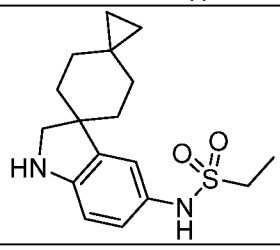
Synthesis of tert-butyl 5'-bromospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (B-12) and N-(spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide (B-13)



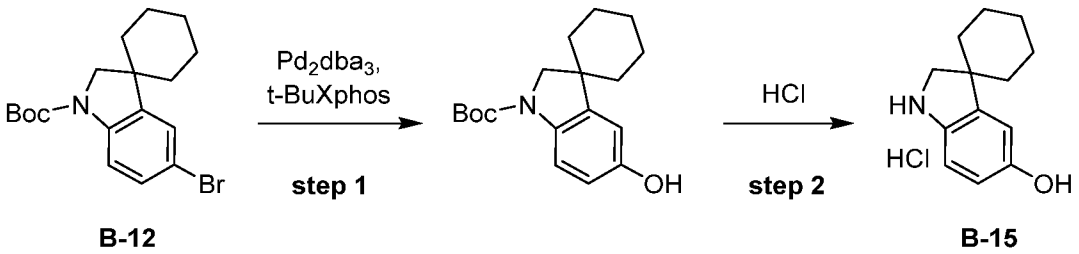
[0227] tert-Butyl 5'-bromospiro[cyclohexane-1,3'-indoline]-1'-carboxylate (**B-12**) and N-(spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide (**B-13**) were prepared from B-03 in the same manner as **B-10** and **B-11**.

[0228] Intermediates in **Table 5.1** were prepared from the indicated indolines and sulfonamides in the manner described for the synthesis of **B-11**.

Table 5.1

Code	Structure	Sulfonamide	indoline
B-14		methanesulfonamide	**B-07**
B-23		ethanesulfonamide	**B-07**

Synthesis of spiro[cyclohexane-1,3'-indolin]-5'-ol hydrochloride (B-15)

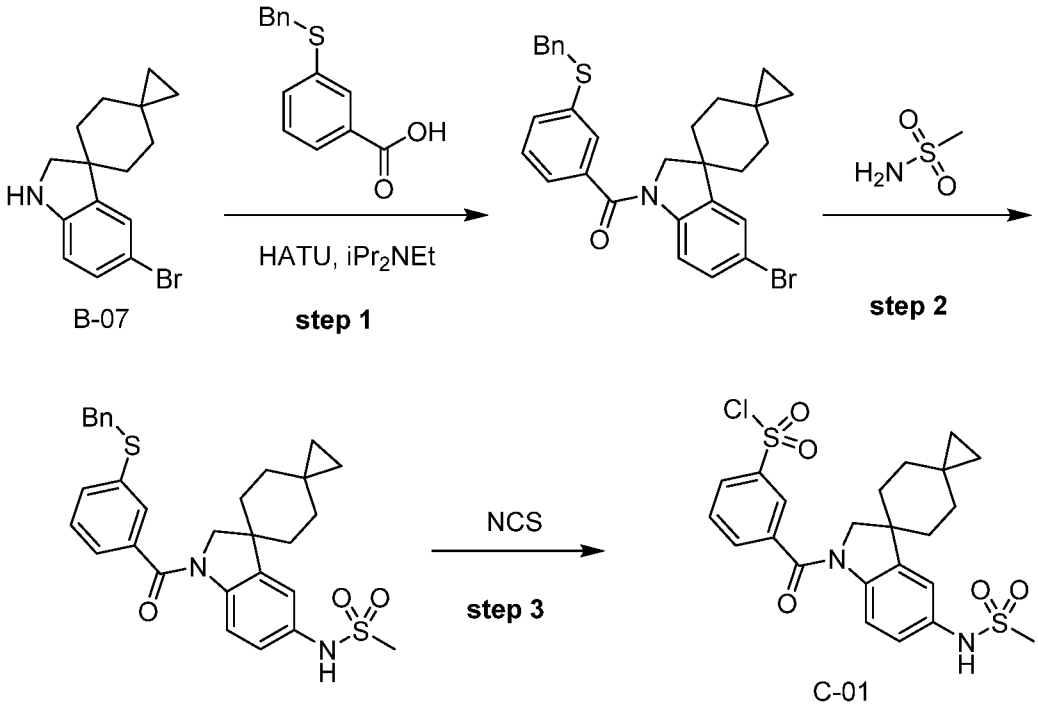


[0229] **Step 1.** A mixture of **B-12** (0.35 g, 0.96 mmol), NMP (8 mL), H_2O (4 mL), was KOH (0.16 g, 2.9 mmol), $Pd_2(dba)_3$ (88 mg, 96 μmol), di-tert-butyl- [2-(2,4,6-triisopropylphenyl)phenyl]phosphane (81 mg, 0.19 mmol) was stirred at 110 °C for 12 h,

diluted with 10 mL of water, and extracted with EtOAc (5 mL x 3). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated, and purified by preparative TLC (SiO_2, 25% EtOAc in petroleum ether) to provide tert-butyl 5'-hydroxyspiro[cyclohexane-1,3'-indoline]-1'-carboxylate (80 mg).

[0230] **Step 2.** A mixture of tert-butyl tert-butyl 5'-hydroxyspiro[cyclohexane-1,3'-indoline]-1'-carboxylate (80 mg, 0.26 mmol) and 1M HCl in EtOAc (2.0 mL) was stirred at 25 °C for 2 h, and was concentrated to provide spiro[cyclohexane-1,3'-indolin]-5'-ol hydrochloride (**B-15**; 60 mg).

Synthesis of 3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonyl chloride (C-01)



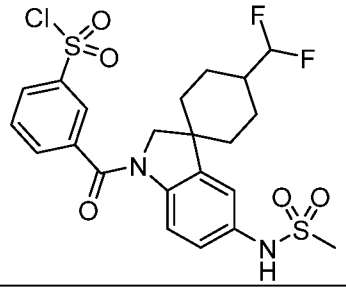
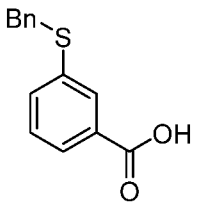
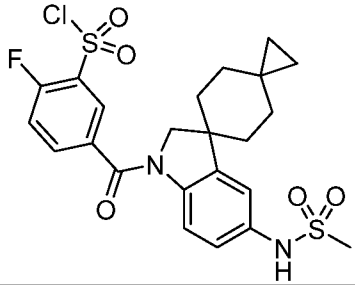
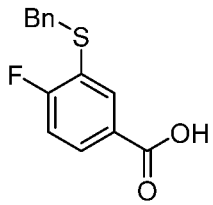
[0231] **Step 1**. A mixture of 3-benzylsulfanylbenzoic acid (1.5 g, 6.1 mmol), DMF (10 mL), HATU (4.7 g, 13 mmol), and iPr_2NEt (3.2 mL, 18 mmol) was stirred at 25 °C for 15 min and **B-07** (1.8 g, 6.1 mmol) was added. The mixture was stirred at 25 °C for 2 h, then was diluted with EtOAc (50 mL), washed with water (30 mLx3) and brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (8-10% EtOAc in petroleum ether) to provide (3-(benzylthio)phenyl)(5''-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)methanone (3.0 g).

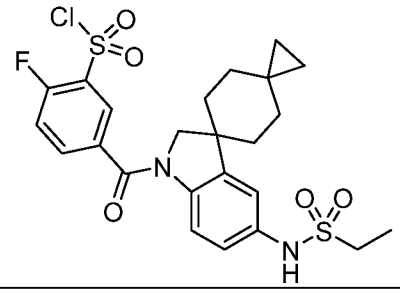
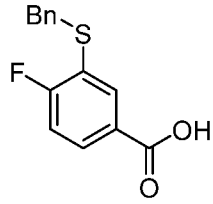
[0232] **Step 2**. A mixture of (3-(benzylthio)phenyl)(5"-bromodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-1"-yl)methanone (2.0 g, 3.9 mmol), DMF (10 mL), methanesulfonamide (1.1 g, 12 mmol), K_3PO_4 (2.5 g, 12 mmol), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.55 g, 3.9 mmol), and CuI (0.74 g, 3.9 mmol) was stirred at 160 °C for 2 h. The mixture was diluted with EtOAc (30 mL), washed with H_2O (30 mLx3) and brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (29-31% EtOAc in petroleum ether) to provide N-(1"-(3-(benzylthio)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (1.84 g).

[0233] **Step 3**. A mixture of N-(1"-(3-(benzylthio)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (1.0 g, 1.9 mmol), NCS (0.50 g, 3.8 mmol), HOAc (1.8 mL), and H_2O (0.2 mL) was stirred at 30 °C for 2 h. The mixture was diluted with EtOAc (50 mL), washed with H_2O (30 mLx3), saturated aqueous $NaHCO_3$ (30mL), and brine (30 mL) before being dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (25-35% EtOAc in petroleum ether) to provide 3-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonyl chloride (**C-01**, 0.36 g).

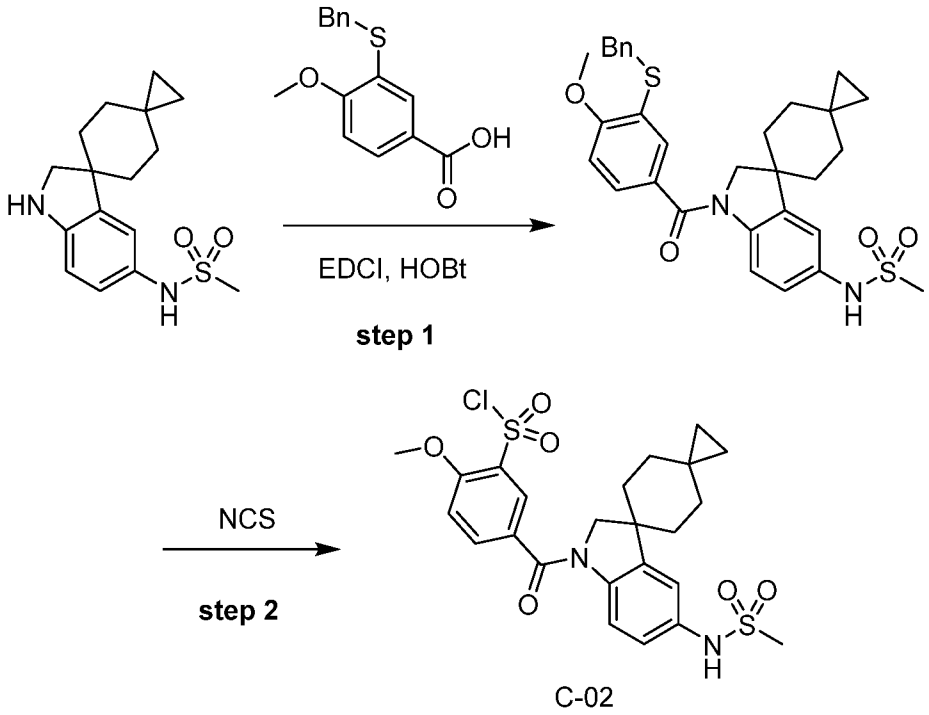
[0234] Compounds in **Table 5.2** were prepared from the indicated carboxylic acid and indoline in the same manner as described for **C-01**.

Table 5.2

Code	Structure	Carboxylic Acid	Indoline
C-03			**B-09**
C-04			**B-07**

Code	Structure	Carboxylic Acid	Indoline
C-05			B-23

Synthesis of 2-methoxy-5-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonyl chloride (C-02)

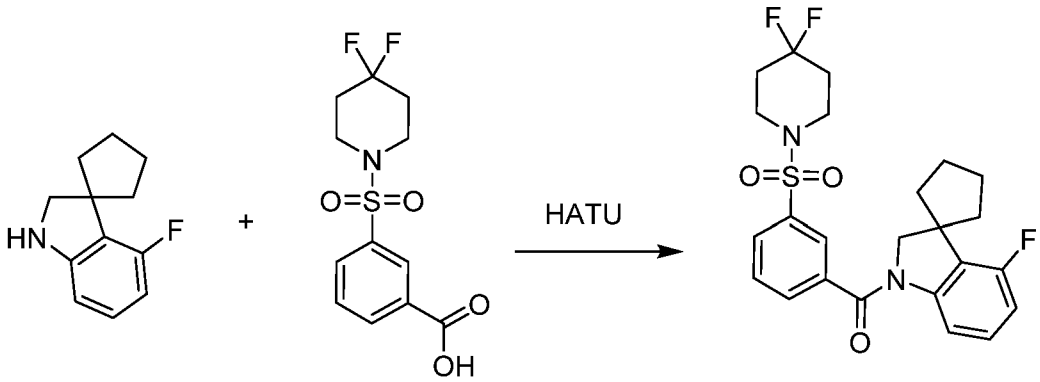


[0235] **Step 1**. A mixture of 3-benzylsulfanyl-4-methoxy-benzoic acid (0.32 mg, 1.2 mmol), **B-14** (0.22 g, 0.73 mmol), DMF (3 mL), HOBt (0.26 g, 1.9 mmol), EDCI (0.37 g, 1.9 mmol), Et_3N (0.54 mL, 3.9 mmol) was stirred at 25 °C for 2 h. The reaction was poured into H_2O (30 mL), extracted with EtOAc (2 x 30 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (40-45% EtOAc in PE) to provide N-(1''-(3-(benzylthio)-4-methoxybenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.22 g).

[0236] **Step 2**. A mixture of N-(1''-(3-(benzylthio)-4-methoxybenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.22 g, 0.36 mmol), NCS (0.14 g, 1.1 mmol), H_2O (0.05 mL), and HOAc (0.45 mL) was stirred at 25 °C for 2 h. The mixture was poured into H_2O (10 mL) and saturated $NaHCO_3$ (10 mL), extracted with EtOAc (2 x 30 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to provide 2-methoxy-5-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonyl chloride (**C-02**, 0.20 g).

Synthetic Example S-001

Synthesis of (3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)methanone (Compound 1)

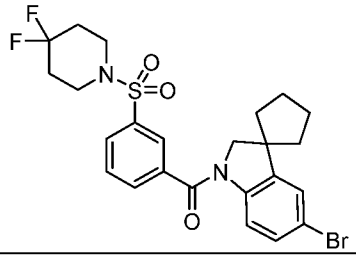
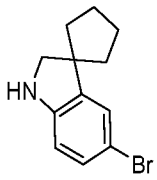
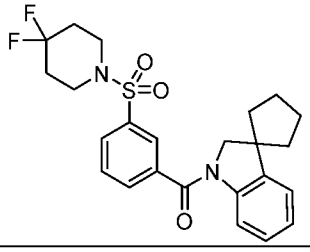
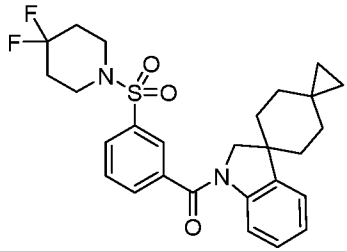
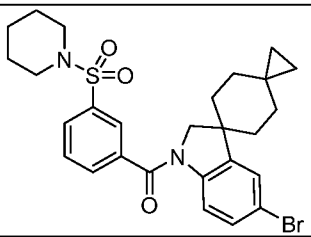
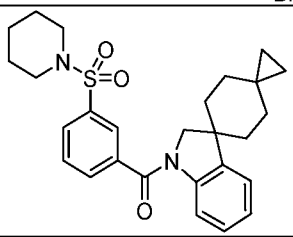
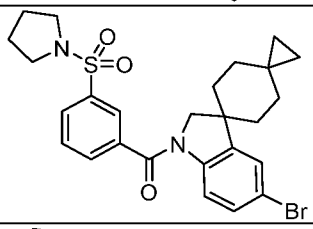
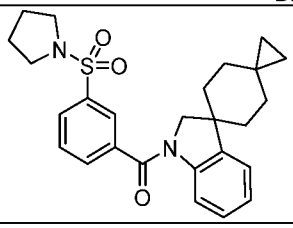


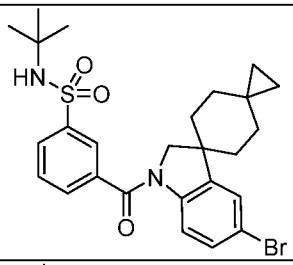
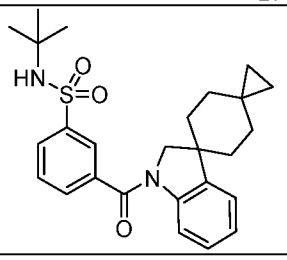
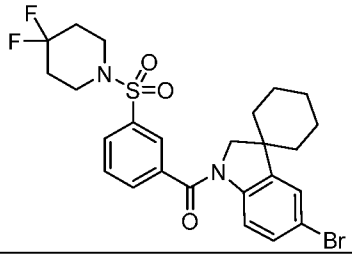
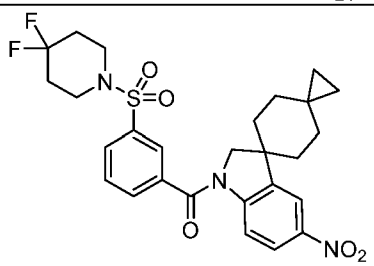
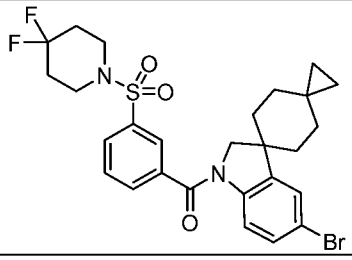
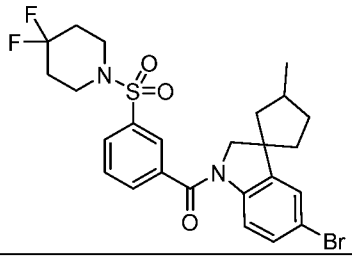
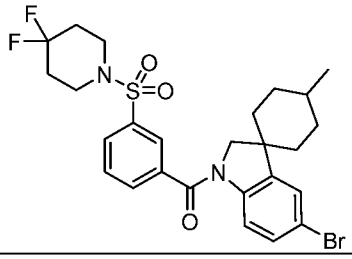
A-04 **Compound 1**

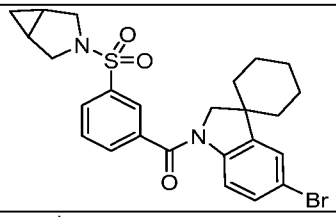
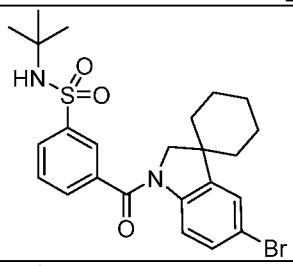
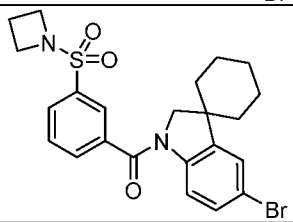
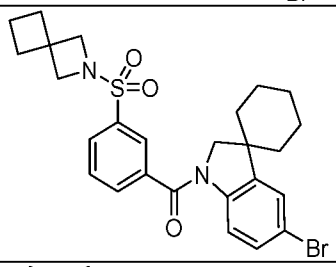
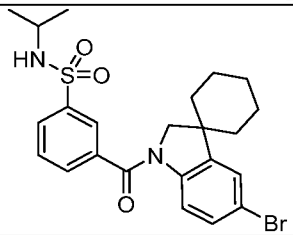
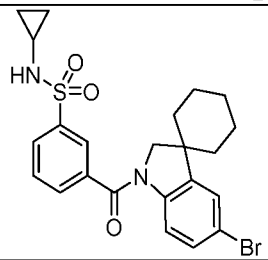
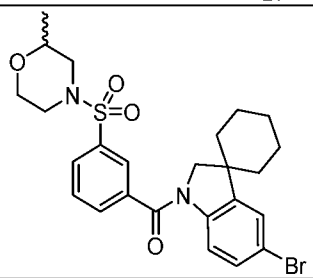
[0237] A mixture of 3-[(4, 4-difluoro-1-piperidyl)sulfonyl]benzoic acid (88 mg, 0.28 mmol), DMF (1.5 mL), Et_3N (0.11 mL, 0.78 mmol), and HATU (0.20 g, 0.52 mmol) was stirred at 20 °C for 30 min, and 4'-fluorospiro [cyclopentane-1,3'-indoline] (50 mg, 0.26 mmol) in DMF (1.0 mL) was added. The resulting mixture was stirred at 20°C for 3.5 h, concentrated, and purified by prep-HPLC (45-75% MeCN in H_2O [10 mM NH_4HCO_3]) to afford (3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)methanone (**Compound 1**) (35 mg). ESI MS m/z: 479.2 (M+H).

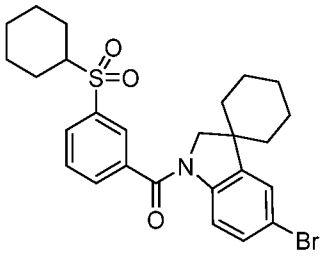
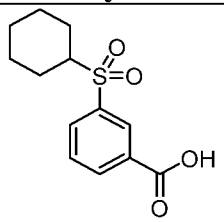
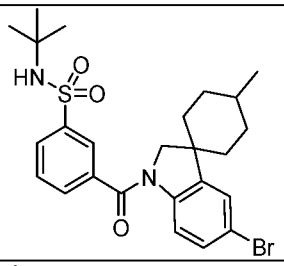
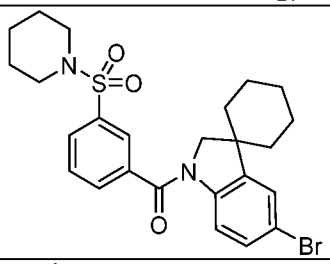
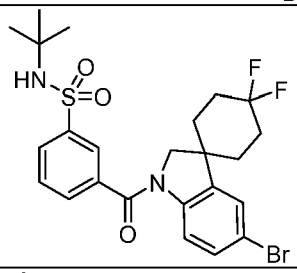
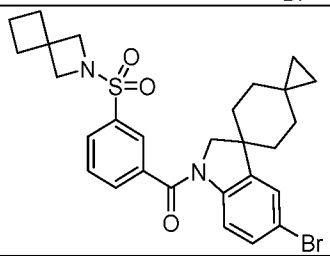
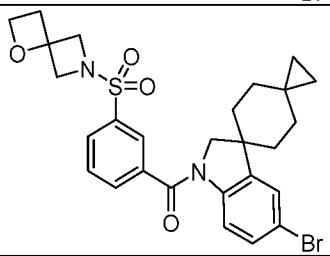
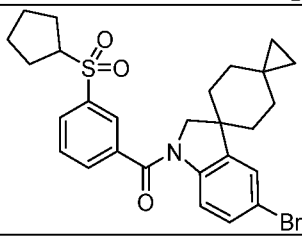
[0238] Compounds in **Table 6** were prepared from the carboxylic acid and indoline analog indicated by the method described for the synthesis of **Compound 1** (Synthetic Example S-001).

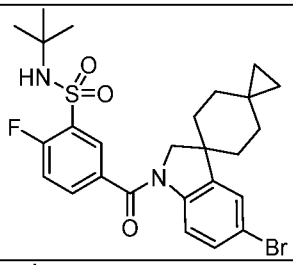
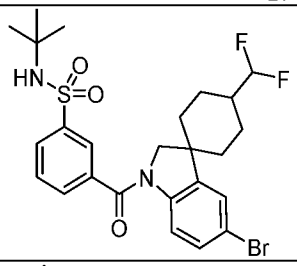
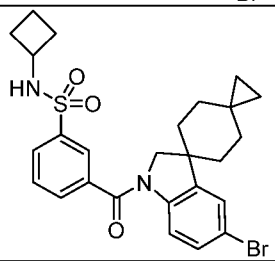
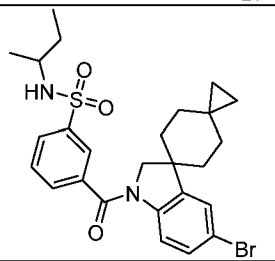
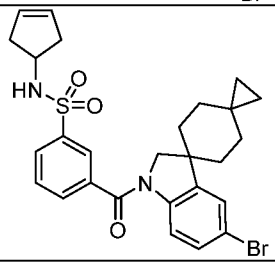
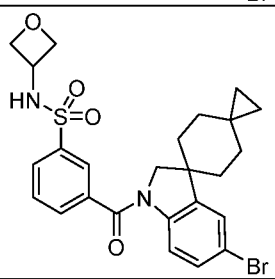
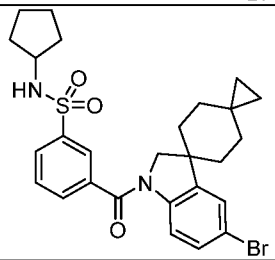
Table 6.

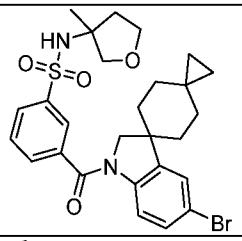
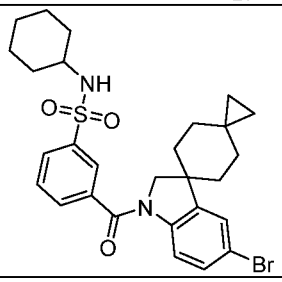
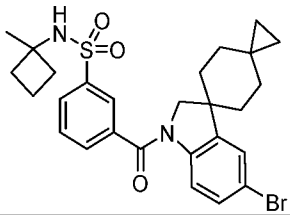
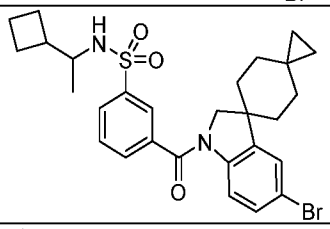
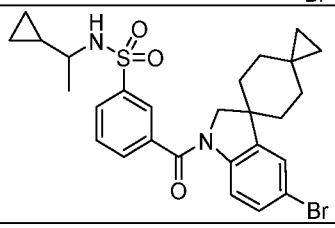
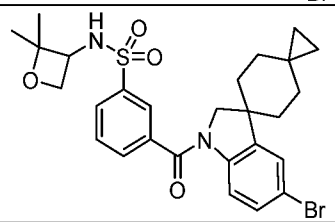
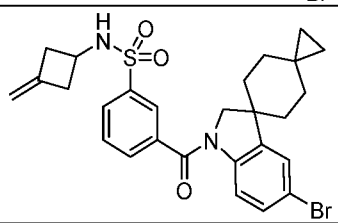
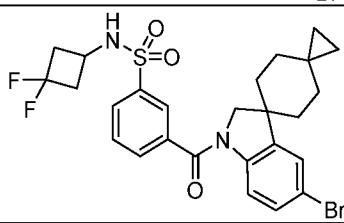
Compound	Structure	Carboxylic Acid	Indoline
Compound 2		A-04	
Compound 3		A-04	B-02
Compound 4		A-04	B-06
Compound 5		A-01	B-07
Compound 6		A-01	B-06
Compound 7		A-02	B-07
Compound 8		A-02	B-06

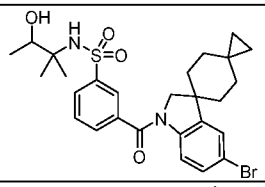
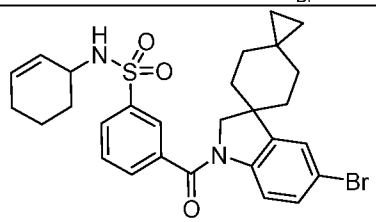
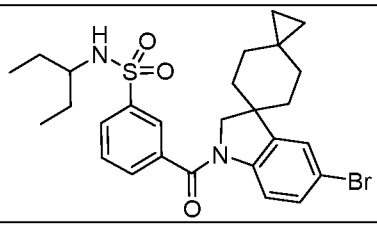
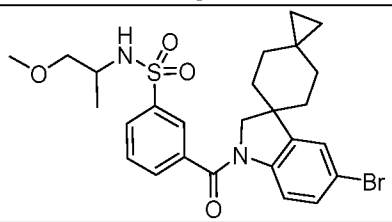
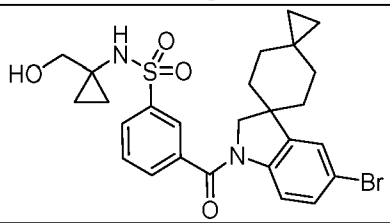
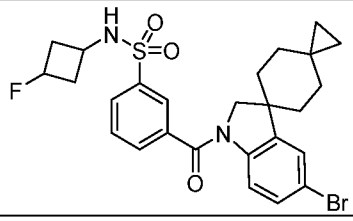
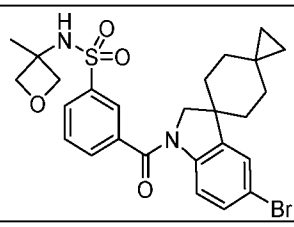
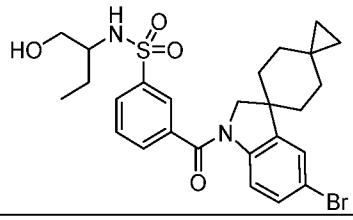
Compound	Structure	Carboxylic Acid	Indoline
Compound 9		**A-03**	**B-07**
Compound 10		**A-03**	**B-06**
Compound 11		**A-03**	**B-03**
Compound 12		**A-04**	**B-01**
Compound 13		**A-04**	**B-07**
Compound 14		**A-04**	**B-04**
Compound 15		**A-04**	**B-05**

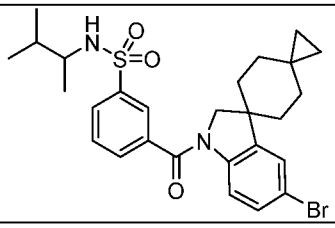
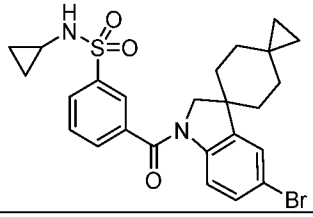
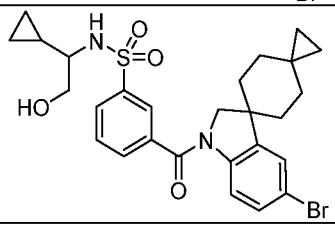
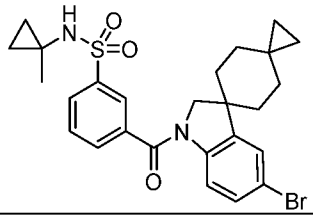
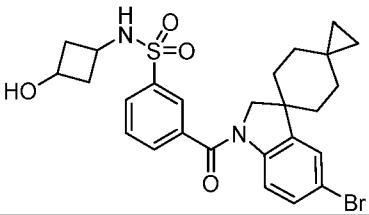
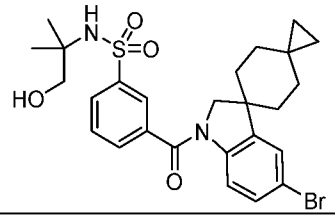
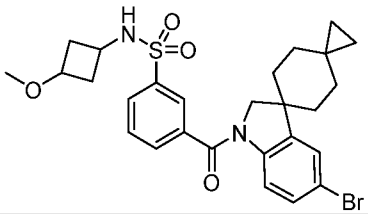
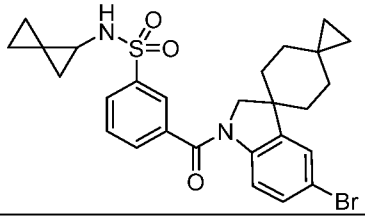
Compound	Structure	Carboxylic Acid	Indoline
Compound 16		**A-05**	**B-03**
Compound 17		**A-03**	**B-03**
Compound 126		**A-06**	**B-03**
Compound 128		**A-07**	**B-03**
Compound 130		**A-08**	**B-03**
Compound 132		**A-09**	**B-03**
Compound 135		**A-11**	**B-03**

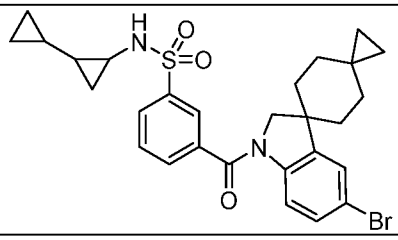
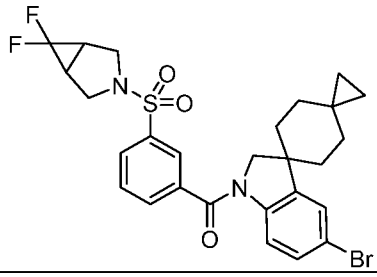
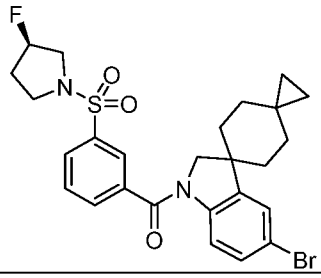
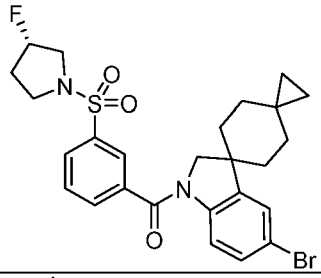
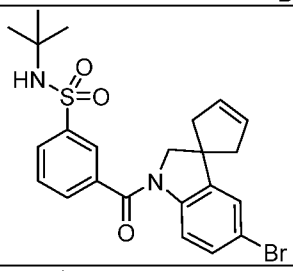
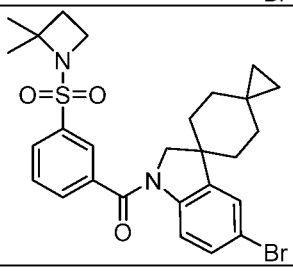
Compound	Structure	Carboxylic Acid	Indoline
Compound 138		 CAS: 1096908-69-8	**B-03**
Compound 139		**A-03**	**B-05**
Compound 142		**A-01**	**B-03**
Compound 143		**A-03**	**B-08**
Compound 150		**A-07**	**B-07**
Compound 152		**A-14**	**B-07**
Compound 154		**A-52**	**B-07**

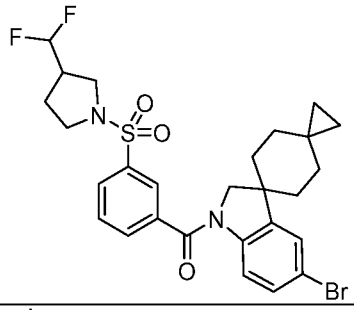
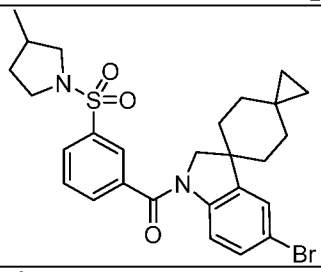
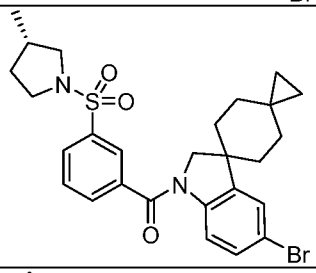
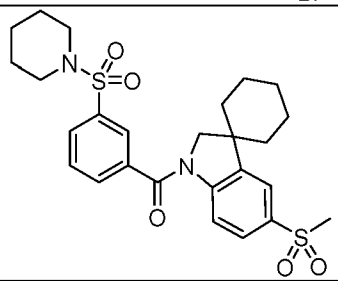
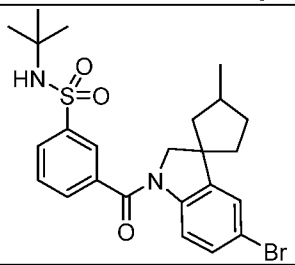
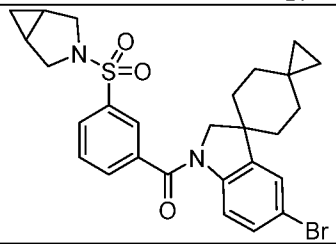
Compound	Structure	Carboxylic Acid	Indoline
Compound 158		**A-22**	**B-07**
Compound 161		**A-03**	**B-09**
Compound 167		**A-24**	**B-07**
Compound 169		**A-25**	**B-07**
Compound 171		**A-26**	**B-07**
Compound 173		**A-27**	**B-07**
Compound 175		**A-28**	**B-07**

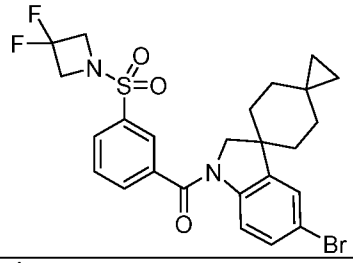
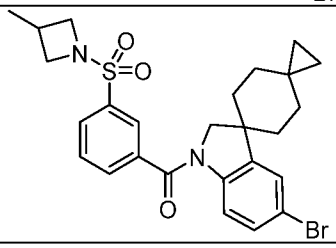
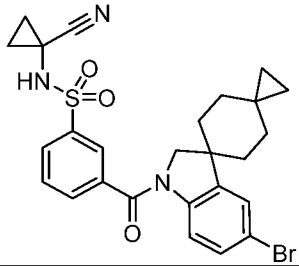
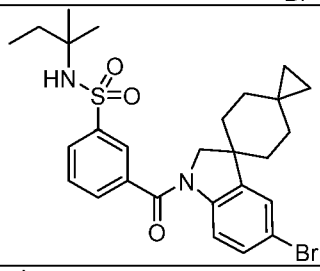
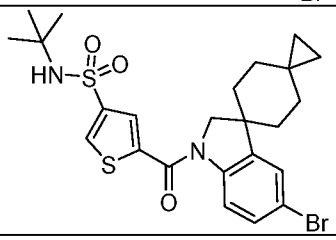
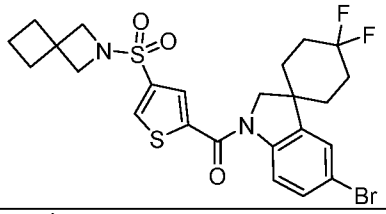
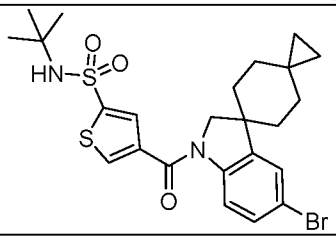
Compound	Structure	Carboxylic Acid	Indoline
Compound 177		A-29	B-07
Compound 179		A-30	B-07
Compound 181		A-31	B-07
Compound 183		A-32	B-07
Compound 185		A-33	B-07
Compound 187		A-34	B-07
Compound 189		A-35	B-07
Compound 191		A-36	B-07

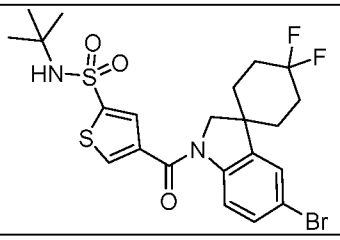
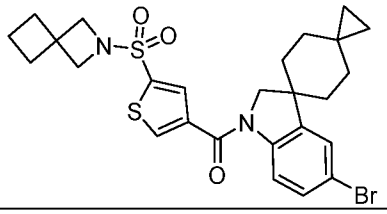
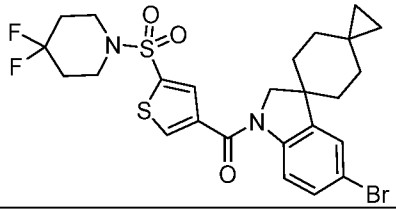
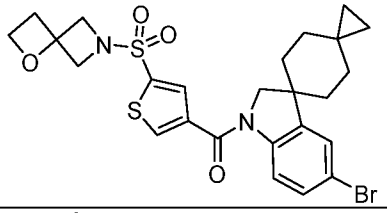
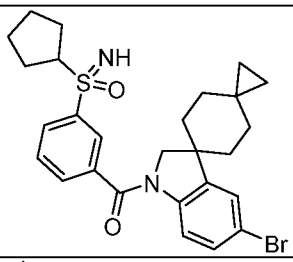
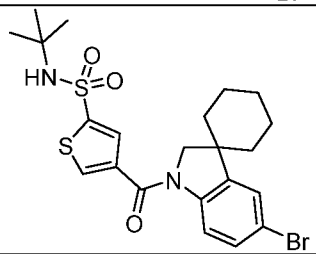
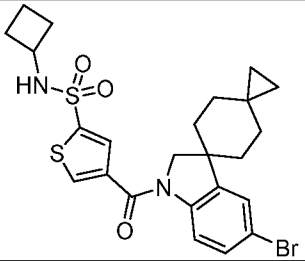
Compound	Structure	Carboxylic Acid	Indoline
Compound 193		**A-37**	**B-07**
Compound 195		**A-38**	**B-07**
Compound 197		**A-39**	**B-07**
Compound 199		**A-40**	**B-07**
Compound 201		**A-41**	**B-07**
Compound 203		**A-42**	**B-07**
Compound 205		**A-43**	**B-07**
Compound 207		**A-44**	**B-07**

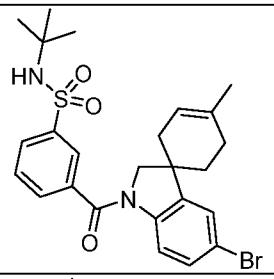
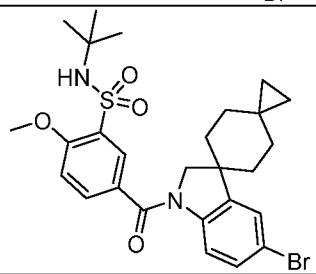
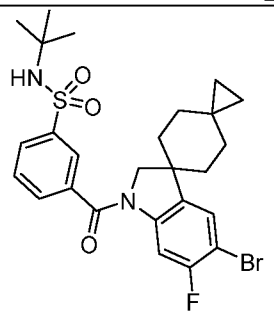
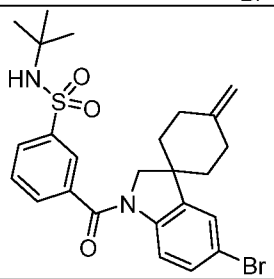
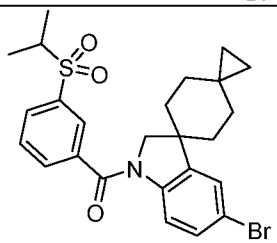
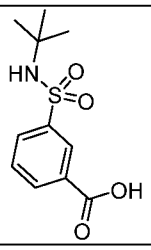
Compound	Structure	Carboxylic Acid	Indoline
Compound 209		**A-45**	**B-07**
Compound 211		**A-09**	**B-07**
Compound 213		**A-46**	**B-07**
Compound 215		**A-47**	**B-07**
Compound 217		**A-48**	**B-07**
Compound 219		**A-49**	**B-07**
Compound 221		**A-50**	**B-07**
Compound 232		**A-56**	**B-07**

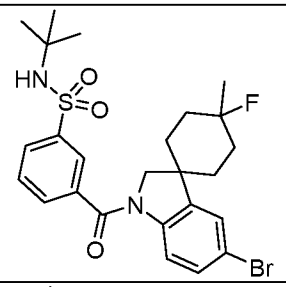
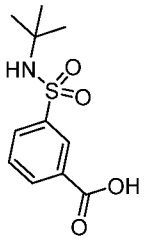
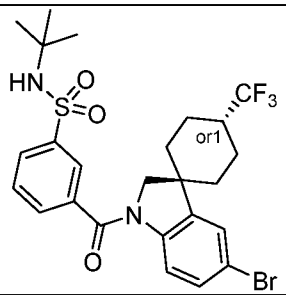
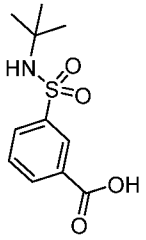
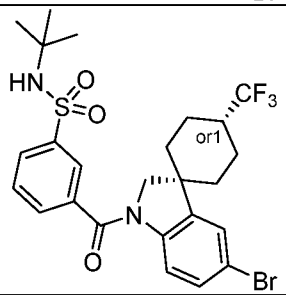
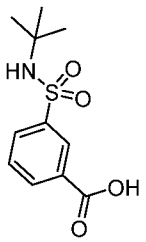
Compound	Structure	Carboxylic Acid	Indoline
Compound 234		**A-57**	**B-07**
Compound 236		**A-58**	**B-07**
(R)-Compound 238		**(R)-A-59**	**B-07**
(S)-Compound 238		**(S)-A-59**	**B-07**
Compound 242		**A-03**	**B-16**
Compound 244		**A-60**	**B-07**

Compound	Structure	Carboxylic Acid	Indoline
Compound 246		**A-61**	**B-07**
Compound 248		**A-13**	**B-07**
(S)-Compound 248		**(S)-A-13**	**B-07**
Compound 250		**A-01**	**B-17**
Compound 251		**A-09**	**B-04**
Compound 253		**A-05**	**B-07**

Compound	Structure	Carboxylic Acid	Indoline
Compound 256		**A-62**	**B-07**
Compound 259		**A-63**	**B-07**
Compound 263		**A-64**	**B-07**
Compound 265		**A-65**	**B-07**
Compound 267		**A-19**	**B-07**
Compound 271		**A-65**	**B-08**
Compound 273		**A-55**	**B-07**

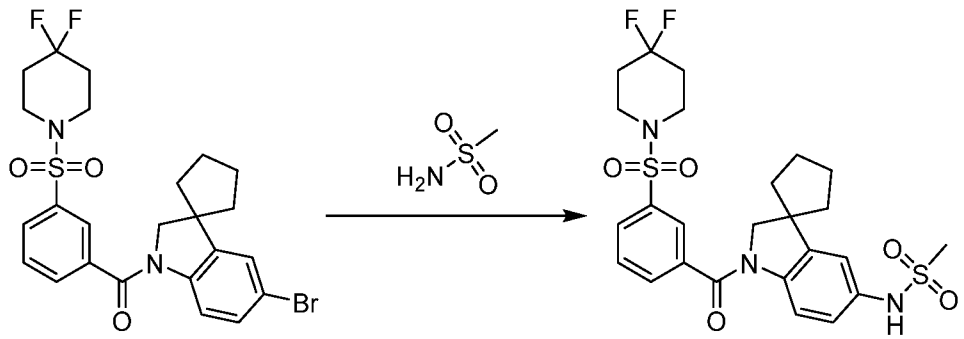
Compound	Structure	Carboxylic Acid	Indoline
Compound 276		**A-55**	**B-08**
Compound 278		**A-67**	**B-07**
Compound 280		**A-68**	**B-07**
Compound 282		**A-69**	**B-07**
Compound 286		**A-72**	**B-07**
Compound 288		**A-55**	**B-03**
Compound 290		**A-70**	**B-07**

Compound	Structure	Carboxylic Acid	Indoline
Compound 294		**A-09**	**B-18**
Compound 296		**A-73**	**B-07**
Compound 307 & Compound 308		**A-09**	**B-19/B-20**
Compound 323		**A-09**	**B-21**
Compound 325			**B-07**

Compound	Structure	Carboxylic Acid	Indoline
Compound 328			**B-22**
Compound 360a			**B-24a**
Compound 360b			**B-24b**

Synthetic Example S-002

Synthesis of N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)methanesulfonamide (Compound 18)



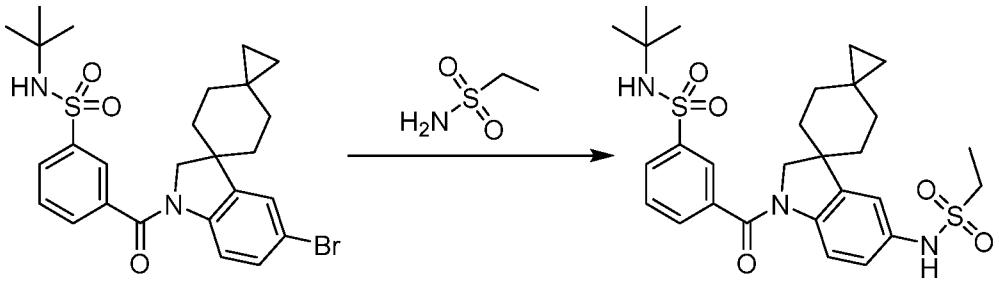
Compound 2 Compound 18

[0239] A degassed mixture of **Compound 2** (50 mg, 93 µmol), methanesulfonamide (13 mg, 0.14 mmol), CuI (9.0 mg, 46 µmol), K_3PO_4 (59 mg, 0.28 mmol), N^1,N^2-dimethylcyclohexane-1,2-diamine (7.0 mg, 46 µmol), and DMF (2.0 mL) was stirred at 150 °C for 2 h in a microwave reactor. The mixture was combined with H_2O (30 mL) and extracted with EtOAc (2 x 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by prep-HPLC (35-0% H_2O [10 mM NH_4CO_3]

in MeCN) to provide N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)methanesulfonamide (**Compound 18**, 8.6 mg).

Synthetic Example S-002a

Synthesis of N-(tert-butyl)-3-(5''-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (Compound 134).

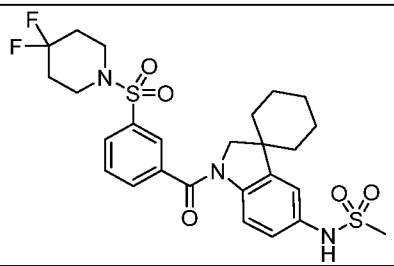
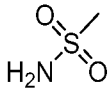


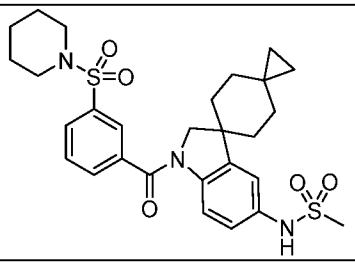
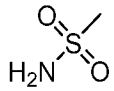
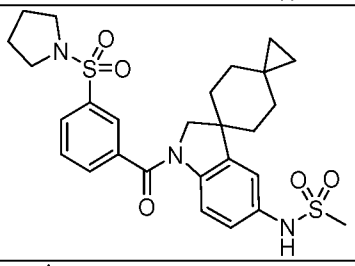
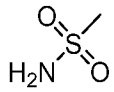
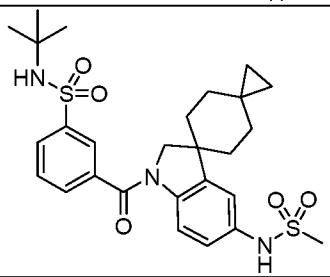
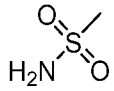
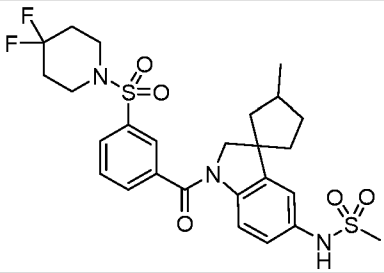
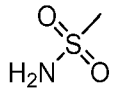
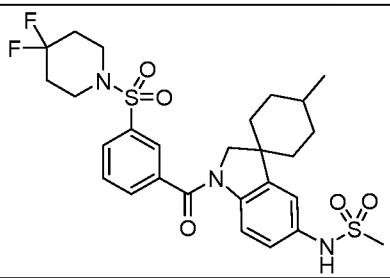
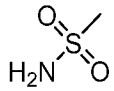
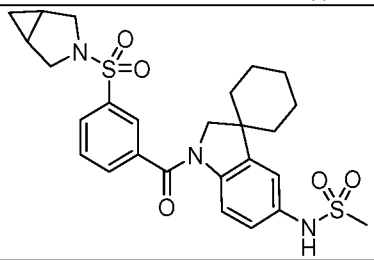
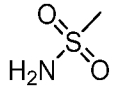
Compound 9 **Compound 134**

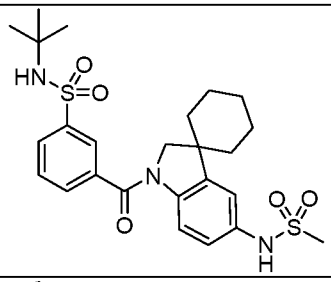
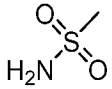
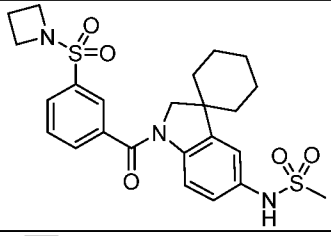
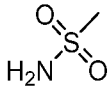
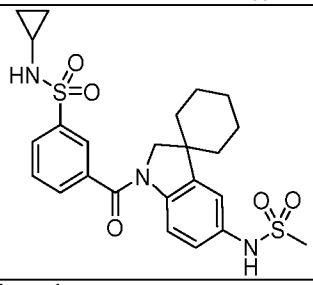
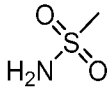
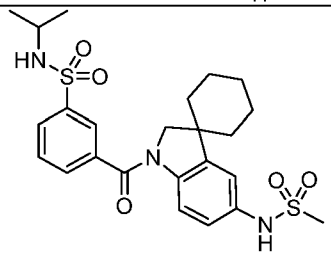
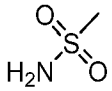
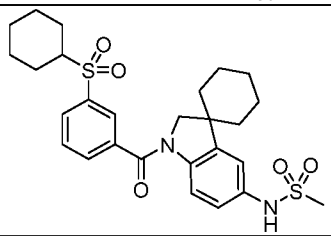
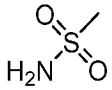
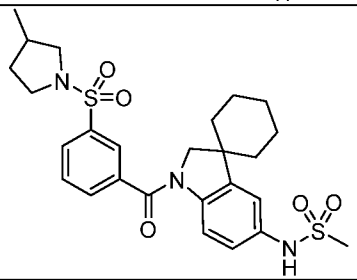
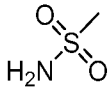
[0240] A degassed mixture of **Compound 2** (1.0 g, 1.9 mmol), ethanesulfonamide (0.60 g, 5.5 mmol), CuI (0.37 g, 1.9 mmol), K_3PO_4 (1.3 g, 6.0 mmol), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.27 g, 1.9 mmol), and DMF (14 mL) was stirred at 150 °C for 3 h. The mixture was combined with H_2O (40 mL). The resulting precipitate was filtered, washed with H_2O (5 mL x 3), dissolved in EtOAc (50 mL), washed with water (20 mL x 2), dried over Na_2SO_4, concentrated, and purified by prep-HPLC (50-20% H_2O [0.1% formic acid] in MeCN) to provide N-(tert-butyl)-3-(5''-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (**Compound 134**, 1.3 g).

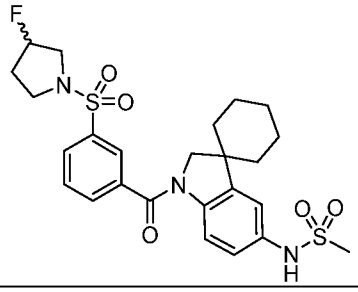
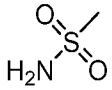
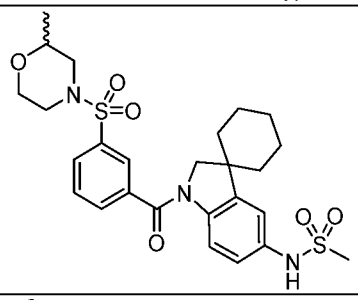
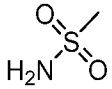
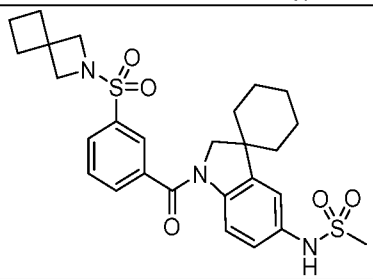
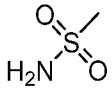
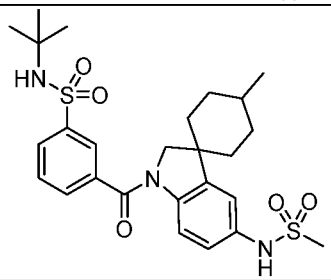
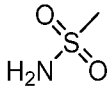
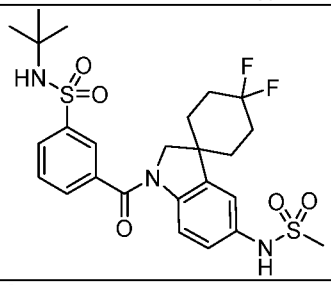
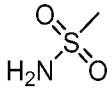
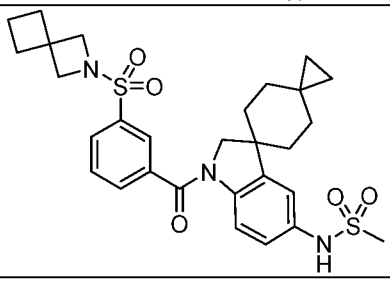
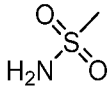
[0241] Compounds in **Table 7** were prepared from the indicated bromoindoline and primary sulfonamide in the same manner as **Compound 18**.

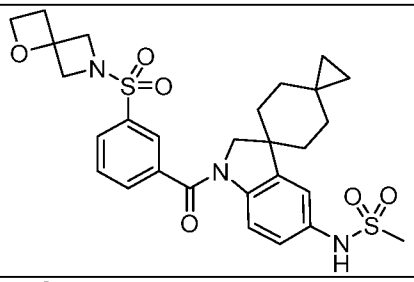
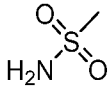
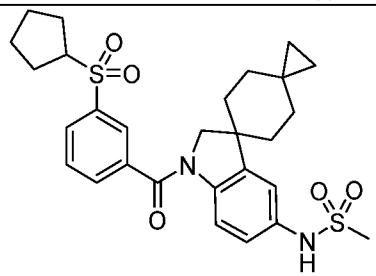
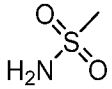
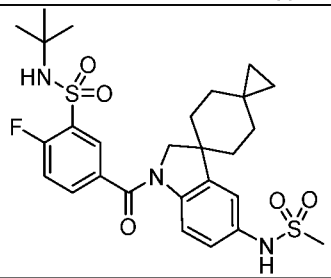
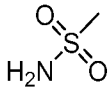
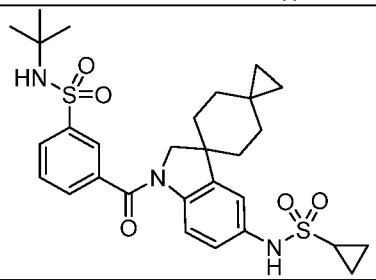
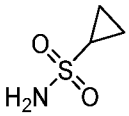
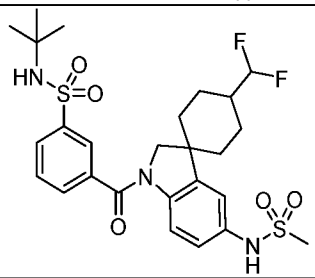
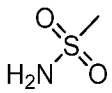
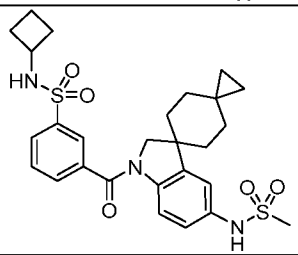
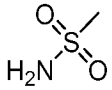
Table 7.

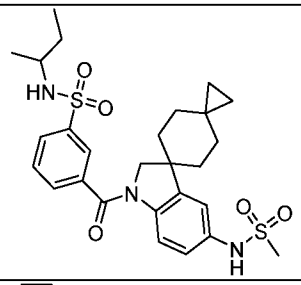
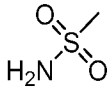
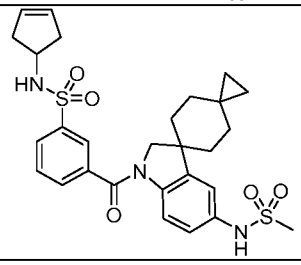
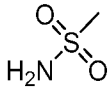
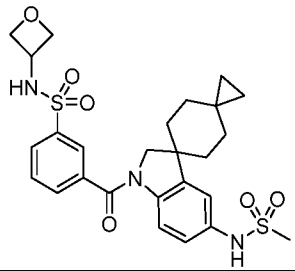
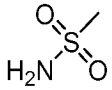
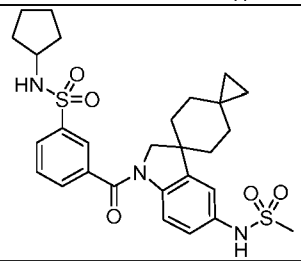
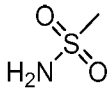
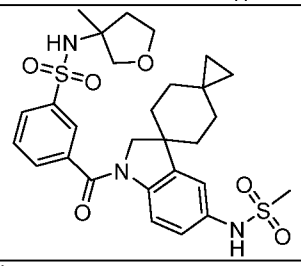
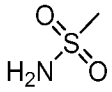
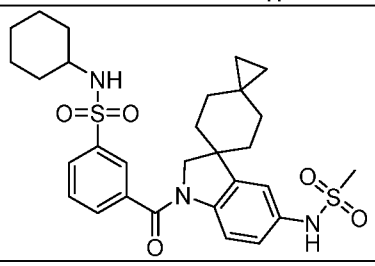
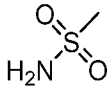
Compound	Structure	Bromide	Sulfonamide
Compound 19		**Compound 11**	

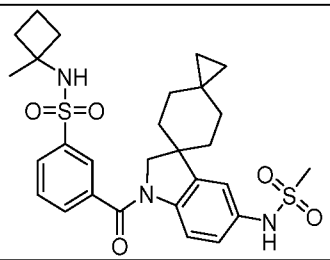
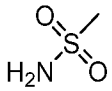
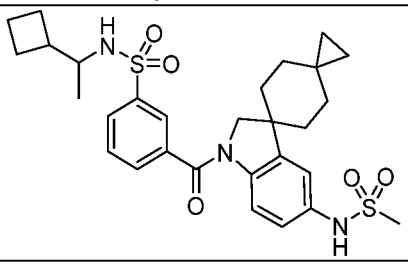
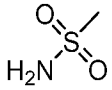
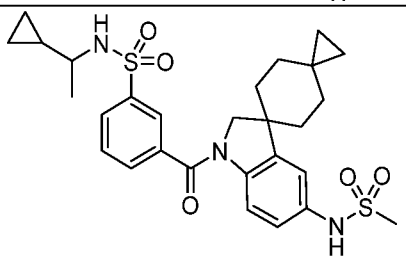
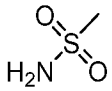
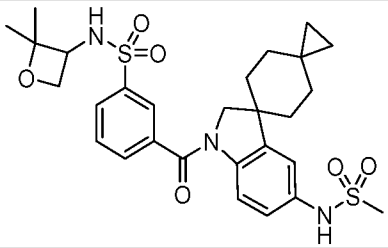
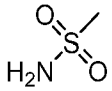
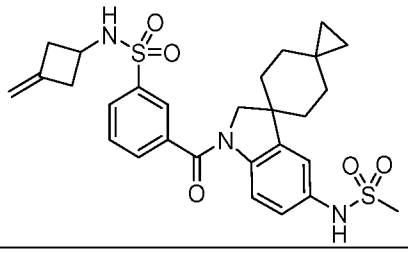
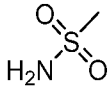
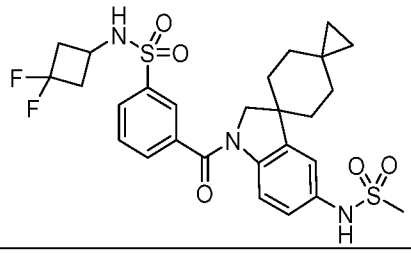
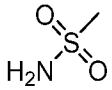
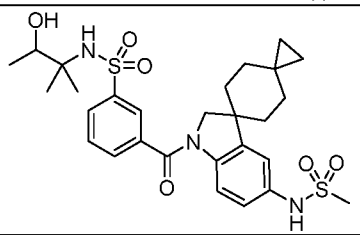
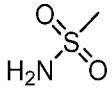
Compound	Structure	Bromide	Sulfonamide
Compound 20		**Compound 5**	
Compound 21		**Compound 7**	
Compound 22		**Compound 9**	
Compound 23		**Compound 14**	
Compound 24		**Compound 15**	
Compound 25		**Compound 16**	

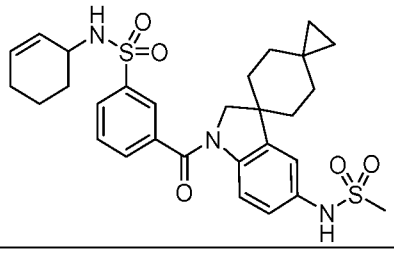
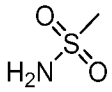
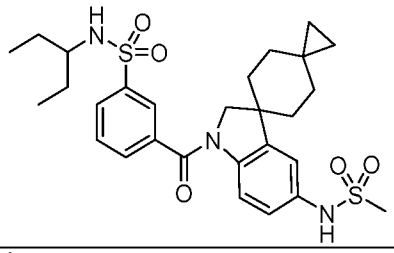
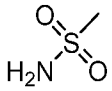
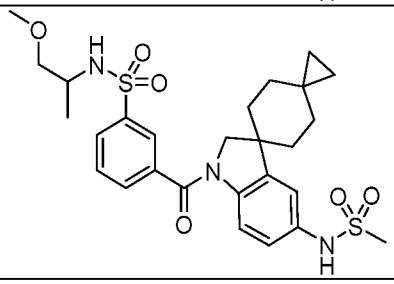
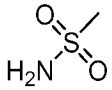
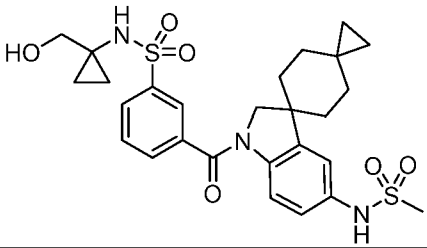
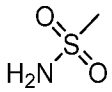
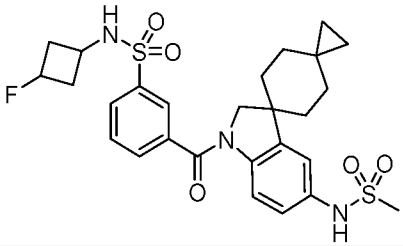
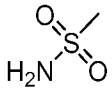
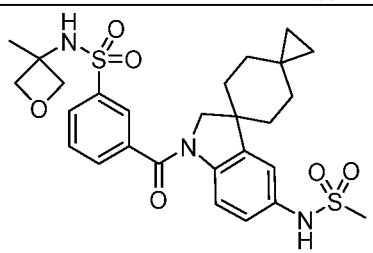
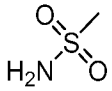
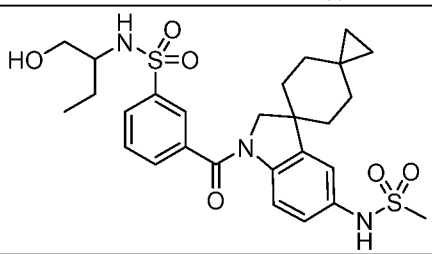
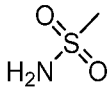
Compound	Structure	Bromide	Sulfonamide
Compound 26		**Compound 17**	
Compound 45		**Compound 126**	
Compound 46		**Compound 132**	
Compound 48		**Compound 130**	
Compound 70		**Compound 138**	
Compound 71		**Compound 137**	

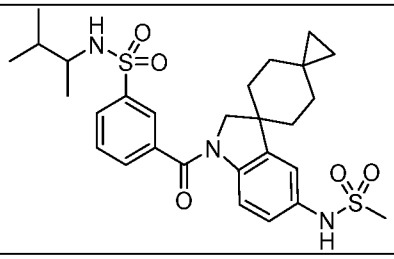
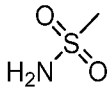
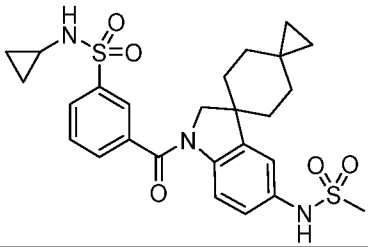
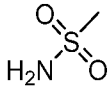
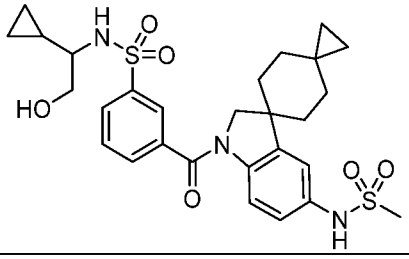
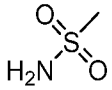
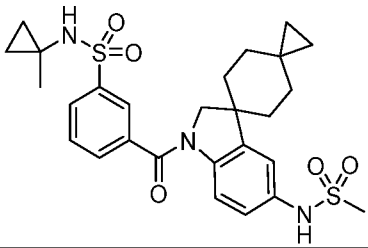
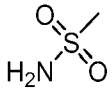
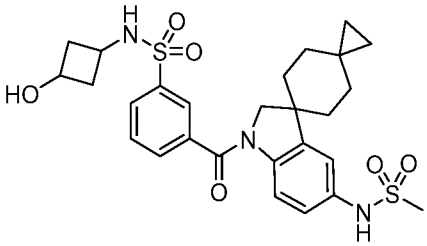
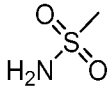
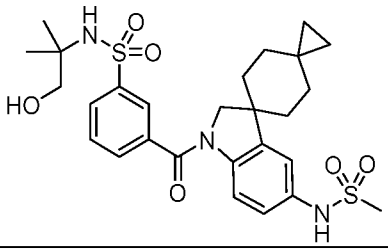
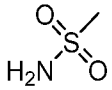
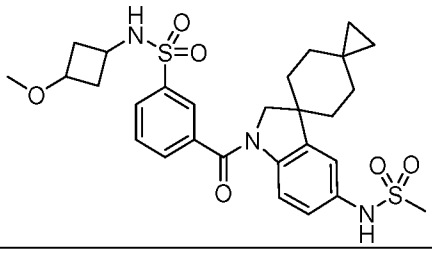
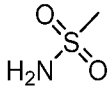
Compound	Structure	Bromide	Sulfonamide
Compound 83		**Compound 136**	
Compound 107		**Compound 135**	
Compound 129		**Compound 128**	
Compound 140		**Compound 139**	
Compound 144		**Compound 143**	
Compound 151		**Compound 150**	

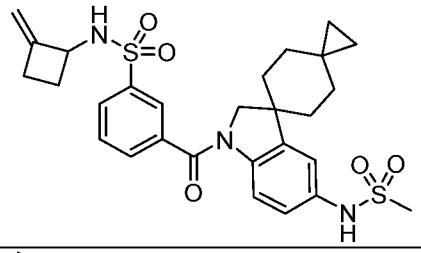
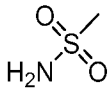
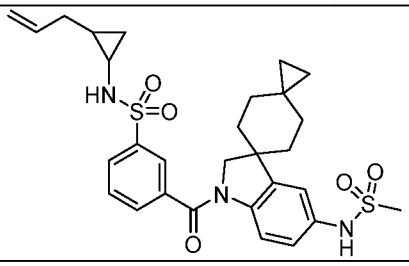
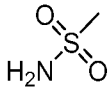
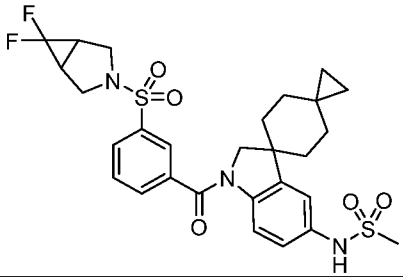
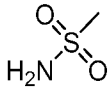
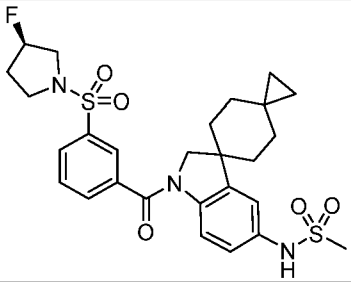
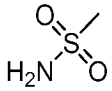
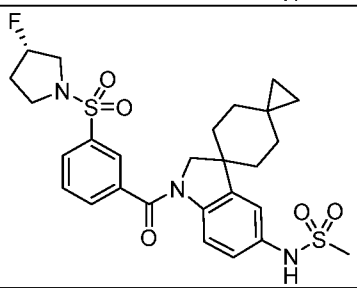
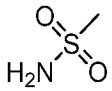
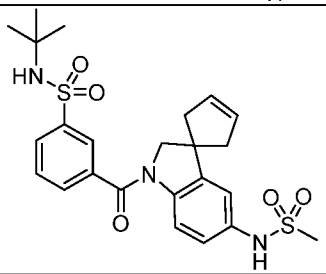
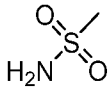
Compound	Structure	Bromide	Sulfonamide
Compound 153		**Compound 151**	
Compound 155		**Compound 154**	
Compound 159		**Compound 158**	
Compound 160		**Compound 9**	
Compound 162		**Compound 161**	
Compound 168		**Compound 167**	

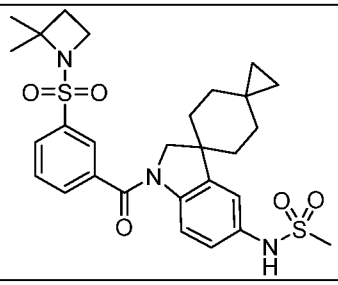
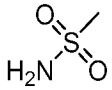
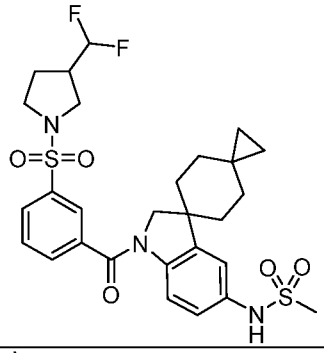
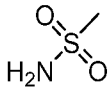
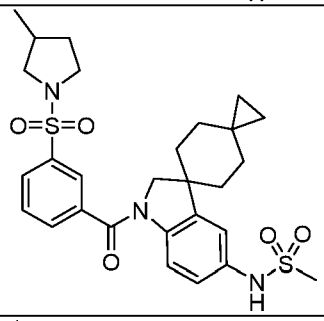
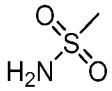
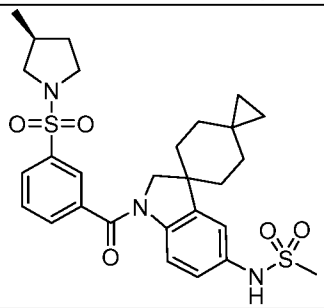
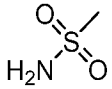
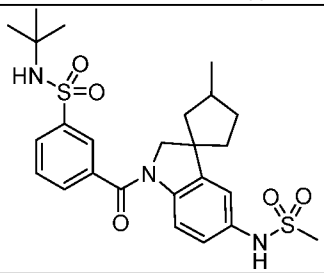
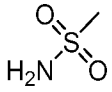
Compound	Structure	Bromide	Sulfonamide
Compound 170		**Compound 168**	
Compound 172		**Compound 171**	
Compound 174		**Compound 173**	
Compound 176		**Compound 175**	
Compound 178		**Compound 177**	
Compound 180		**Compound 179**	

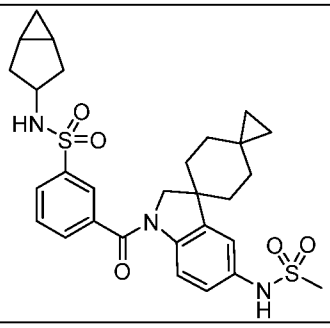
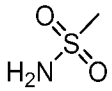
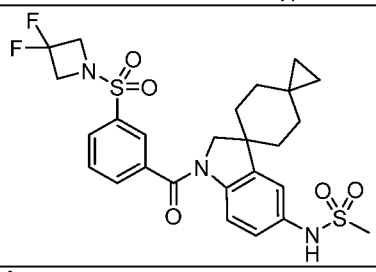
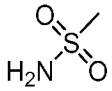
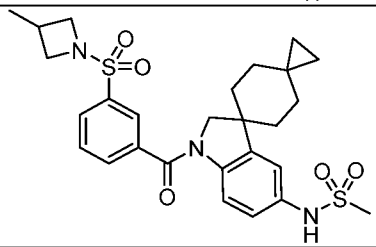
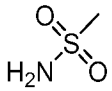
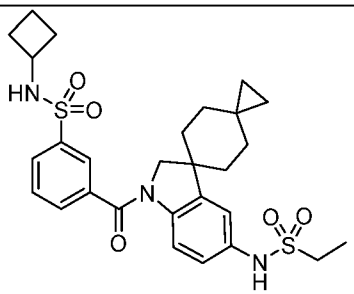
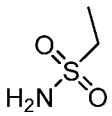
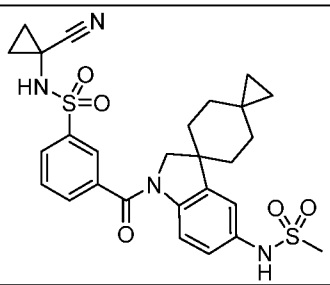
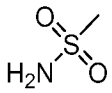
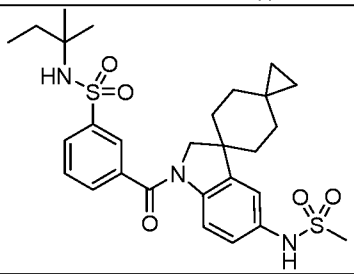
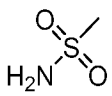
Compound	Structure	Bromide	Sulfonamide
Compound 182		**Compound 181**	
Compound 184		**Compound 183**	
Compound 186		**Compound 185**	
Compound 188		**Compound 187**	
Compound 190		**Compound 189**	
Compound 192		**Compound 191**	
Compound 194		**Compound 193**	

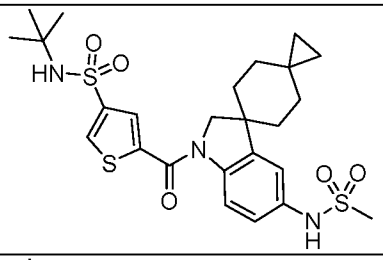
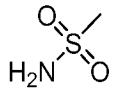
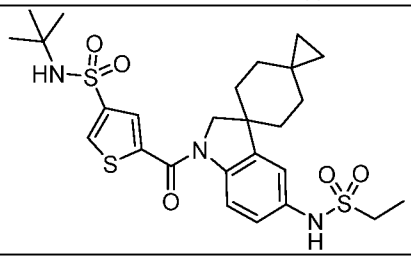
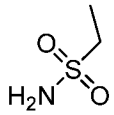
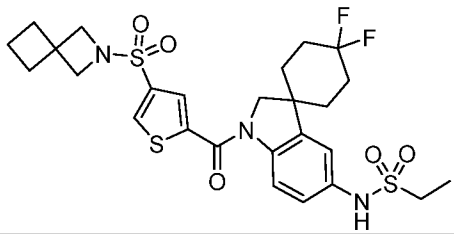
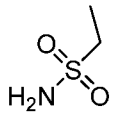
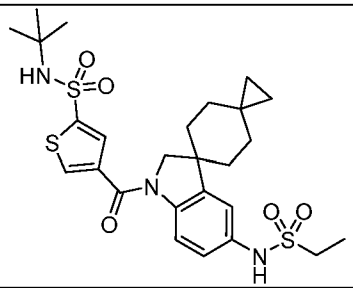
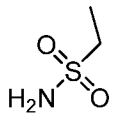
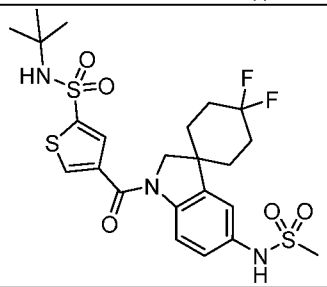
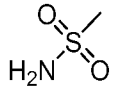
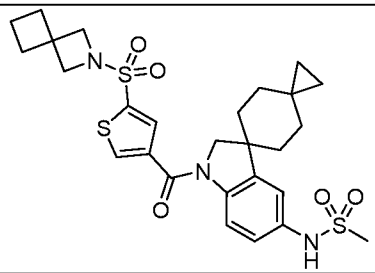
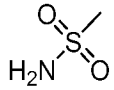
Compound	Structure	Bromide	Sulfonamide
Compound 196		**Compound 195**	
Compound 198		**Compound 197**	
Compound 200		**Compound 199**	
Compound 202		**Compound 201**	
Compound 204		**Compound 203**	
Compound 206		**Compound 205**	
Compound 208		**Compound 207**	

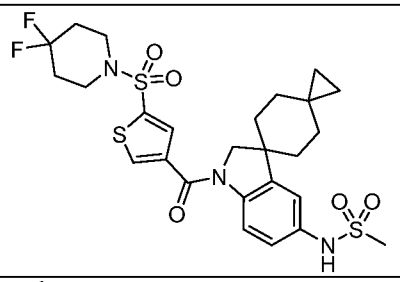
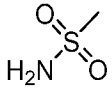
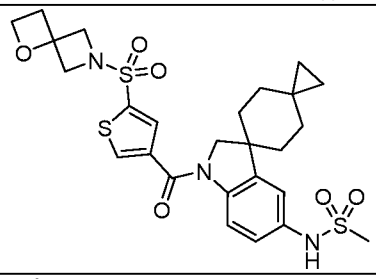
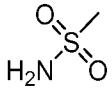
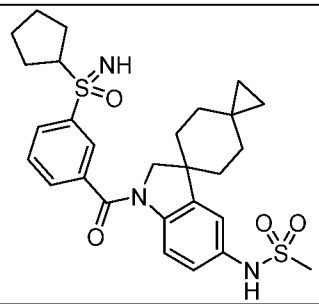
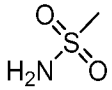
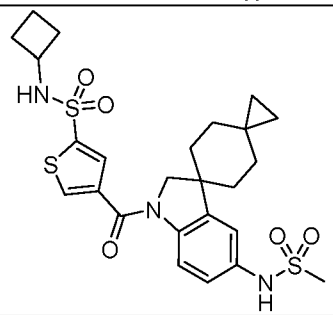
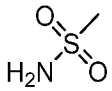
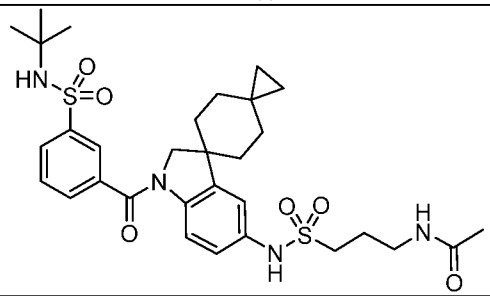
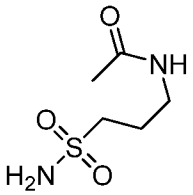
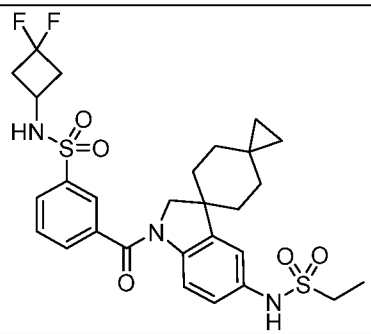
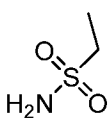
Compound	Structure	Bromide	Sulfonamide
Compound 210		**Compound 209**	
Compound 212		**Compound 211**	
Compound 214		**Compound 213**	
Compound 216		**Compound 215**	
Compound 218		**Compound 217**	
Compound 220		**Compound 219**	
Compound 222		**Compound 221**	

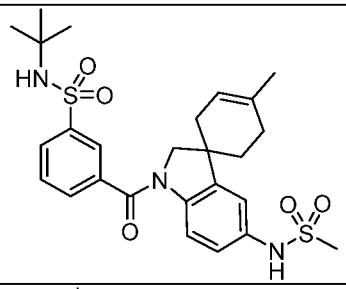
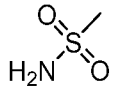
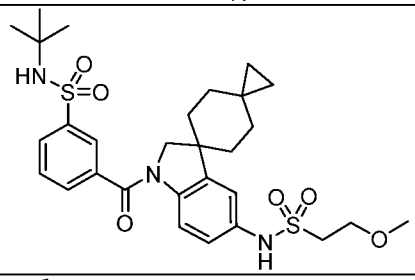
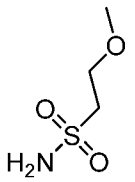
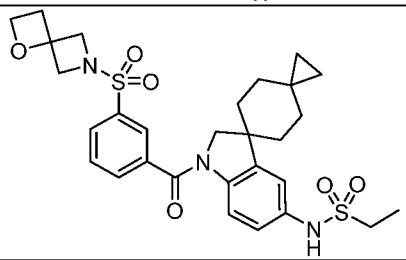
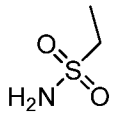
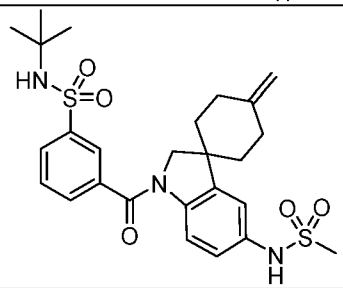
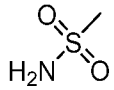
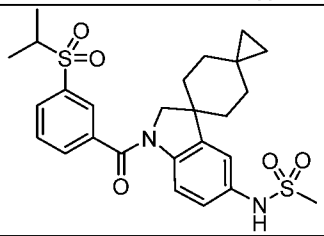
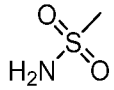
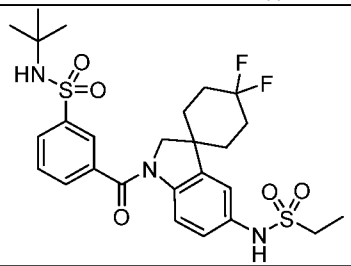
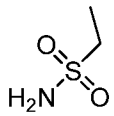
Compound	Structure	Bromide	Sulfonamide
Compound 233		**Compound 232**	
Compound 235		**Compound 234**	
Compound 237		**Compound 236**	
(R)-Compound 239		**(R)-Compound 238**	
(S)-Compound 239		**(S)-Compound 238**	
Compound 243		**Compound 242**	

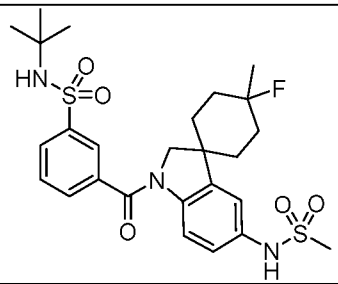
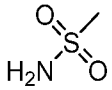
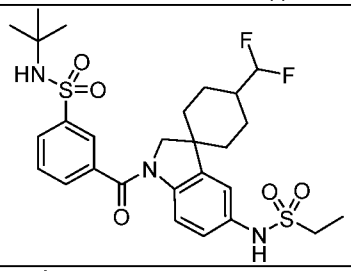
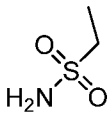
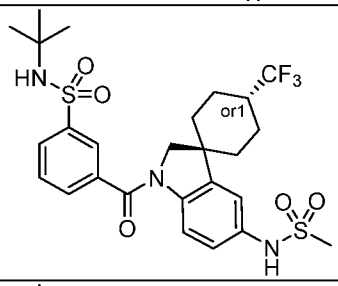
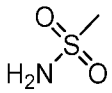
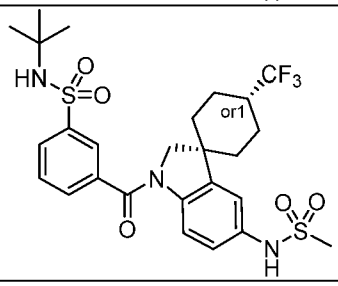
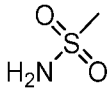
Compound	Structure	Bromide	Sulfonamide
Compound 245		**Compound 244**	
Compound 247		**Compound 246**	
Compound 249		**Compound 248**	
(S)-Compound 249		**(S)-Compound 248**	
Compound 252		**Compound 251**	

Compound	Structure	Bromide	Sulfonamide
Compound 254		**Compound 253**	
Compound 257		**Compound 256**	
Compound 260		**Compound 259**	
Compound 261		**Compound 167**	
Compound 264		**Compound 263**	
Compound 266		**Compound 265**	

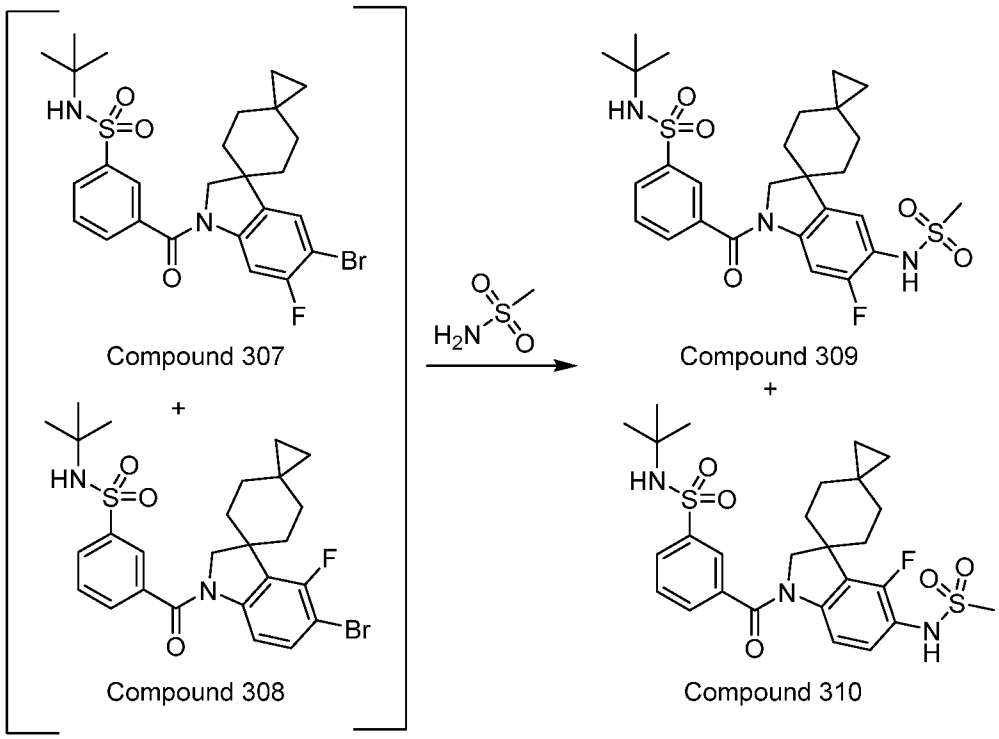
Compound	Structure	Bromide	Sulfonamide
Compound 268		**Compound 267**	
Compound 269		**Compound 267**	
Compound 272		**Compound 271**	
Compound 275		**Compound 273**	
Compound 277		**Compound 275**	
Compound 279		**Compound 278**	

Compound	Structure	Bromide	Sulfonamide
Compound 281		**Compound 280**	
Compound 283		**Compound 282**	
Compound 287		**Compound 287**	
Compound 291		**Compound 290**	
Compound 292		**Compound 9**	
Compound 293		**Compound 191**	

Compound	Structure	Bromide	Sulfonamide
Compound 295		**Compound 294**	
Compound 300		**Compound 9**	
Compound 320		**Compound 152**	
Compound 324		**Compound 323**	
Compound 326		**Compound 325**	
Compound 327		**Compound 143**	

Compound	Structure	Bromide	Sulfonamide
Compound 329		**Compound 328**	
Compound 333		**Compound 161**	
Compound 361a		**Compound 360a**	
Compound 361b		**Compound 360b**	

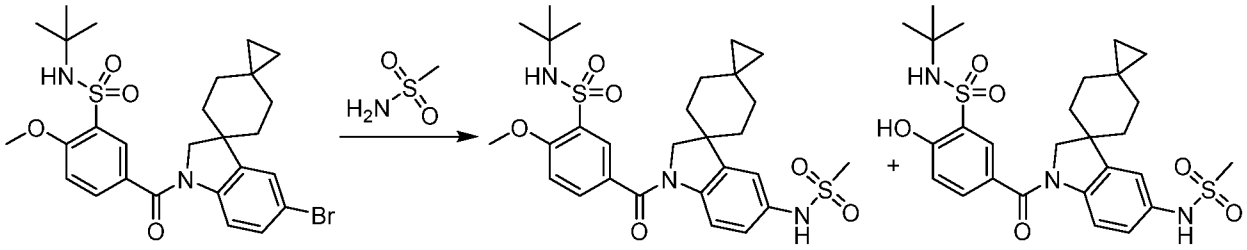
Synthesis of N-(tert-butyl)-3-(6''-fluoro-5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide and N-(tert-butyl)-3-(4''-fluoro-5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide



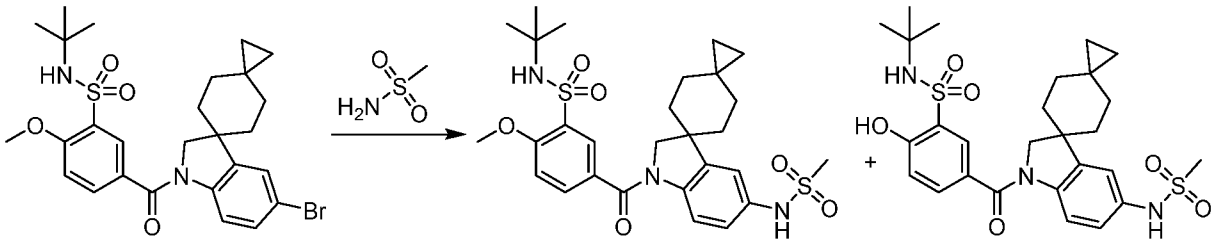
[0242] A ~3/1 mixture **Compound 307** and **Compound 308** (0.55 g, 1.0 mmol), methanesulfonamide (0.29 g, 3.0 mmol), CuI (0.11 g, 0.60 mmol), DMF (5 mL), *N1,N2*-dimethylcyclohexane-1,2-diamine (85 mg, 0.60 mmol) and K_3PO_4 (0.64 g, 3.0 mmol) was stirred at 160 °C for 2 h. The mixture was concentrated, combined with H_2O (10 mL), extracted with EtOAc (2 x 10 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (35-65% MeCN/H_2O [formic acid]) to provide *N*-(tert-butyl)-3-(6"-fluoro-5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (**Compound 309**, 23.2 mg) and N-(tert-butyl)-3-(4"-fluoro-5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (**Compound 310**, 5.1 mg).

Synthetic Example S-002b

Synthesis of N-(tert-butyl)-2-methoxy-5-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (Compound 297) and N-(tert-butyl)-2-hydroxy-5-(5"-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (Compound 298).



Compound 296 Compound 297 Compound 298

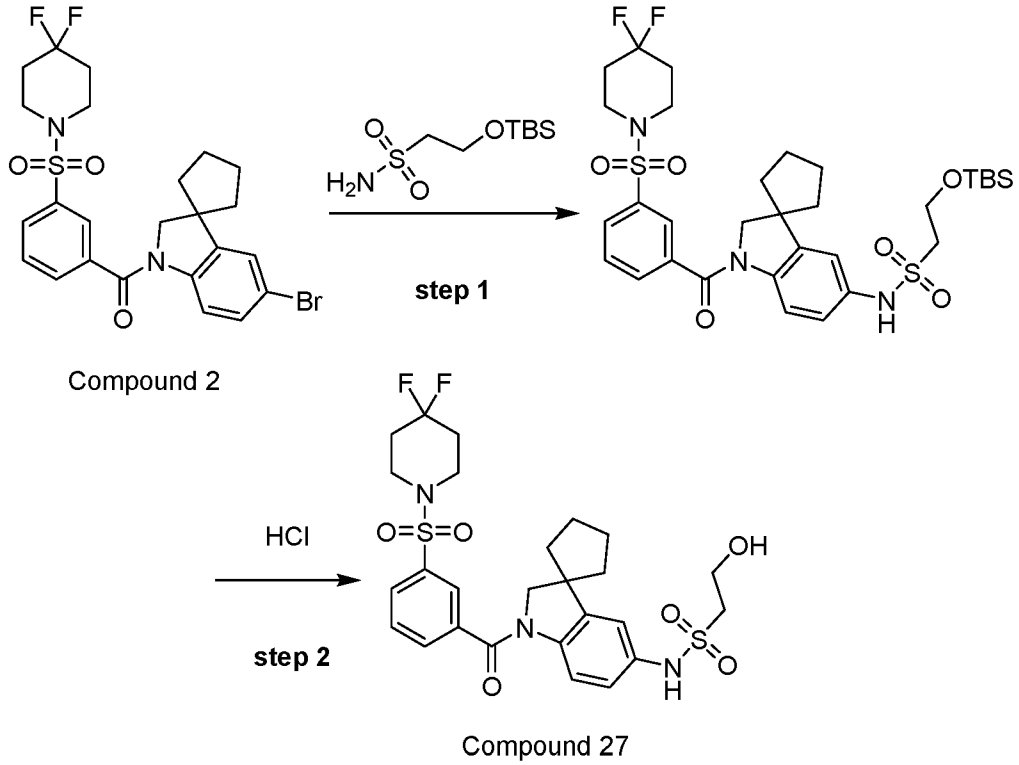


Compound 296 Compound 297 Compound 298

[0243] A mixture of **Compound 296** (0.10 g, 0.18 mmol), methanesulfonamide (51 mg, 0.53 mmol), CuI (34 mg, 0.18 mmol), K_3PO_4 (0.11 g, 0.53 mmol), N^1,N^2-dimethylcyclohexane-1,2-diamine (25 mg, 0.18 mmol), and DMF (2 mL) was stirred as 150 °C for 1.5 h. The mixture was then poured into 30 mL of H_2O, extracted with EtOAc (2 x 30 mL) and the extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentration and purified by reverse-phase HPLC (C18, 30-60% MeCN/water [0.1 mM formic acid]) to provide 13 mg of **Compound 297** and 26 mg of **Compound 298**.

Synthetic Example S-003

Synthesis of N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)-2-hydroxyethane-1-sulfonamide (Compound 27)



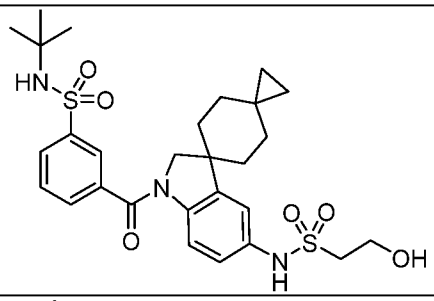
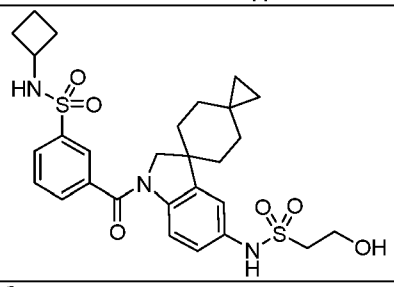
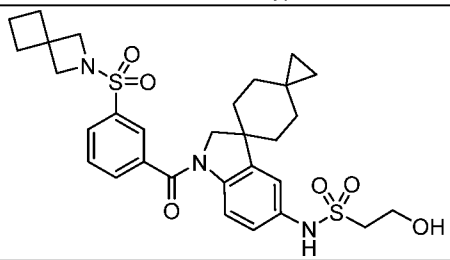
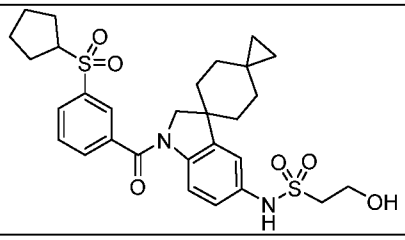
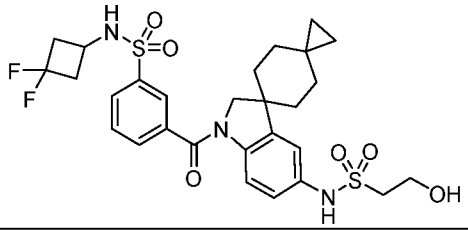
[0244] **Step 1**. A degassed mixture of **Compound 2** (50 mg, 93 µmol), 2-((tert-butyldimethylsilyl)oxy)ethane-1-sulfonamide (33 mg, 0.14 mmol), CuI (9 mg, 46 µmol), K_3PO_4 (59 mg, 0.28 mmol) and N^1,N^2-dimethylcyclohexane-1,2-diamine (7 mg, 46 µmol), and DMF (2.0 mL) was stirred at 150 °C for 2 h in a microwave reactor. The mixture was poured into water H_2O (30 mL) and extracted with EtOAc (2 x 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, and concentrated to provide 2-((tert-butyldimethylsilyl)oxy)-N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)ethane-1-sulfonamide (65 mg).

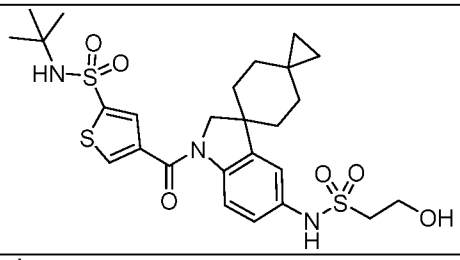
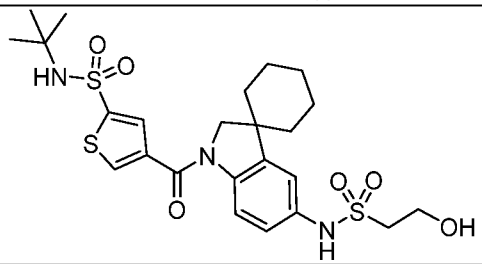
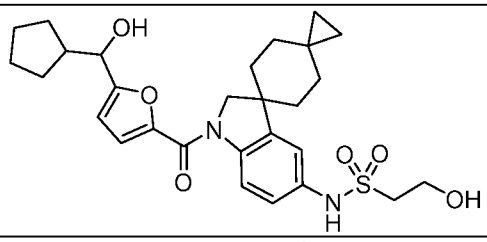
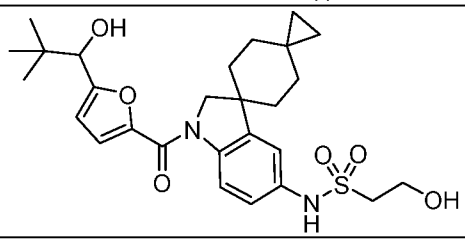
[0245] **Step 2**. A mixture of 2-((tert-butyldimethylsilyl)oxy)-N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)ethane-1-sulfonamide (65 mg, 93 µmol), MeOH (5.0 mL), and HCl (2M, 5.0 mL) was stirred at 20 °C for 1 h, concentrated, aqueous saturated $NaHCO_3$ was added to bring the pH to 9. The mixture was extracted with EtOAc (2 x 30 mL) and the extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by prep-HPLC (30-60% MeCN

in H_2O [10 mM NH_4HCO_3]) to provide N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)-2-hydroxyethane-1-sulfonamide (**Compound 27**, 8.5 mg).

[0246] Compounds in **Table 7.1** were prepared from the indicated bromoindoline and 2-[(tert-butyldimethylsilyl)oxy]ethane-1-sulfonamide in the same manner as **Compound 29**.

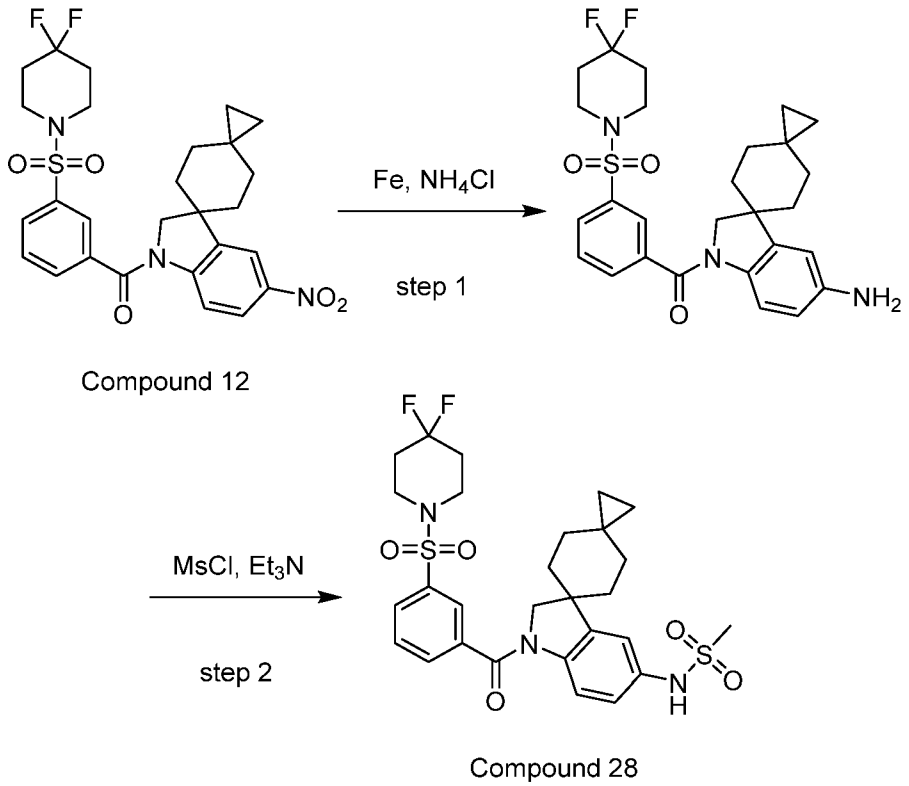
Table 7.1

Compound	Structure	Bromoindole
Compound 148		**Compound 9**
Compound 227		**Compound 167**
Compound 228		**Compound 150**
Compound 229		**Compound 154**
Compound 230		**Compound 191**

Compound	Structure	Bromoindole
Compound 274		**Compound 273**
Compound 289		**Compound 288**
Compound 368		**Compound 366**
Compound 371		**Compound 370**

Synthetic Example S-004

Synthesis of N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide
(Compound 28)



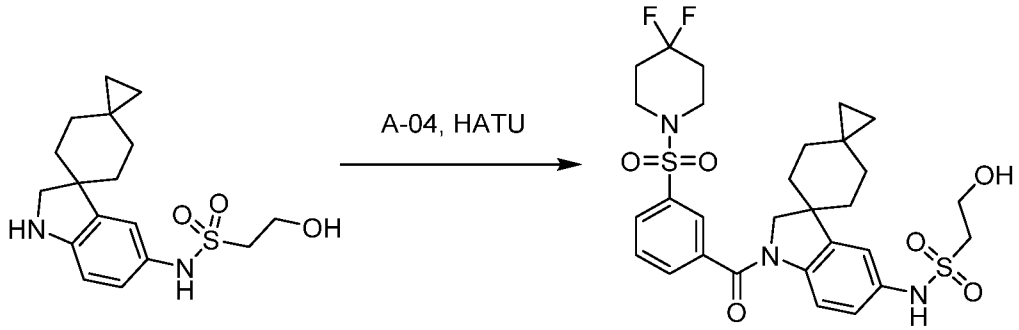
[0247] Step 1. To a mixture of Compound 12 (0.18 g, 0.33 mmol), and Fe (0.20 g, 3.6 mmol), EtOH (10 mL), THF (10 mL), and H_2O (4.0 mL) was added NH_4Cl (0.2 g, 3.7 mmol) and the mixture was stirred at 80 °C for 3 h. The mixture was filtered through celite, and the filter cake was washed with THF (10 mL x 2) and MeOH (10 mL x 2). The filtrate was concentrated to ~20 mL, diluted with EtOAc (30 mL), washed with H_2O (15 mL x 2), brine (15 mL), dried over Na_2SO_4, filtered, and concentrated to (5''-aminodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone (0.17 g).

[0248] **Step 2**. To a mixture of (5''-aminodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)(3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)methanone (0.15 g, 0.29 mmol), and Et_3N (88 0.12 mL, 0.87 mmol), and CH_2Cl_2 (14 mL) was added slowly a mixture of methanesulfonyl chloride (68 µg, 0.87 mmol) and CH_2Cl_2 (1.0 mL) and the mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2 (15 mL) and the extract was washed with H_2O (5.0 mL x 2) and brine (5.0 mL), dried

over Na_2SO_4, filtered, concentrated, and purified by prep-HPLC (40-70% MeCN in water [0.1% formic acid]) to provide N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 28**, 55 mg).

Synthetic Example S-005

N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)-2-hydroxyethane-1-sulfonamide (Compound 29)

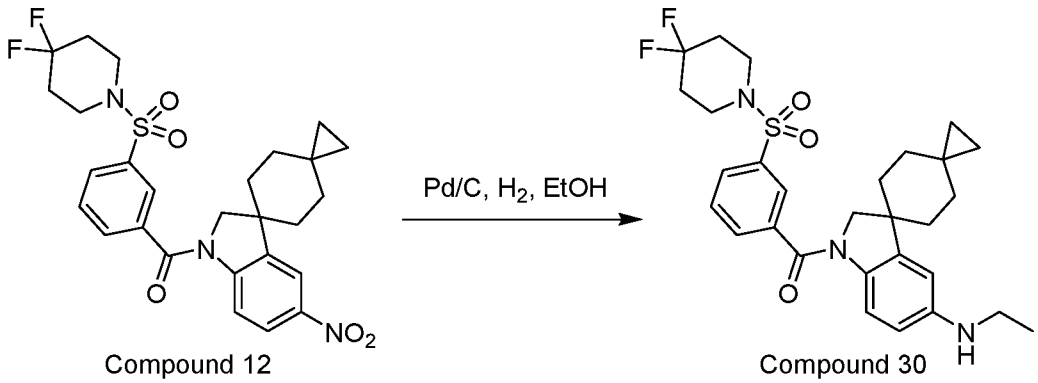


B-08b Compound 29

[0249] A mixture of **A-04** (16 mg, 53 µmol), DMF (1.0 mL), HATU (46 mg, 0.12 mmol) and iPr_2NEt (18 µg, 0.10 mmol) was stirred at 25 °C for 15 min and a mixture of N-{1'',2''-dihydrodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indol]-5''-yl}-2-hydroxyethane-1-sulfonamide (42 mg, 48 µmol), iPr_2NEt (89 µg, 0.51 µmol), and DMF (1.0 mL) was added. After stirring at 25 °C for 5 h, the mixture was filtered and the filtrate was concentrated and purified by prep-HPLC (20-60% MeCN in H_2O [0.1% formic acid]) to provide N-(1''-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)-2-hydroxyethane-1-sulfonamide (**Compound 29,** 2 mg).

Synthetic Example S-006

Synthesis of (3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(5''-(ethylamino)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)methanone (Compound 30)

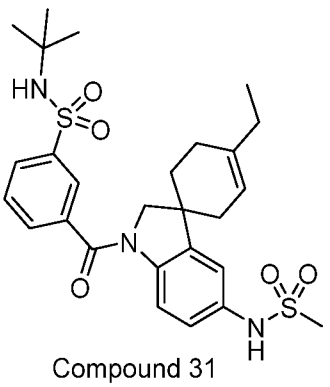


Compound 12 Compound 30

[0250] A mixture of **Compound 12** (0.15 g, 0.28 mmol), Pd/C (0.15 g, 10%) and EtOH (15 mL) was stirred under H_2 (15 psi) at 25 °C for 12 h. The mixture was flushed with N_2, filtered through celite, and the filtrate was concentrated and the minor product was isolated by prep-HPLC (45 – 80% MeCN in H_2O [10 mM NH_4HCO_3]), and further by prep-HPLC (35 – 75% MeCN in H_2O [0.1% formic acid]) to provide (3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(5''-(ethylamino)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-1''-yl)methanone (**Compound 30**, 7.9 mg).

Synthetic Example S-007

Isolation of N-(tert-butyl)-3-(4-ethyl-5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indolin]-3-en-1'-carbonyl)benzenesulfonamide (Compound 31)

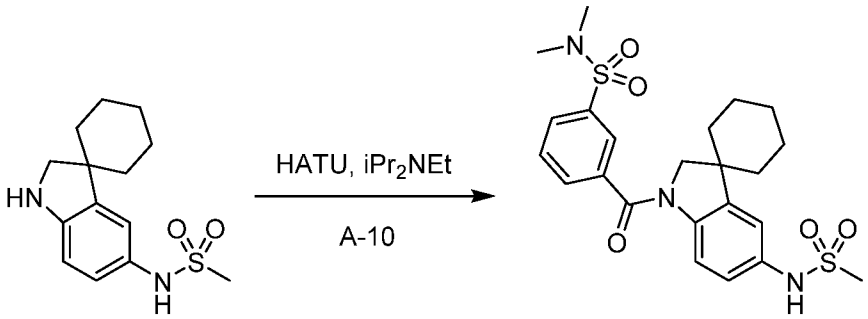


Compound 31

[0251] **Compound 31** was isolated as a side-product during the purification of **Compound 22**: prep-HPLC (40-60% MeCN in H_2O [10 mM NH_4HCO_3].

Synthetic Example S-008

Preparation of N,N-dimethyl-3-(5'-(methylsulfonamido)spiro[cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide (Compound 42)

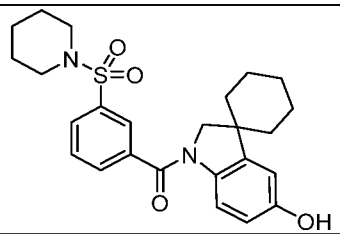
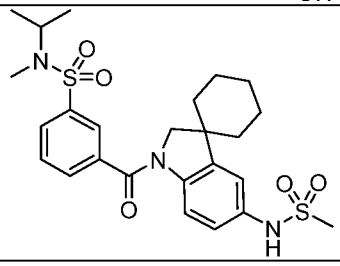


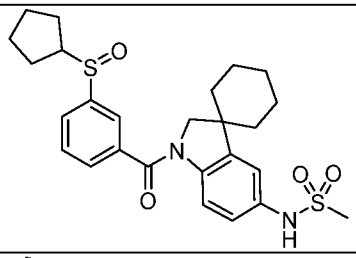
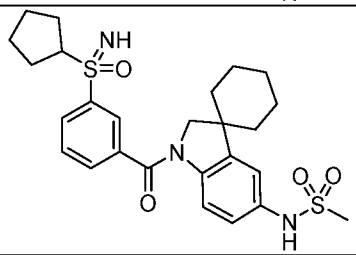
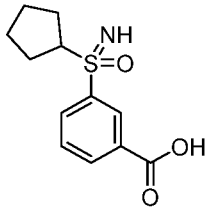
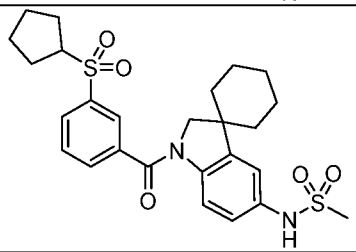
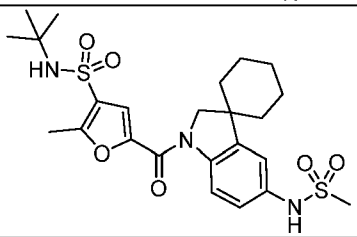
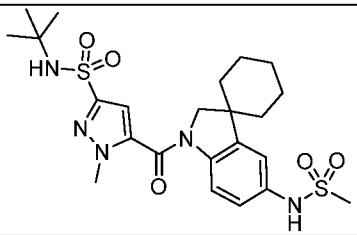
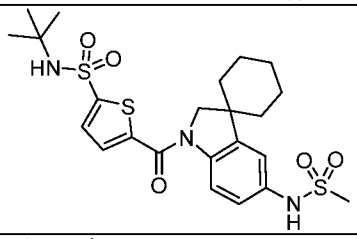
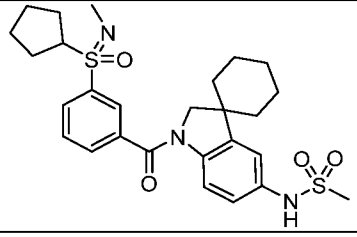
B-13 Compound 42

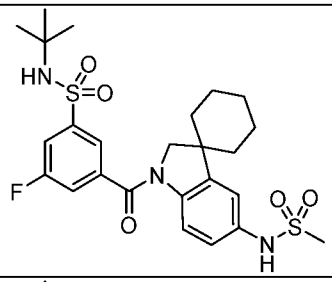
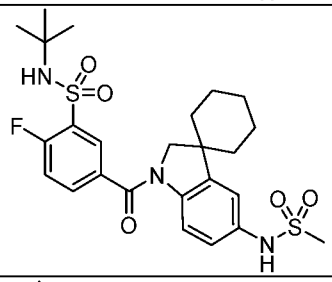
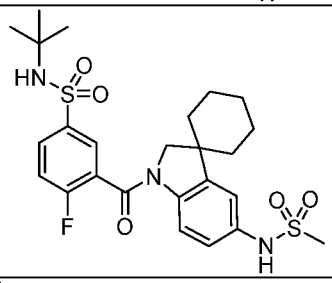
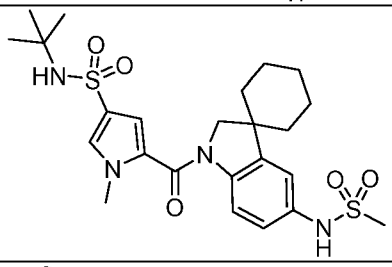
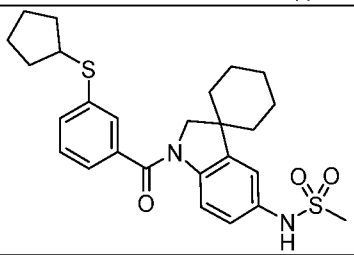
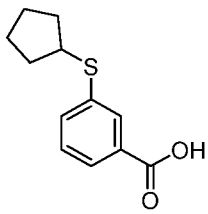
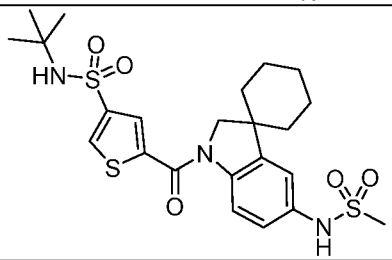
[0252] To a mixture of **A-10** (50 mg, 0.22 mmol) and DMF (3 mL) were added HATU (0.12 g, 0.33 mmol) and iPr_2NEt (0.11 mL, 0.65 mmol). After 20 min, **B-13** (73 mg, 0.26 mmol) was added and the mixture was stirred at 60 °C for 2 h, concentrated, and purified by prep-HPLC (45-65% MeCN in H_2O (0.1 M HCl)) to provide N,N-dimethyl-3-(5'-(methylsulfonamido)spiro [cyclohexane-1,3'-indoline]-1'-carbonyl)benzenesulfonamide (**Compound 42**, 50 mg).

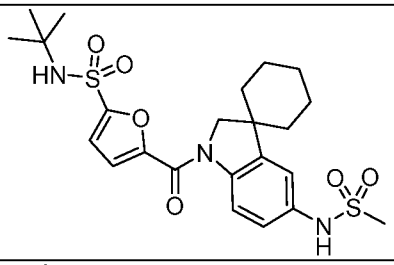
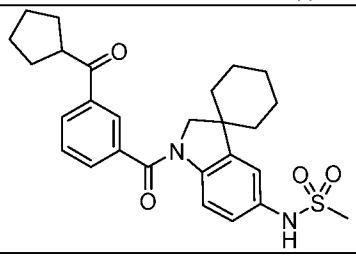
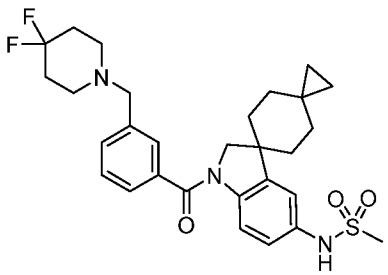
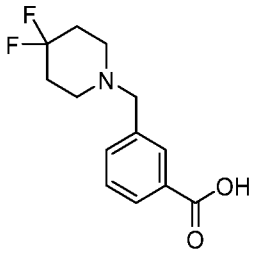
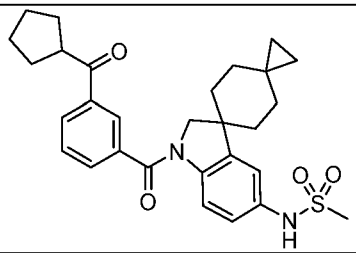
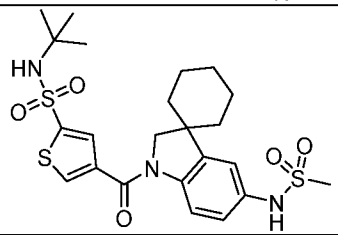
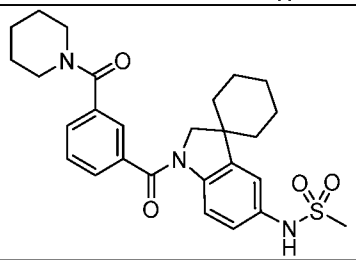
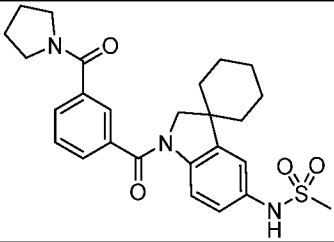
[0253] Compounds in **Table 7.2** were prepared from the indicated indoline and carboxylic acid in the same manner as **Compound 42**.

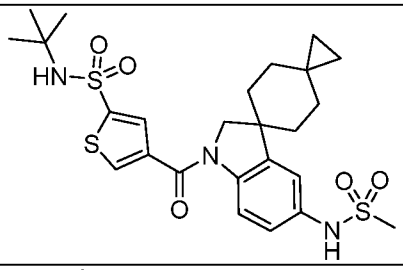
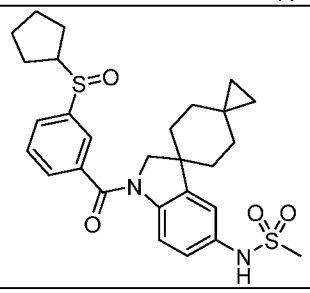
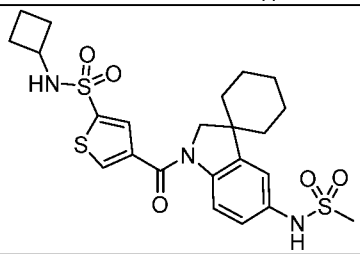
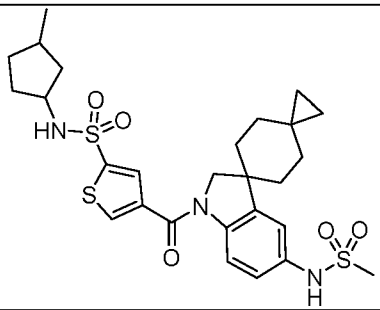
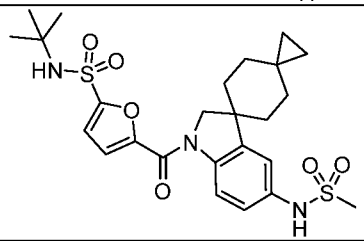
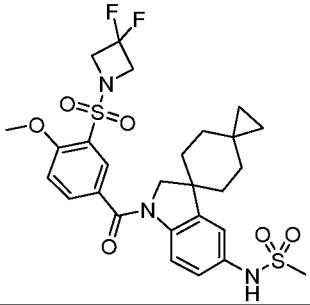
Table 7.2

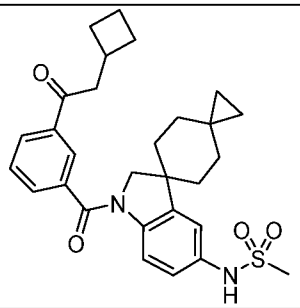
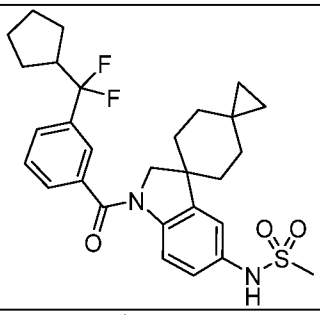
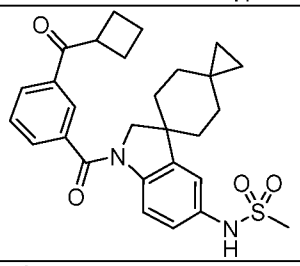
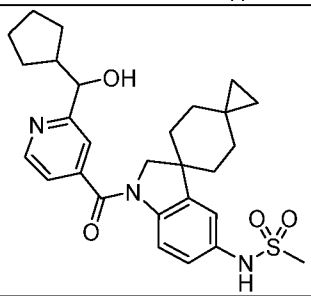
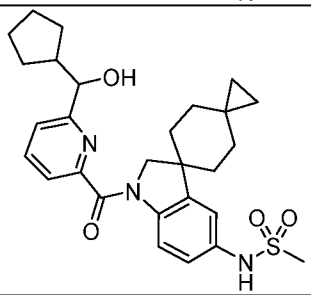
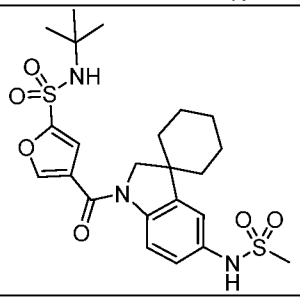
Compound	Structure	Indoline	Carboxylic acid
Compound 166		**B-15**	**A-14**
Compound 55		**B-13**	**A-12**

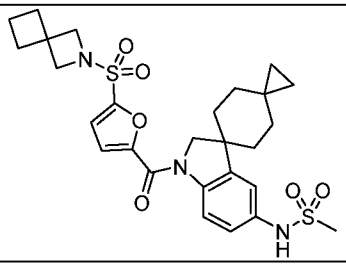
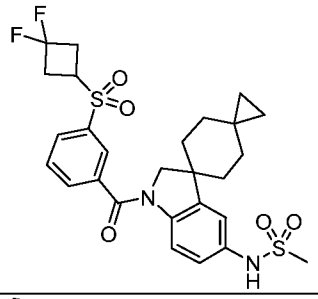
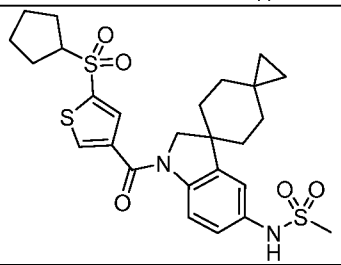
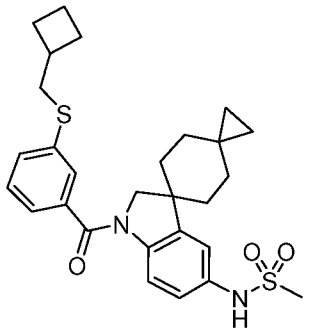
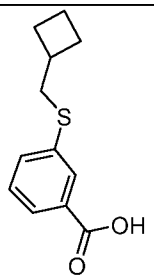
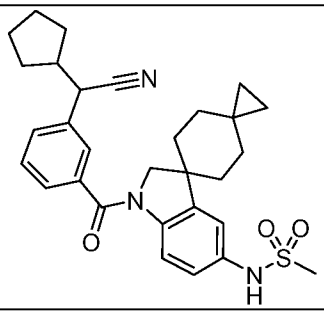
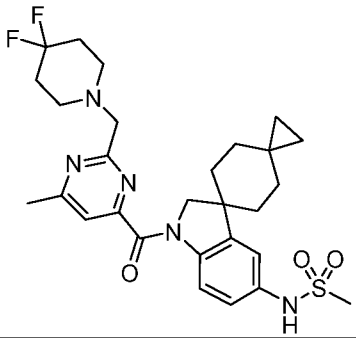
Compound	Structure	Indoline	Carboxylic acid
Compound 43		**B-13**	**A-51**
Compound 49		**B-13**	
Compound 50		**B-13**	**A-52**
Compound 57		**B-13**	**A-16**
Compound 59		**B-13**	**A-15**
Compound 60		**B-13**	**A-21**
Compound 67		**B-13**	**A-53**

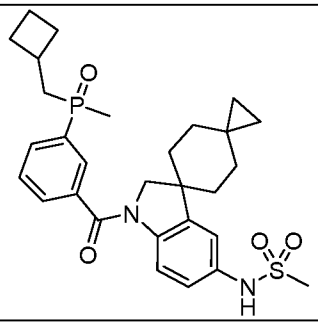
Compound	Structure	Indoline	Carboxylic acid
Compound 95		**B-13**	**A-20**
Compound 96		**B-13**	**A-22**
Compound 97		**B-13**	**A-18**
Compound 145		**B-13**	**A-17**
Compound 146		**B-13**	
Compound 147		**B-13**	**A-19**

Compound	Structure	Indoline	Carboxylic acid
Compound 149		**B-13**	**A-23**
Compound 156		**B-13**	**A-54**
Compound 163		**B-14**	 CAS: 1783412-42-9
Compound 164		**B-14**	**A-54**
Compound 231		**B-09**	**A-55**
Compound 240		**B-13**	**A-01**
Compound 241		**B-13**	**A-02**

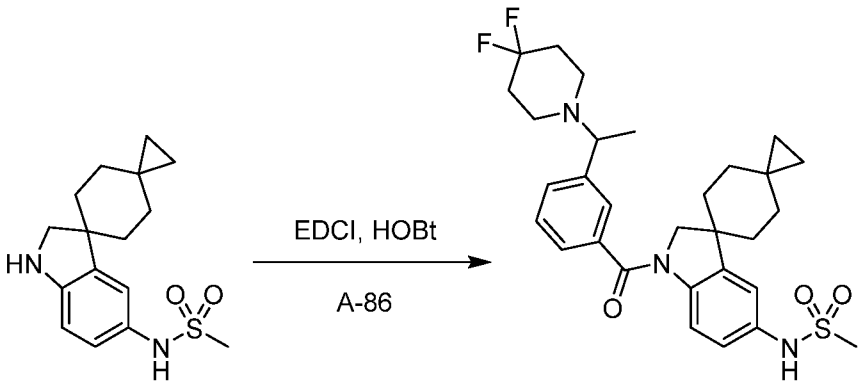
Compound	Structure	Indoline	Carboxylic acid
Compound 262		**B-14**	**A-55**
Compound 270		**B-14**	**A-51**
Compound 284		**B-13**	**A-70**
Compound 285		**B-14**	**A-71**
Compound 299		**B-14**	**A-23**
Compound 302		**B-14**	**A-74**

Compound	Structure	Indoline	Carboxylic acid
Compound 304		**B-14**	**A-75**
Compound 306		**B-14**	**A-76**
Compound 312		**B-14**	**A-77**
Compound 316		**B-14**	**A-78**
Compound 317		**B-14**	**A-79**
Compound 318		**B-13**	**A-80**

Compound	Structure	Indoline	Carboxylic acid
Compound 321		**B-14**	**A-81**
Compound 322		**B-14**	**A-82**
Compound 330		**B-14**	**A-83**
Compound 334		**B-14**	 **A-84** CAS: 1468983-59-6
Compound 339		**B-14**	**A-85**
Compound 343		**B-14**	**A-88**

Compound	Structure	Indoline	Carboxylic acid
Compound 362		**B-14**	**A-97**

Preparation of *N*-(1''-(3-(1-(4,4-difluoropiperidin-1-yl)ethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 341)

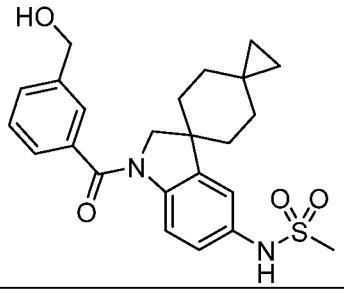
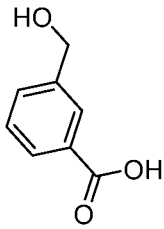
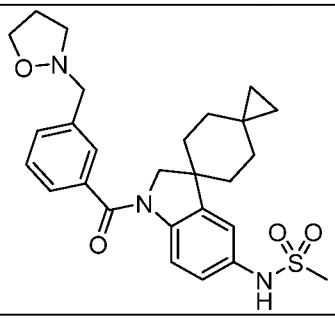
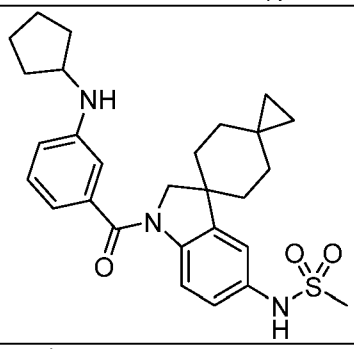
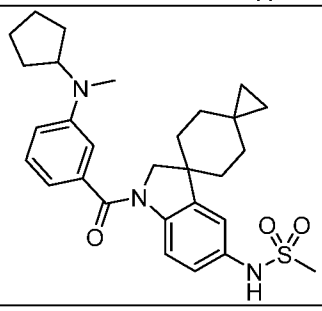
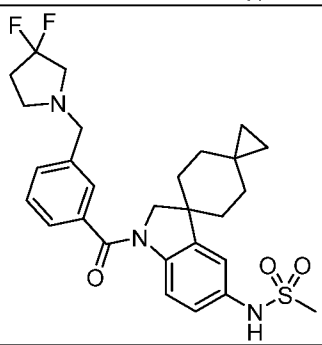


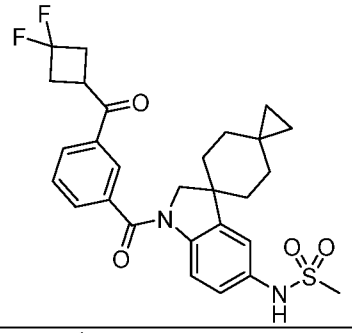
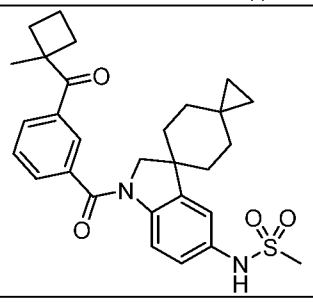
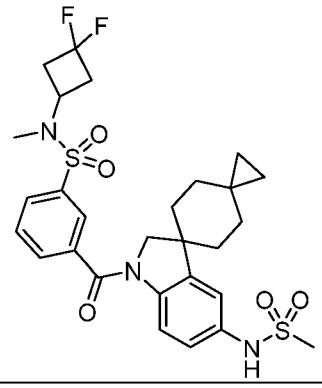
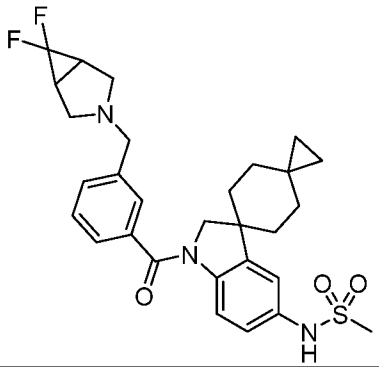
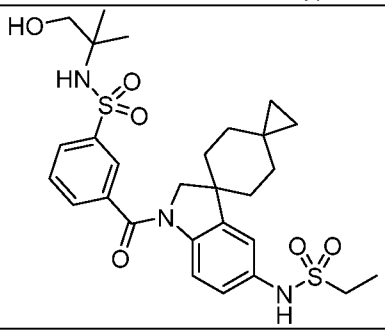
B-14 Compound 341

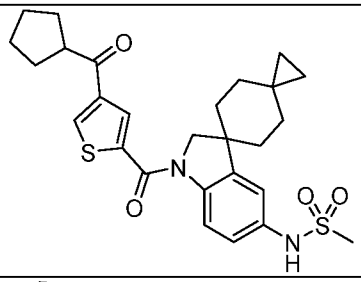
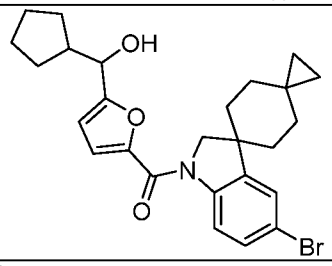
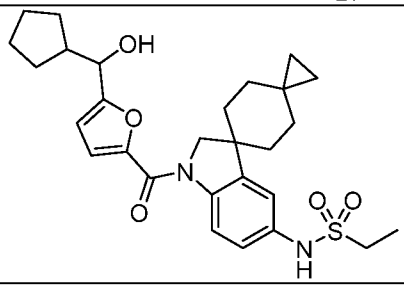
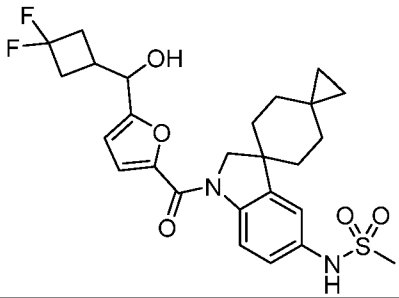
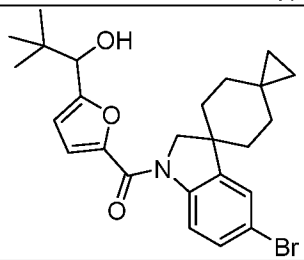
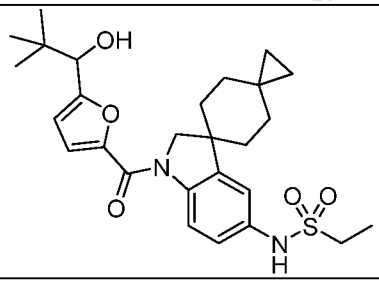
[0254] A mixture of **A-86** (0.55 g, 2.0 mmol), DMF (5.5 mL), Et_3N (0.85 mL, 6.1 mmol), EDCI (1.4 g, 7.1 mmol), HOBt (0.96 g, 7.1 mmol) was stirred at 20 °C for 0.5 h, and then **B-14** (0.25 g, 0.81 mmol) was added. The mixture was stirred at 20°C for 12 h, poured into H_2O (16 mL), and extracted with EtOAc (2 x 16 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 20-55% MeCN in H_2O [formic acid])provide *N*-(1''-(3-(1-(4,4-difluoropiperidin-1-yl)ethyl)benzoyl)dispiro [cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 341**, 30 mg).

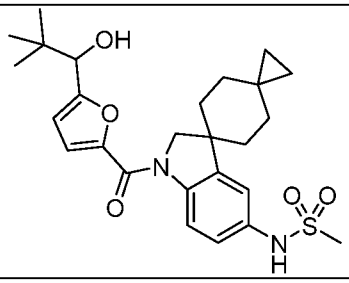
[0255] Compounds in **Table 7.3** were prepared from the indicated indoline and carboxylic acid in the same manner as **Compound 341.**

Table 7.3

Code	Structure	Carboxylic Acid	Indoline
Example 344			**B-14**
Compound 346		**A-89**	**B-14**
Compound 347		**A-90**	**B-14**
Compound 348		**A-91**	**B-14**
Compound 349		**A-92**	**B-14**

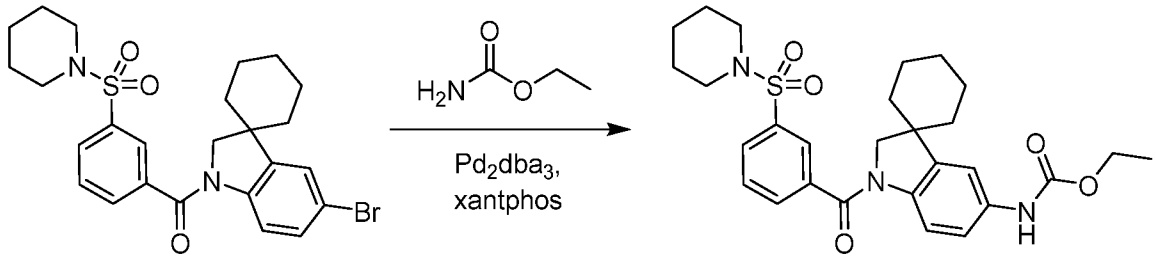
Code	Structure	Carboxylic Acid	Indoline
Compound 350		**A-93**	**B-14**
Compound 353		**A-94**	**B-14**
Compound 356		**A-95**	**B-14**
Compound 358		**A-96**	**B-14**
Compound 359		**A-49**	**B-23**

Code	Structure	Carboxylic Acid	Indoline
Compound 363		**A-98**	**B-14**
Compound 366		**A-99**	**B-07**
Compound 367		**A-99**	**B-23**
Compound 368		**A-100**	**B-14**
Compound 370		**A-101**	**B-07**
Compound 372		**A-101**	**B-23**

Code	Structure	Carboxylic Acid	Indoline
Compound 373		**A-101**	**B-14**

Synthetic Example S-009

Preparation of ethyl (1'-(3-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)carbamate (Compound 141)

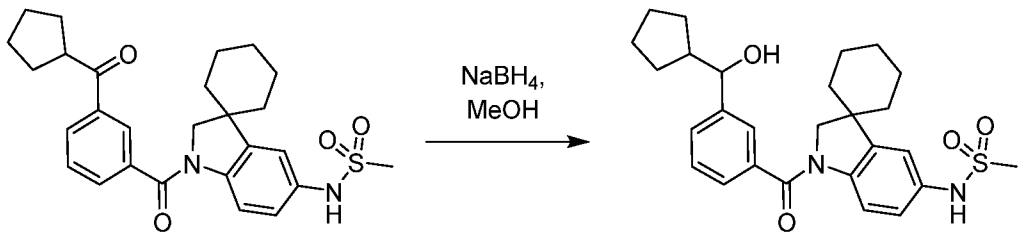


Compound 142 Compound 141

[0256] A mixture of **Compound 142** (0.20 g, 0.39 mmol), dioxane (10 mL), Cs_2CO_3 (0.38 g, 1.2 mmol), $Pd_2(dba)_3$ (35 mg, 39 µmol), Xantphos (22 mg, 39 µmol) and ethyl carbamate (52 mg, 0.58 mmol) was stirred at 110 °C for 12 h. The mixture was concentrated and purified by preparative HPLC (70-90% MeCN in H_2O [0.1 M HCl]) to provide ethyl (1'-(3-(piperidin-1-ylsulfonyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)carbamate (**Compound 141**, 21 mg).

Synthetic Example S-010

Preparation of N-(1'-(3-(cyclopentyl(hydroxy)methyl)benzoyl)spiro[cyclohexane-1,3'-indolin]-5'-yl)methanesulfonamide (Compound 157)

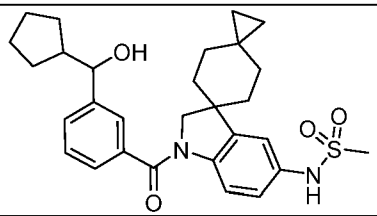
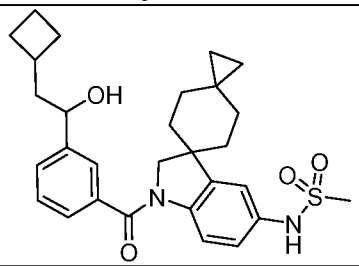
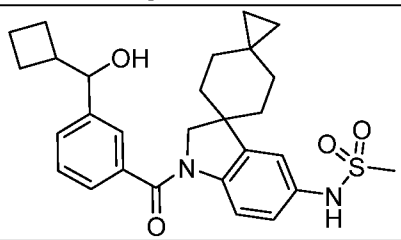
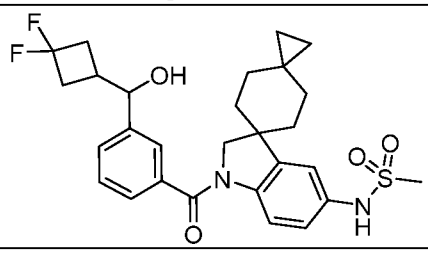


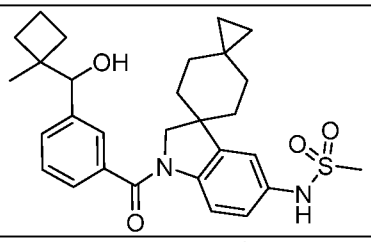
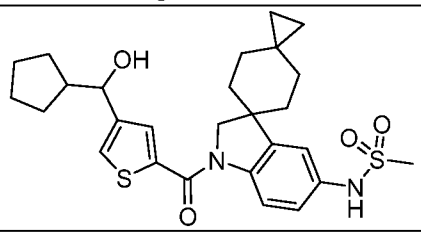
Compound 156 Compound 157

[0257] A degassed mixture of **Compound 156** (0.10 g, 0.21 mmol), NaBH4 (16 mg, 0.42 mmol), and MeOH (2 mL) was stirred under an N_2 atmosphere at 0 °C for 3 h. The mixture was concentrated and extracted with EtOAc (10 mL). The extract was washed with water (5 mL x 2) and brine (3 mL), dried over Na_2SO_4, filtered, concentrated, and purified by preparative HPLC (42-72 % MeCN in H_2O [0.1% formic acid]) to provide N-(1'-(3-(cyclopentyl (hydroxy) methyl) benzoyl) spiro [cyclohexane-1, 3'-indolin] -5'-yl) methanesulfonamide (**Compound 157**, 20 mg).

[0258] Compounds in **Table 7.4** were prepared from the indicated ketone in the manner described for the synthesis of **Compound 157**.

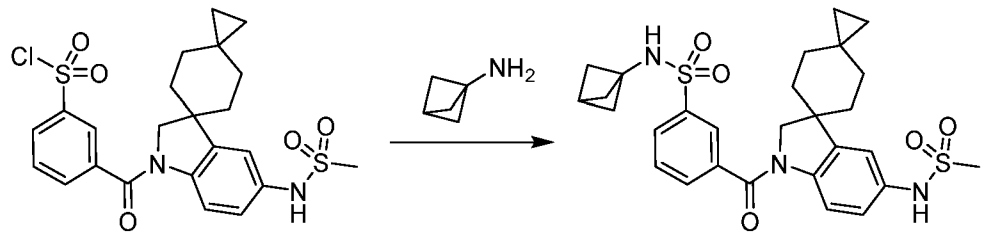
Table 7.4

Compound	Structure	Ketone
Compound 165		**Compound 164**
Compound 305		**Compound 304**
Compound 313		**Compound 312**
Compound 351		**Compound 350**

Compound 354		**Compound 353**
Compound 364		**Compound 363**

Synthetic Example S-011

Preparation of N-(bicyclo[1.1.1]pentan-1-yl)-3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide

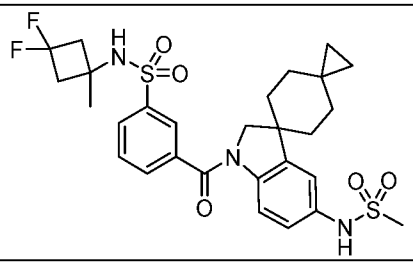
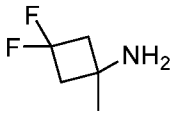
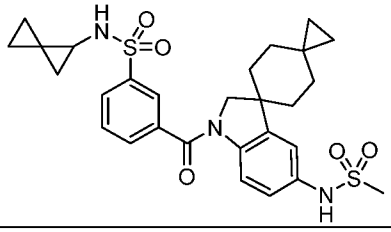
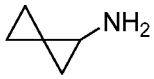
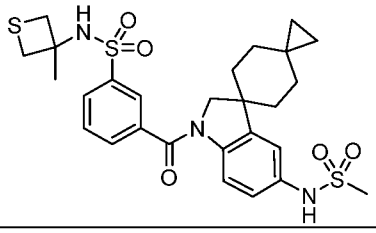
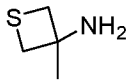
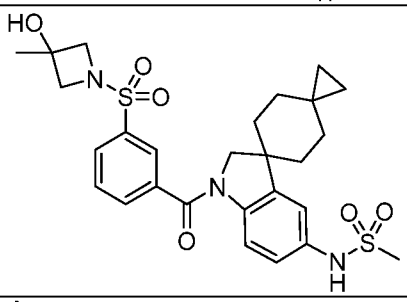
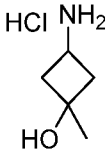
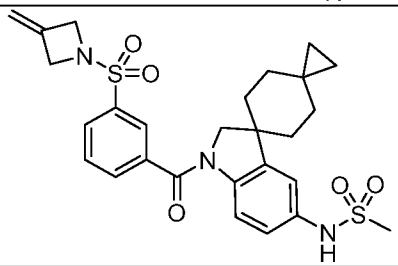
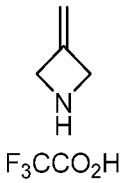
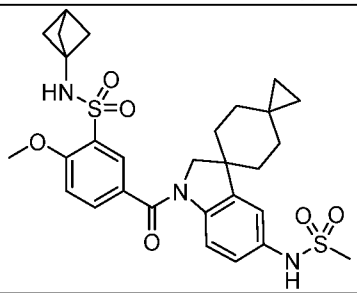
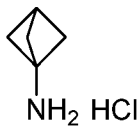


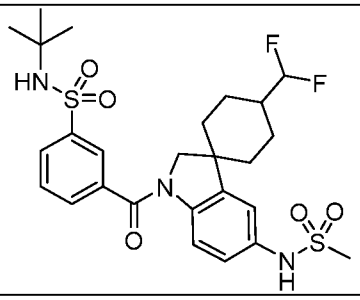
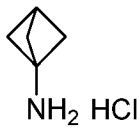
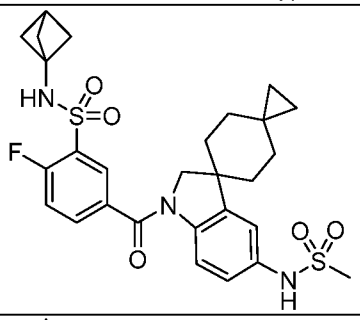
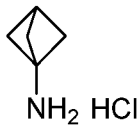
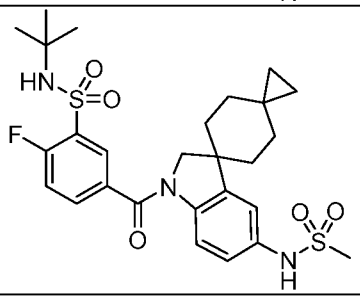
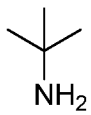
C-01 Compound 223

[0259] To a mixture of bicyclo[1.1.1]pentan-1-amine (16 mg, 196 μmol), CH_2Cl_2 (1.0 mL) was added Et_3N (82 μg, 0.59 mmol) and **C-01** (100 mg, 0.20 mmol). The resulting mixture was stirred at 25 °C for 1 h, then was concentrated and partitioned between H_2O (30 mL) and EtOAc (2 x 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (35-65% MeCN in H_2O [0.1% formic acid]) to provide N-(bicyclo[1.1.1]pentan-1-yl)-3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (**Compound 223**, 15 mg).

[0260] Compounds in **Table 7.5** were prepared from the indicated sulfonyl chloride and amine in the same manner as **Compound 223**.

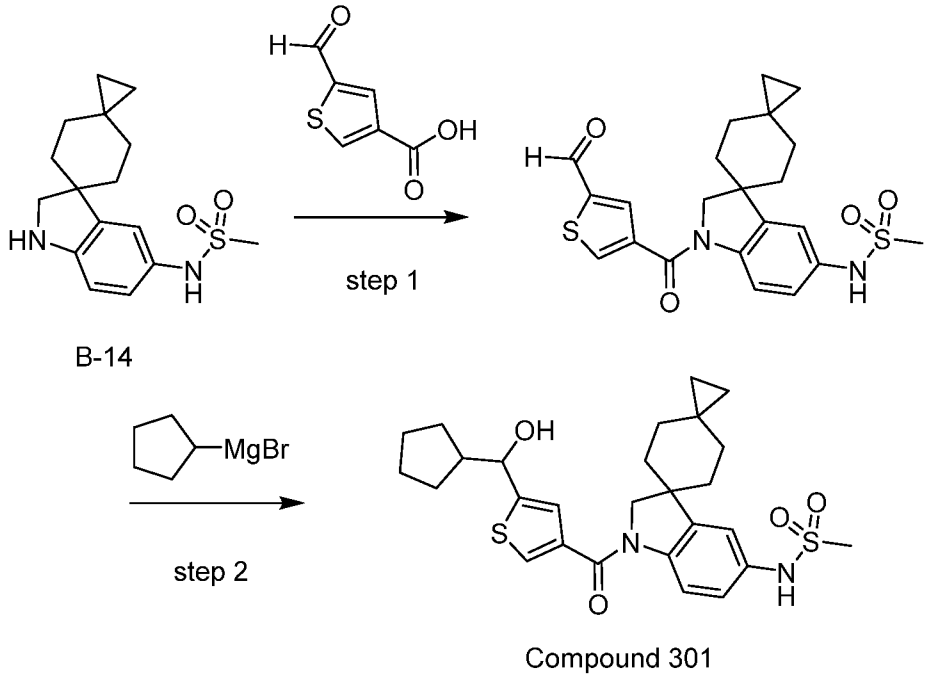
Table 7.5

Compound	Structure	Sulfonyl chloride	amine
Compound 224		**C-01**	
Compound 225		**C-01**	
Compound 226		**C-01**	
Compound 255		**C-01**	
Compound 258		**C-01**	
Compound 311		**C-02**	

Compound	Structure	Sulfonyl chloride	amine
Compound 336		**C-03**	
Compound 337		**C-04**	
Compound 340		**C-05**	

Synthetic Example S-012

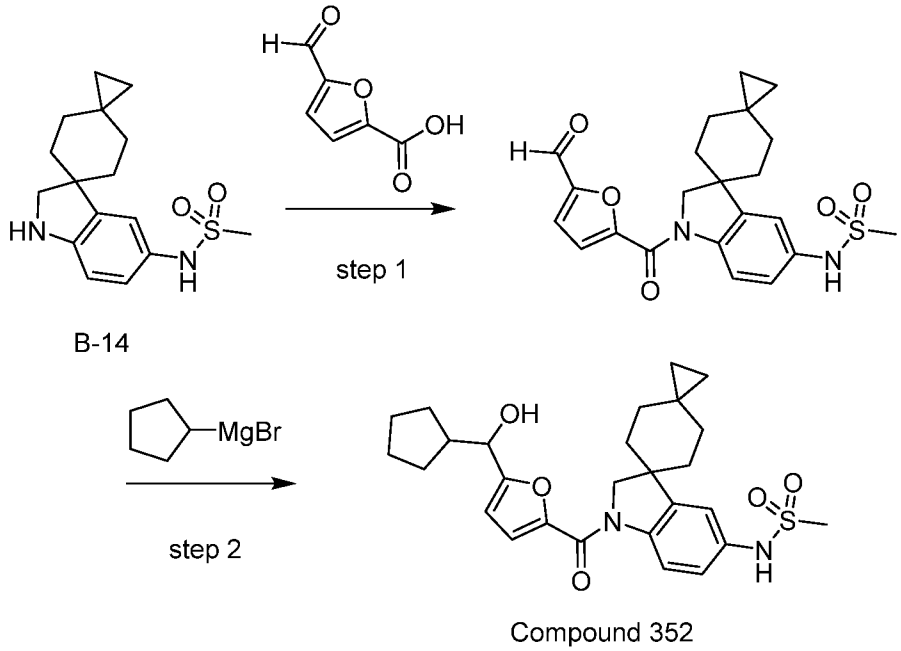
Preparation of *N*-(1''-(5-(cyclopentyl(hydroxy)methyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 301)



[0261] **Step 1**. To a mixture of 5-formylthiophene-3-carboxylic acid (0.12 mg, 0.74 mmol) and DMF (1.5 mL) was added HATU (0.42 g, 1.1 mmol), and iPr_2NEt (0.39 mL, 2.2 mmol). After stirring for 30 min, **B-14** (0.27 mg, 0.88 mmol) was added and the mixture was stirred at 80 °C for 1.5 h, diluted with H_2O (4 mL), and extracted with EtOAc (10 mL x 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (0-100% EtOAc/PE) to provide *N*-(1"-(5-formylthiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (0.31 g). ^1H NMR (400 MHz, DMSO-d^6) δ ppm 10.00 – 9.91 (m, 1 H) 8.14 (s, 1 H) 8.08 – 7.96 (m, 1 H) 7.26 - 7.19 (m, 2 H) 7.15 - 7.00 (m, 1 H) 4.08 (d, J=6.58 Hz, 2 H) 2.98 (s, 3 H) 1.27 - 1.24 (m, 8 H) 0.36 - 0.28 (m, 4 H).

[0262] **Step 2**. To a mixture of *N*-(1"-(5-formylthiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (0.25 g, 0.56 mmol) and THF (3 mL) was added bromo(cyclopentyl)magnesium (1 M, 2.8 mL). The mixture was stirred at -70 °C for 2, slowly poured into ice (5 mL), and extracted with EtOAc (10 ml x 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 45%-75% MeCN in H_2O [NH_4HCO_3]) to provide N-(1"-(5-(cyclopentyl(hydroxy)methyl)thiophene-3-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (**Compound 301**, 3.5 mg).

Preparation of N-(1''-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 352)

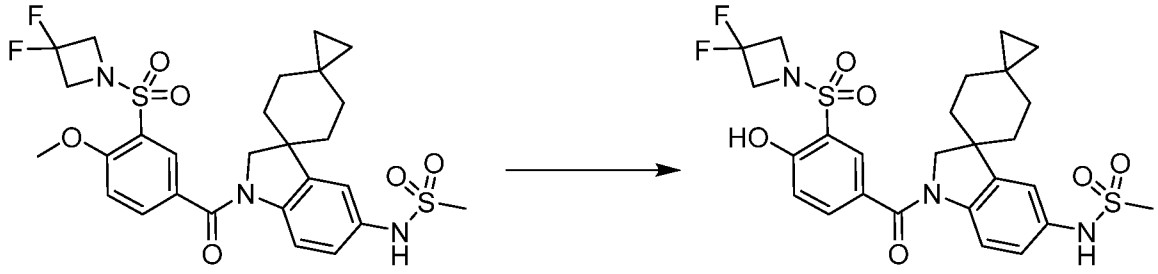


[0263] **Step 1**. A mixture of 5-formylfuran-2-carboxylic acid (0.20 g, 1.4 mmol), DMF (3 mL), EDCI (0.55 g, 2.9 mmol), HOBt (0.39 g, 2.9 mmol), and iPr_2Net (0.75 mL, 4.3 mmol) was stirred at 20 °C for 30 min., and **B-14** (0.44 g, 1.4 mmol) in DMF (0.5 mL) was added dropwise at 20 °C. The mixture was stirred at 20 °C for 12 h, poured into water (20 mL), and extracted with EtOAc (2 x20 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, concentrated, purified by silica chromatography (10-50% EtOAc in PE) to provide N-(1''-(3-formylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.23 g).

[0264] **Step 2**. To a mixture of N-(1''-(3-formylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.20 g, 0.37 mmol) and THF (3 mL) was added bromo(cyclopentyl)magnesium (1 M, 0.47 mL). The mixture was stirred at -60 °C for 0.5 h, poured into saturated NH_4Cl (5 mL), and extracted with EtOAc (2 x10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, purified by preparative HPLC (C18, 30-70% MeCN in H_2O [formic acid]) to provide N-(1''-(5-(cyclopentyl(hydroxy)methyl)furan-2-carbonyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 352**, 7.0 mg).

Synthetic Example S-013

Preparation of *N*-(1''-(3-((3,3-difluoroazetidin-1-yl)sulfonyl)-4-hydroxybenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 303)

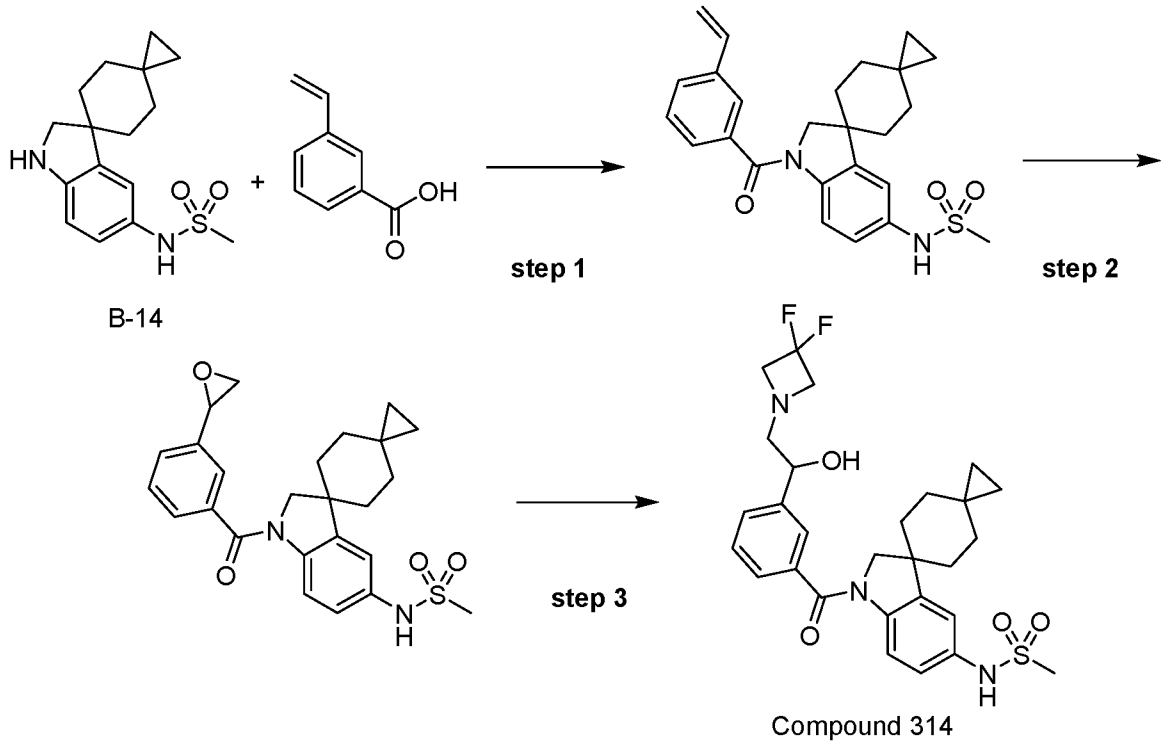


Compound 302 Compound 303

[0265] Two mixtures of **Compound 302** (90 & 40 mg, 0.15 & 0.067 mmol), DMF (3 & 1.3 mL), LiCl (19 & 8.5 mg, 0.45 & 0.20 mmol) were stirred at 160 °C for 4 h. The mixtures were combined and poured into H_2O (10 mL) and extracted with EtOAc (2 x10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 15-55% MeCN in H_2O [NH_4HCO_3]) to provide *N*-(1''-(3-((3,3-difluoroazetidin-1-yl)sulfonyl)-4-hydroxybenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 303**, 10 mg).

Synthetic Example S-014

Preparation of *N*-(1''-(3-(2-(3,3-difluoroazetidin-1-yl)-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 314)



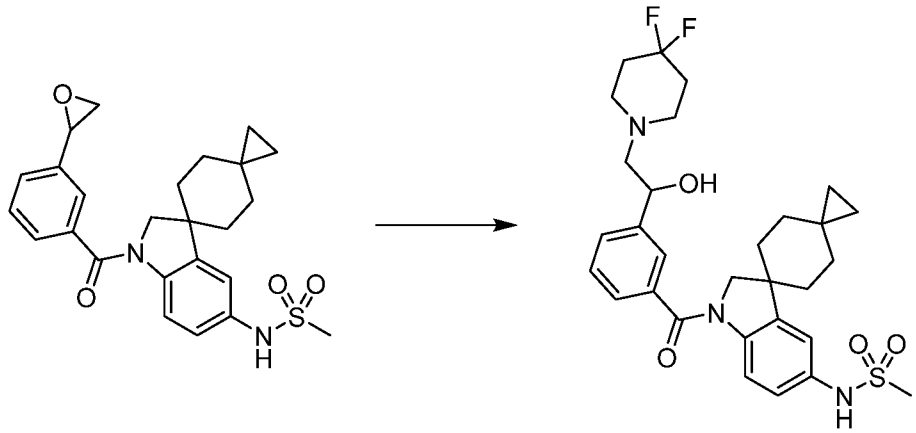
[0266] **Step 1**. A mixture of 3-vinylbenzoic acid (0.13 g, 0.89 mmol), DMF (3 mL), **B-14** (0.30 mg, 0.98 mmol), HOBt (0.24 mg, 1.8 mmol), EDCI (0.34 g, 1.8 mmol), Et_3N (0.37 mL, 2.7 mmol) was stirred at 20 °C for 2 h then poured into water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-40% EtOAc in PE) to provide *N*-(1''-(3-vinylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.30 g).

[0267] **Step 2**. To a mixture of *N*-(1''-(3-vinylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.15 g, 0.34 mmol) and CH_2Cl_2 (1 mL) was added m-CPBA (0.14 g, 0.60 mmol, 85% purity) at 0 °C. The mixture was stirred at 20 °C for 12 h, poured into Na_2SO_3 (1M, 30 mL), and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (0-30% EtOAc in PE) to provide *N*-(1''-(3-(oxiran-2-yl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.10 g).

[0268] **Step 3**. A mixture of 3,3-difluoroazetidine hydrochloride (39 mg, 0.30 mmol), iPr_2NEt (0.10 mL, 0.60 mmol), EtOH (1 mL), and *N*-(1''-(3-(oxiran-2-yl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide

(90 mg, 0.20 mmol) was stirred at 80 °C for 12 h. The mixture was concentrated and purified by preparative HPLC (35-65% MeCN in H_2O [formic acid]) to provide N-(1''-(3-(2-(3,3-difluoroazetidin-1-yl)-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 314**, 22 mg).

Preparation of *N*-(1''-(3-(2-(4,4-difluoropiperidin-1-yl)-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 315)

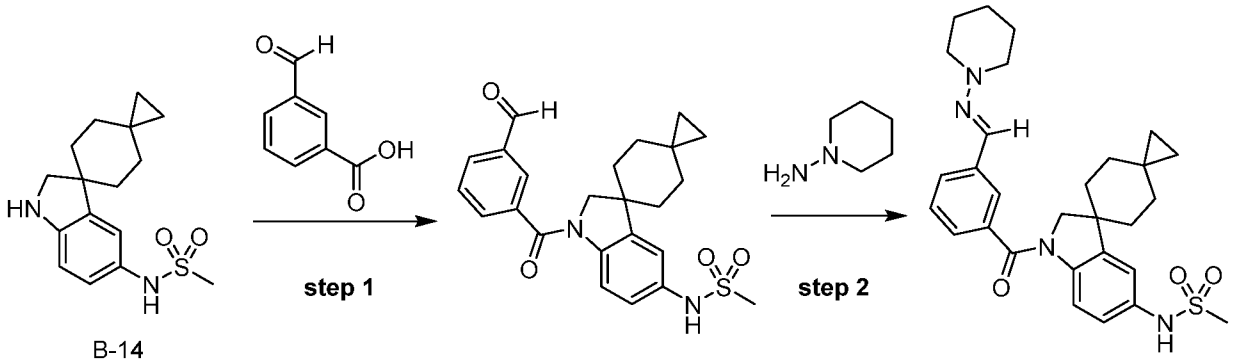


Compound 315

[0269] (**Compound 315**) was prepared from *N*-(1''-(3-vinylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide and 3,3-difluoropiperidine hydrochloride by the method described for **Compound 314**.

Synthetic Example S-015

Preparation of *N*-(1''-(3-((piperidin-1-ylimino)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 318)



B-14

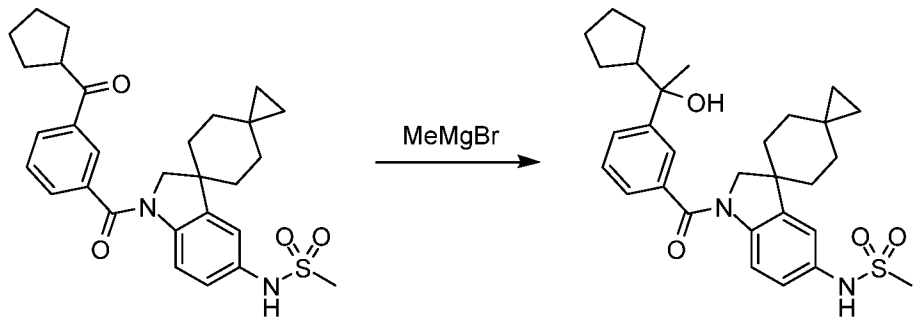
Compound 318

[0270] **Step 1**. Three mixtures of 3-formylbenzoic acid (0.20, 0.10, and 0.10 g, 1.3, 0.65, and 0.65 mmol), THF (10, 5, and 5 mL), EDCI (0.51, 0.25, and 0.25 g, 2.7, 1.4, and 1.4 mmol), HOBt (0.36, 0.18, and 0.18 g, 2.7. 1.4, and 1.4 mmol), Et_3N (0.56, 0.28, and 0.28 mL, 4.0, 2.0, and 2.0 mmol) were stirred at this 20 °C for 0.5 h, and then **B-14** (0.41, 0.21, 0.21 g, 1.3, 0.65, and 0.65 mmol) was added to the mixtures and they were stirred at 20 °C for 12 h. The mixtures were combined, poured into water (20 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were washed with brine (10 mL), dried over Na2SO4, concentrated, and purified by silica chromatography (20-100% EtOAc in PE) to provide *N*-(1''-(3-formylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.36 g).

[0271] **Step 2**. A mixture of *N*-(1''-(3-formylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.31 g, 0.73 mmol), EtOAc (3 mL), TFA (81 µg, 1.1 mmol), and piperidin-1-amine (0.47 g, 4.4 mmol) was stirred at 80 °C for 12 h. The mixture was concentrated, added to water (30 mL), and extracted with EtOAc (2 x 30 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 40-80% MeCN in H_2O [formic acid]) to provide *N*-(1''-(3-((piperidin-1-ylimino)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.17 g).

Synthetic Example S-016

Preparation of *N*-(1''-(3-(1-cyclopentyl-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 331)



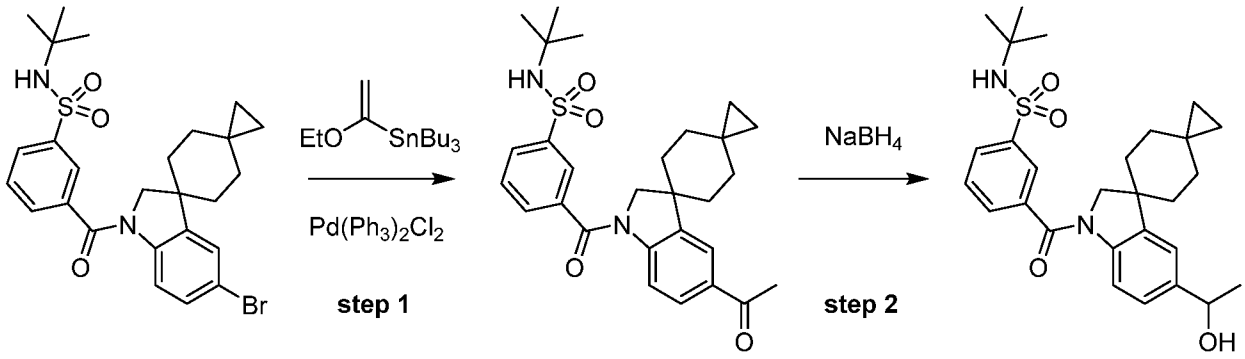
Compound 164 Compound 331

[0272] To **Compound 164** (50 mg, 99 µmol) in THF (1 mL) was added MeMgBr (3 M, 99 uL, 0.30 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 h, poured into H_2O (3 mL), concentrated, and purified by preparative HPLC (40-80% MeCN in H_2O [formic acid]) to

provide N-(1''-(3-(1-cyclopentyl-1-hydroxyethyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 331**, 6 mg).

Synthetic Example S-017

Preparation of N-(tert-butyl)-3-(5''-(1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (Compound 332)



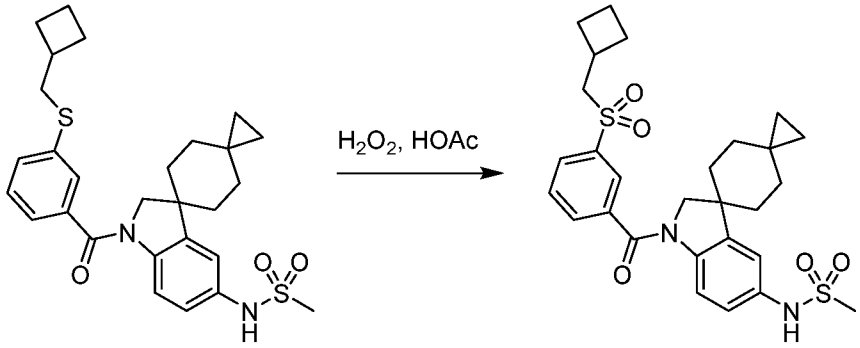
Compound 9 Compound 332

[0273] **Step 1**. A degassed mixture of **Compound 9** (0.20 g, 0.38 mmol), tributyl(1-ethoxyvinyl)stannane (0.19 mL, 0.56 mmol), $Pd(PPh_3)_2Cl_2$ (53 mg, 75 μmol), CsF (0.11 g, 0.75 mmol), and dioxane (4 mL) was stirred at 130 °C for 2 h under an N_2 atmosphere. A solution of KF (0.10 g) in H_2O (20 mL) and the mixture was stirred at 20 °C for 0.5 h. The mixture was extracted with EtOAc (20 x 2 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and purified by silica chromatography (0-50% EtOAc in PE) to provide 3-(5''-acetyldispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)-N-(tert-butyl)benzenesulfonamide (0.11 g).

[0274] **Step 1**. To a mixture of 3-(5''-acetyldispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)-N-(tert-butyl)benzenesulfonamide (0.11 g, 0.22 mmol) and MeOH (10 mL) was added $NaBH_4$ (25 mg, 0.67 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for 3 h, poured into saturated NH_4Cl (20 mL), and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 45-75% MeCN in H_2O [formic acid]) to provide *N*-(tert-butyl)-3-(5''-(1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (**Compound 332**, 25 mg).

Synthetic Example S-018

Preparation of *N*-(1''-(3-((cyclobutylmethyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 335)

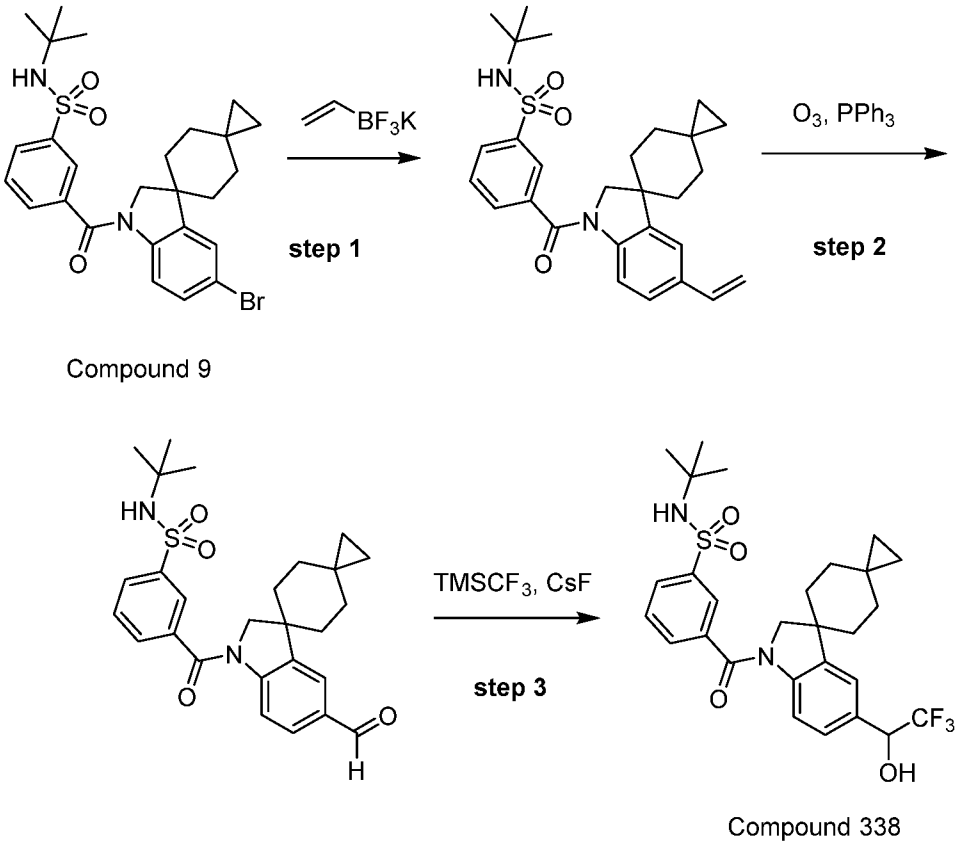


Compound 334 Compound 335

[0275] A mixture of **Compound 334** (0.20 g, 0.39 mmol), HOAc (2 mL), and 30% H_2O_2 (0.11 mL, 1.2 mmol) was stirred at 20 °C for 2 h. The mixture was combined with saturated Na_2SO_3 (20 mL) and H_2O (30 mL) and extracted with EtOAc (2×30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 35-65% MeCN in H_2O [formic acid]) to provide N-(1''-(3-((cyclobutylmethyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 335**, 76 mg, 35.40% yield, 99.00% purity) as a white solid.

Synthetic Example S-019

Preparation of *N*-(tert-butyl)-3-(5''-(2,2,2-trifluoro-1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (Compound 338)



Compound 9

Compound 338

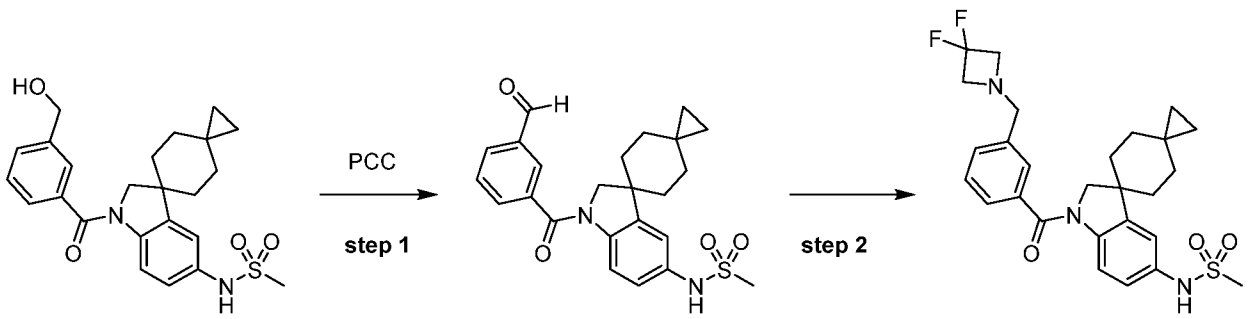
[0276] **Step 1**. A degassed mixture of **Compound 9** (0.50 g, 0.94 mmol) and KBF_3(vinyl) (0.63 g, 4.7 mmol), K_2CO_3 (0.65 g, 4.7 mmol), $PdCl_2$ (0.12 g, 0.66 mmol), and DMSO (5 mL) was was stirred at 100 °C for 3 h under an N_2 atmosphere. The mixture was poured into H_2O (20 mL, extracted with CH_2Cl_2 (2 x 20 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, purified by silica chromatography (30-50% EtOAc in PE) to provide *N*-(tert-butyl)-3-(5"-vinyldispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (0.32 mg).

[0277] **Step 2**. A mixture of *N*-(tert-butyl)-3-(5"-vinyldispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (0.32 g, 0.67 mmol), CH_2Cl_2 (10 mL), and MeOH (10 mL) was treated with O_3 (32 mg, 669 umol, 1.0 eq) for 0.5 hour at 0 °C. The solution was purged with O_2 (21mg, 669 umol, 1.0 eq) for 0.5 hour at 0 °C, then stirred with PPh_3 (0.35 g, 1.3 mmol) for 1 h at 20 °C, poured into H_2O (20 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (30-50% EtOAc in PE) to provide *N*-(tert-butyl)-3-(5"-formyldispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (0.25 g).

[0278] **Step 3**. To a mixture of *N*-(tert-butyl)-3-(5''-formyldispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (0.15 g, 0.31 mmol) and DMF (2 mL) were added $TMSCF_3$ (89 mg, 0.62 mmol) and CsF (95 mg, 0.62 mmol) at 50 °C. The mixture was stirred at 50 °C for 12 h, concentrated, added to H_2O (30 mL), and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC(C18, 35-75% MeCN in H_2O [formic acid]) to provide *N*-(tert-butyl)-3-(5''-(2,2,2-trifluoro-1-hydroxyethyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (**Compound 338**, 11 mg).

Synthetic Example S-20

Preparation of *N*-(1''-(3-((3,3-difluoroazetidin-1-yl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (Compound 345)



Compound 344 Compound 345

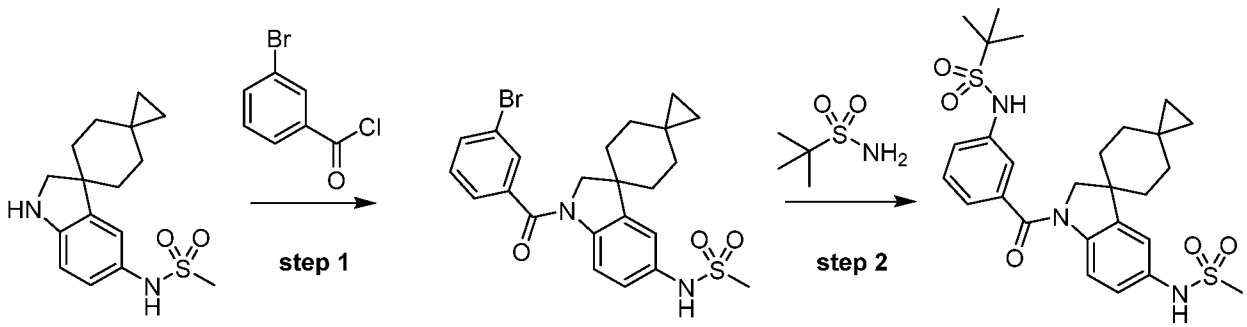
[0279] **Step 1**. A mixture of Compound **344** (0.28 g, 0.64 mmol), CH_2Cl_2 (5 mL), and PCC (0.27 g, 1.3 mmol) was stirred at 20 °C for 2 h, diluted with CH_2Cl_2 (10 mL), washed with H_2O (5 mL),saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), then dried over Na_2SO_4, concentrated, and purified by flash silica chromatography (0-50% EtOAc in PE) to provide N-(1''-(3-formylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.18 g).

[0280] **Step 2**. A mixture of N-(1''-(3-formylbenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.10 g, 0.23 mmol), MeOH (1 mL), THF (1 mL), 3,3-difluoroazetidine hydrochloride (44 mg, 0.34 mmol), and HOAc (26 µL, 0.46 mmol) was stirred at 20 °C for 2 h and $NaBH_3CN$ (43 mg, 0.68 mmol) was added and the miixture was stirred at 20 °C for 10 h. The mixture was treated with H_2O (5 mL) at 0 °C

and extracted with CH_2Cl_2 (10 mL). The combined extracts were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 25-65% MeCN in H_2O [formic acid]) to provide N-(1''-(3-((3,3-difluoroazetidin-1-yl)methyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (**Compound 345**, 6 mg).

Synthetic Example S-21

[0281] Preparation of 2-methyl-N-(3-(5''-(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)phenyl)propane-2-sulfonamide (Compound 355)



B-14 Compound 355

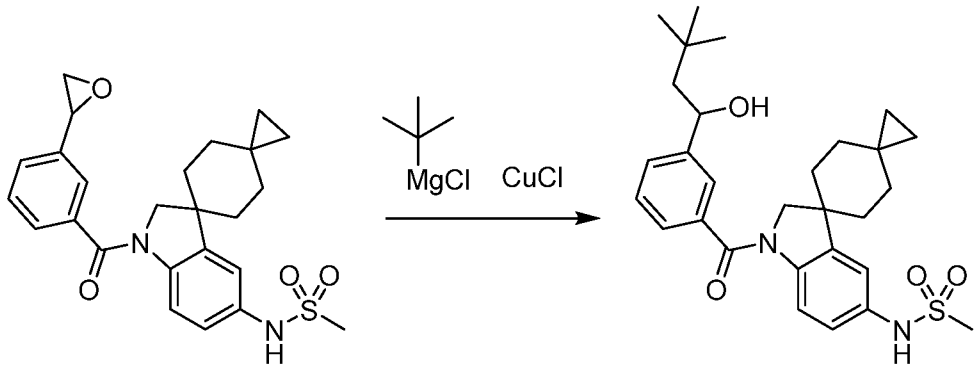
[0282] Step 1. A mixture of **B-14** (0.20 g, 0.65 mmol), CH_2Cl_2 (4 mL), iPr_2NEt (0.34 mL, 2.0 mmol) and 3-bromobenzoyl chloride (0.10 mL, 0.78 mmol) was stirred at 20 °C for 1 h and then concentration and poured into water (5 mL). The resulting mixture was extracted with EtOAc (10 mL x 2) and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica chromatography (10-100% EtOAc in PE) to provide N-(1''-(3-bromobenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.21 g).

[0283] Step 2. A degassed mixture of N-(1''-(3-bromobenzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)methanesulfonamide (0.10 g, 0.20 mmol), 2-methylpropane-2- sulfonamide (0.11 g, 0.82 mmol), CuI (78 mg, 0.41 mmol), N1,N2-dimethylcyclohexane-1,2-diamine dihydrochloride (88 mg, 0.41 mmol), K_3PO_4 (0.13 g, 0.61 mmol), and DMF (2 mL) was stirred at 160 °C for 2 h under an N_2 atmosphere. The mixture was poured into water (10 mL), extracted with EtOAc (10 mLx2), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 35-65% MeCN in H_2O [NH_4CO_3]) to provide 2-methyl-N-(3-(5''-

(methylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)phenyl)propane-2-sulfonamide (**Compound 355**, 16 mg).

Synthetic Example S-22

[0284] Preparation of N-(1"-(3-(1-hydroxy-3,3-dimethylbutyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (Compound 357)

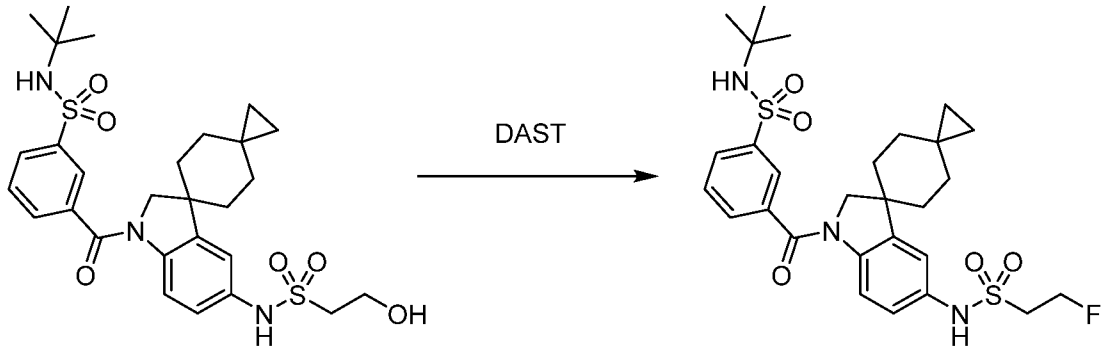


Compound 357

[0285] To mixture of N-(1"-(3-(oxiran-2-yl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (50 mg, 0.11 mmol), $CuCl_2$ (15 mg, 0.11 mmol), LiCl (5 mg, 0.11 mmol), and THF (1 mL) was added dropwise t-BuMgCl (1 M, 0.44 mL). The mixture was stirred at 20 °C for 2 h, poured into saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by preparative HPLC (C18, 45- 85% MeCN in H_2O [formic acid]) to provide N-(1"-(3-(1-hydroxy-3,3-dimethylbutyl)benzoyl)dispiro [cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)methanesulfonamide (8.0 mg).

Synthetic Example S-23

Preparation of N-(tert-butyl)-3-(5"-((2-fluoroethyl)sulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (Compound 365)



Compound 148 Compound 365

[0286] To a mixture of **Compound 148** (50 mg, 87 µmol) in CH_2Cl_2 (1.5 mL) was added DAST (23 µL, 0.18 mmol) at 0 °C. The mixture was stirred at 20 °C for 1 h under N_2, poured into H_2O (30 mL), and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated, purified by preparative HPLC (C18, 45-75% MeCN in H_2O [formic acid]) to provide N-(tert-butyl)-3-(5"-((2-fluoroethyl)sulfonamido) dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline]-1"-carbonyl)benzenesulfonamide (**Compound 365**, 13 mg).

[0287] **Table 7c** describes the chromatography separation of isomers for specific examples.

Table 7c.

Compound	Conditions	First	Purity %	Second	Purity %
24	Chiralpak AD (250mm x 30mm, 10µm) 15-40% [0.1% NH_3/H_2O in iPrOH] in supercritical CO_2	**24a**	100% (er)	**24b**	99.5% (er)
140	Chiralpak AD (250mm x 30mm, 10µm) 45-75% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**140a**	100%	**140b**	99.5%
162	Phenomenex Luna C18 (200 x 40 mm, 10 µm) 30-60% MeCN in H_2O [0.1 M formic acid]	**162a**	100%	**162b**	100%
165	Chiralpak AD (250mm x 30mm, 10µm) 35% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**165a**	>99.5% (er)	**165b**	98.9% (er)

Compound	Conditions	First	Purity %	Second	Purity %
249	Chiralpak OD (250mm x 30mm, 10µm) 45% [0.1% NH_3/H_2O in iPrOH] in supercritical CO_2	**(R)-249**	100% (er)	**(S)-249**	98.9% (er)
287	Regis (S,S)-Whelk-O®1 (250mm x 25mm, 10µm) 60% EtOH in supercritical CO_2	**287a**	99.7% (er)	**287b**	97.8% (er)
305	Chiralcel OD (250mm x 30mm, 10µm) 44% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**305a**	99.7% (er)	**205b**	99.0% (er)
313	Chiralpak AD (250mm x 30mm, 10µm) 35% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**313a**	>99.5% (er)	**313b**	99.2% (er)
316	Chiralcel OD (250mm x 30mm, 10µm) 45% [0.1% NH_3/H_2O in iPrOH] in supercritical CO_2	**316a**	>99.5% (er)	**316b**	99.7% (er)
317	Chiralcel OD (250mm x 30mm, 10µm) 40% [0.1% NH_3/H_2O in iPrOH] in supercritical CO_2	**317a**	>99.5% (er)	**317b**	98.7 (er)
333	Phenomenex Luna C18 (100 x 40 mm, 3 µm) 20-60% MeCN in H_2O [0.1 M formic acid]	**333a**	100%	**333b**	100%
336	Phenomenex Luna C18 (200 x 40 mm, 10 µm) 45-80% MeCN in H_2O [0.1 M formic acid]	**336a**	100%	**336b**	100%
338	Chiralpak AD (250mm x 30mm, 10µm) 27-75% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**338a**	>99.9% (er)	**338b**	99.2% (er)
341	Chiralpak AD (250mm x 30mm, 10µm) 25% [0.1% NH_3/H_2O in iPrOH] in supercritical CO_2	**341a**	>99.9% (er)	**341b**	99.8% (er)
351	Chiralpak IC (250mm x 30mm, 10µm) 50% [0.1% NH_3/H_2O in iPrOH] in supercritical CO_2	**351a**	99.9% (er)	**351a**	99.2% (er)
352	Chiralpak AD (250mm x 30mm, 10µm) 40% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**352a**	>99.9% (er)	**352b**	>99.95% (er)
367	Chiralpak AD (250mm x 30mm, 10µm) 40% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**367a**	>99.9% (er)	**367b**	>99.9% (er)

Compound	Conditions	First	Purity %	Second	Purity %
368	Chiralpak AD (250mm x 30mm, 10µm) 40% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**368a**	>99.9% (er)	**368b**	>99.9% (er)
371	Chiralpak AD (250mm x 30mm, 10µm) 22% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**371a**	>99.9% (er)	**371b**	98.6% (er)
372	Chiralcel OJ (250mm x 30mm, 10µm) 30% [0.1% NH_3/H_2O in MeOH] in supercritical CO_2	**372a**	>99.9% (er)	**372b**	99.9% (er)
373	Chiralpak AD (250mm x 30mm, 10µm) 30% [0.1% NH_3/H_2O in EtOH] in supercritical CO_2	**373a**	>99.9% (er)	**373b**	99.3% (er)

Table 8.

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 1	479.2 (M+H)	(DMSO-d^6) δ 7.98 (dt, J = 15.13, 7.44 Hz, 4H), 7.86-7.77 (m, 1H), 7.29 (br s, 1H), 6.94 (br t, J = 8.94 Hz, 1H), 3.85 (br s, 2H), 3.33 (s, 1H), 3.15 (br d, J = 5.00 Hz, 4H), 2.14-1.96 (m, 6H), 1.86 (br s, 2H), 1.77 (br s, 2H), 1.56 (br s, 2H).
Compound 2		(DMSO-d^6) δ 8.11-7.89 (m, 3H), 7.85-7.77 (m, 1H), 7.51 (d, J = 2.00 Hz, 2H), 3.82 (br s, 2H), 3.21-3.09 (m, 4H), 2.16-1.98 (m, 4H), 1.91-1.70 (m, 6H), 1.66-1.43 (m, 2H)
Compound 3	461.1 $(M+H)^+$	(DMSO-d^6) δ 8.33-7.83 (m, 3H), 7.83-7.74 (m, 1H), 7.45-6.95 (m, 3H), 3.85-3.72 (m, 2H), 3.12 (br d, J = 4.88 Hz, 4H), 2.13-1.98 (m, 4H), 1.87-1.69 (m, 6H), 1.65-1.48 (m, 2H).
Compound 4	501.1 $(M+H)^+$	(DMSO-d^6) δ 7.88 - 8.27 (m, 4 H) 7.77 - 7.85 (m, 1 H) 7.31 (br d, J=7.82 Hz, 1 H) 6.98 - 7.30 (m, 1 H) 6.98 - 7.30 (m, 1 H) 3.89 (br s, 2 H) 3.13 (br s, 4 H) 2.01 - 2.12 (m, 4 H) 1.36 - 1.90 (m, 6 H) 0.85 (br d, J=10.64 Hz, 2 H) 0.26 (br s, 4 H)
Compound 6	465.1 $(M+H)^+$	(DMSO-d^6) δ 8.21-7.86 (m, 4H) 7.83-7.73 (m, 1H), 7.31 (d, J = 7.88 Hz, 2H) 7.11 (br d, J = 2.25 Hz, 1H), 3.92 (br s, 2 H) 2.98-2.88 (m, 4H), 1.77-1.62 (m, 5 H), 1.55 (br s, 5H), 1.41-1.32 (m, 2H), 0.93-0.79 (m, 2H), 0.33-0.20 (m, 4H).
Compound 8	451.1 $(M+H)^+$	(DMSO-d^6) δ 8.22-7.85 (m, 4H), 7.80-7.73 (m, 1H), 7.30 (d, J = 8.38 Hz, 2H), 7.10 (m, 1H), 3.95-3.82 (m, 2H), 3.18 (br s, 4H), 1.79-1.50 (m, 10H), 0.93-0.78 (m, 2H), 0.34-0.17 (m, 4H).
Compound 9		(DMSO-d^6) δ 8.04 (s, 1H), 7.99 (d, J = 7.2 Hz 2H), 7.85 (d, J = 7.2 Hz, 1H), 7.73- 7.69 (t, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.51 (s, 1H), 7.41 (br s, 1H), 3.90 (s, 2H), 1.77-1.74 (m, 2H), 1.65-1.62 (m, 4H), 1.11 (s, 9H), 0.84-0.81 (br d, J = 12.8 Hz, 2H), 0.26 (m, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 10	453.1 $(M+H)^+$	(DMSO-d^6) δ 8.19-7.92 (m, 3H) 7.83 (br d, J = 5.63 Hz, 1H) 7.75-7.60 (m, 2H), 7.31 (d, J = 8.25 Hz, 2H), 7.10 (br s, 1H), 3.92-3.83 (m, 2H),1.81-1.55 (m, 6H), 1.10 (s, 9H) 0.88-0.81 (m, 2H), 0.26 (br s, 4H)
Compound 15	567.0 $(M+H)^+$	(DMSO-d^6) δ 8.12-7.91 (m, 4H), 7.87-7.76 (m, 1H), 7.66 (s, 1H), 7.53-7.35 (m, 1H), 3.92-3.75 (m, 2H), 3.19-3.06 (m, 4H), 2.15-1.99 (m, 4H), 1.85-1.77 (m, 1H), 1.71-1.31 (m, 8H), 1.04 (br d, J = 6.8 Hz, 1H), 0.90-0.73 (m, 3H)
Compound 18	554.0 $(M+H)^+$	(CD_3OD) δ 8.23-7.96 (m, 3H), 7.93 (br d, J = 5.63 Hz, 1H), 7.85-7.77 (m, 1H), 7.32-6.96 (m, 2H), 4.09-3.83 (m, 2H), 3.26 (br s, 4H), 2.96 (br s, 3H), 2.18-2.04 (m, 4H), 1.89 (br s, 6H), 1.80-1.57 (m, 2H).
Compound 19	568.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (br s, 1H), 8.09-8.08 (m, 1H), 8.10-7.89 (m, 4H), 7.87-7.75 (m, 1H), 7.11 (s, 2H), 3.84 (br s, 2H), 3.13 (br s, 4H), 2.94 (s, 3H), 2.14-1.97 (m, 4H), 1.77-1.45 (m, 8H), 1.24 (br s, 1H), 1.13 (br d, J = 14.26 Hz, 1H)
Compound 20	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br d, J = 2.13 Hz, 1H), 8.12-7.84 (m, 4H), 7.82-7.75 (m, 1H), 7.13 (d, J = 1.75 Hz, 2H), 3.92 (br s, 2H), 2.94 (s, 7H), 1.72-1.49 (m, 10H), 1.37 (br d, J = 5.00 Hz, 2H), 0.96-0.79 (m, 2H), 0.35-0.19 (m, 4H).
Compound 21	544.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.11-7.89 (m, 4H), 7.82-7.73 (m, 1H), 7.18-7.03 (m, 2H), 3.90 (br d, J = 2.88 Hz, 2H), 3.22-3.16 (m, 4H), 2.94 (s, 3H), 1.74-1.49 (m, 10H), 0.94-0.80 (m, 2H), 0.28 (br s, 4H).
Compound 22	546.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.11-7.91 (m, 3H), 7.88-7.67 (m, 1H), 7.74-7.59 (m, 2H), 7.14 (d, J = 1.88 Hz, 2H) 3.88 (br d, J = 1.63 Hz, 2H), 2.94 (s, 3H), 1.74-1.49 (m, 6H), 1.11 (s, 9H), 0.94-0.80 (m, 2H), 0.34-0.18 (m, 4H).
Compound 23	568.1 $(M+H)^+$	(DMSO-d^6) δ 9.67-9.54 (m, 1H), 8.17-7.89 (m, 4H), 7.86-7.73 (m, 1H), 7.02 (br d, J = 3.5 Hz, 2H), 3.96-3.75 (m, 2H), 3.22-3.06 (m, 4H), 2.95 (s, 3H), 2.16-2.01 (m, 6H), 1.99-1.90 (m, 2H), 1.85-1.77 (m, 1H), 1.72-1.61 (m, 1H), 1.47-1.28 (m, 1H), 1.20-1.08 (m, 1H), 1.07-0.92 (m, 3H)
Compound 24	582.1 $(M+H)^+$	(DMSO-d^6) δ 9.24-9.51 (m, 1H), 7.72-8.05 (m, 4H), 7.35-7.42 (m, 1H), 7.19-6.99 (m, 2H), 3.95-3.70 (m, 2H), 3.28-3.18 (m, 3H), 2.99-2.91 (m, 4H), 2.17-1.98 (m, 4H), 1.77-1.57 (m, 6H), 1.52-1.35 (m, 2H), 1.04 (d, J = 6.7 Hz, 1H), 0.91-0.76 ppm (m, 3H)
Compound 24a	582.1 $(M+H)^+$	(DMSO-d^6) δ 9.52 (s, 1H), 8.15-7.89 (m, 4H), 7.86-7.73 (m, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.22-7.03 (m, 1H), 3.88-3.67 (m, 2H), 3.19-3.07 (m, 4H), 2.95 (s, 3H), 2.14-2.00 (m, 5H), 1.81-1.70 (m, 2H), 1.66-1.57 (m, 1H), 1.54-1.34 (m, 6H), 1.06-0.96 (m, 3H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 24b	582.1 $(M+H)^+$	(DMSO-d^6) δ 9.65-9.54 (m, 1H), 8.12-7.89 (m, 4H), 7.84-7.77 (m, 1H), 7.09 (d, J = 1.9 Hz, 2H), 3.95-3.75 (m, 2H), 3.19-3.09 (m, 4H), 2.94 (s, 3H), 2.13-1.96 (m, 5H), 1.74-1.52 (m, 7H), 1.47-1.37 (m, 2H), 0.87-0.75 (m, 3H)
Compound 25	530.1 $(M+H)^+$	(DMSO-d^6) δ 8.32-8.09 (m, 1H), 8.03-7.87 (m, 2H), 7.80 (br d, J = 7.25 Hz, 1H), 7.74-7.63 (m, 1H), 7.19-7.12 (m, 1H), 7.10-6.93 (m, 1H), 6.49-6.37 (m, 1H), 3.99-3.70 (m, 2H), 3.63-3.49 (m, 2H), 3.22-3.08 (m, 2H), 3.04-2.93 (m, 3H), 1.80-1.62 (m, 8H), 1.50-1.44 (m, 2H), 1.38-1.23 (m, 2H), 0.66-0.56 (m, 1H), 0.39-0.31 (m, 1H)
Compound 26	520.1 $(M+H)^+$	(DMSO-d^6) δ 8.32-7.92 (m, 3H), 7.81-7.70 (m, 1H), 7.68-7.57 (m, 1H), 7.21-7.11 (m, 1H), 7.08-6.90 (m, 1H), 6.65-6.43 (m, 1H), 4.85-4.51 (m, 1H), 4.06-3.65 (m, 2H), 3.07-2.91 (m, 3H), 1.71 (br d, J = 11.88 Hz, 10H), 1.28-1.21 (m, 9H)
Compound 27	558.1 $(M+H)^+$	(DMSO-d^6) δ 8.10 (br d, J = 2.13 Hz, 4H), 7.84-7.69 (m, 1H), 7.21-6.94 (m, 2H), 3.91-3.76 (m, 2H), 3.73 (br t, J = 6.57 Hz, 2H), 3.19-3.05 (m, 6H), 2.14-1.99 (m, 4H), 1.92-1.69 (m, 6H), 1.63-1.44 (m, 2H).
Compound 28	594.1 $(M+H)^+$	(DMSO-d^6) δ 9.68-9.48 (m, 1H), 8.21-7.88 (m, 1H), 8.15-7.88 (m, 3H), 7.86-7.74 (m, 1H), 7.13 (br d, J = 1.75 Hz, 2H), 4.02-3.79 (m, 2H), 3.13 (br s, 4H), 3.02-2.84 (m, 3H), 2.17-1.97 (m, 3H), 2.15-1.96 (m, 1H), 1.76-1.62 (m, 1H), 1.74-1.48 (m, 1H), 1.67 (br s, 4H), 0.93-0.78 (m, 2H), 0.27 (br s, 3H), 0.37-0.12 (m, 1H)
Compound 29	624.0 $(M+H)^+$	(DMSO-d^6) δ 8.17 (br d, J = 7.25 Hz, 1H), 8.03-7.89 (m, 2H), 7.84 (br d, J = 7.50 Hz, 1H), 7.75-7.67 (m, 1H), 7.25 (d, J = 1.88 Hz, 1H), 7.20-6.99 (m, 1H), 6.67 (br s, 1H), 4.13 (br t, J = 4.88 Hz, 1H), 3.89 (br s, 2H), 3.25 (br s, 6H), 2.51 (br s, 1H), 2.18-2.03 (m, 4H), 1.90-1.80 (m, 2H), 1.69 (br d, J = 12.26 Hz, 4H), 0.94 (br d, J = 11.76 Hz, 2H), 0.32 (br s, 4H)
Compound 30	544.1 $(M+H)^+$	(DMSO-d^6) δ 8.39-8.30 (m, 1H), 8.01-7.83 (m, 3H), 7.82-7.75 (m, 1H), 8.02-7.73 (m, 1H), 6.49 (d, J = 2.13 Hz, 1H), 6.44 (br d, J = 8.00 Hz, 1H), 5.50-5.39 (m, 1H), 3.84-3.75 (m, 1H), 3.79 (s, 1H), 3.16-3.09 (m, 1H), 3.16-3.08 (m, 1H), 3.13 (br s, 2H), 3.07-2.98 (m, 2H), 2.14-1.98 (m, 4H), 1.75-1.47 (m, 6H), 1.16 (br t, J = 7.00 Hz, 2H), 1.22-1.03 (m, 1H), 0.83 (br d, J = 12.76 Hz, 2H), 0.41-0.16 (m, 1H), 0.23 (br d, J = 6.13 Hz, 3H)
Compound 31	546.1 $(M+H)^+$	(DMSO-d^6) δ 7.92-8.02 (m, 2H), 7.81-7.74 (m, 1H), 7.72-7.64 (m, 1H), 7.38 (br s, 1H), 7.12 (s, 1H), 7.05 (br s, 1H), 5.39 (br s, 1H), 3.84-3.67 (m, 2H), 2.92 (s, 3H), 2.29-2.10 (m, 2H), 1.90–2.08 (m, 4H), 1.88-1.77 (m, 1H), 1.69-1.59 (m, 1H), 1.15 (s, 9H), 0.98-0.94 (m, 3H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 32	622.2 $(M+H)^+$	($CDCl_3$) δ 8.38-8.11 (m, 1H), 7.97 (br s, 1H), 7.93 (br d, J = 7.75 Hz, 1H), 7.84 (br d, J = 7.51 Hz, 1H), 7.76-7.65 (m, 1H), 7.26-7.08 (m, 2H), 4.06-3.81 (m, 2H), 3.73 (br d, J = 6.91 Hz, 2H), 3.26 (br t, J = 5.30 Hz, 4H), 2.90 (s, 3H), 2.18-2.03 (m, 4H), 1.92-1.79 (m, 2H), 1.72 (br d, J = 11.80 Hz, 4H), 1.16 (br t, J = 7.03 Hz, 3H), 0.96 (br s, 2H), 0.33 (s, 4H)
Compound 42	492.0 $(M+H)^+$	(DMSO-d^6) δ 9.77-9.41 (m, 1H), 8.15-7.83 (m, 4H), 7.82-7.75 (m, 1H), 7.15-7.00 (m, 2H), 3.93-3.79 (m, 2H), 2.98-2.88 (m, 3H), 2.64 (s, 6H), 1.79-1.43 (m, 7H), 1.38-0.89 (m, 3H)
Compound 43	501.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.14-7.97 (m, 1H), 7.95-7.85 (m, 1H), 7.81 (br d, J = 7.1 Hz, 1H), 7.78-7.67 (m, 2H), 7.19-6.96 (m, 2H), 3.95-3.79 (m, 2H), 3.39-3.29 (m, 1H), 2.99-2.90 (m, 3H), 1.97-1.78 (m, 3H), 1.67-1.39(m, 12H), 1.34-1.05 (m, 3H)
Compound 45	504.1 $(M+H)^+$	(DMSO-d^6) δ 8.31-8.10 (br s, 1H), 8.09-7.95 (m, 2H), 7.85 (br d, J = 7.6 Hz, 1H), 7.75-7.71 (m, 1H), 7.16 (s, 1H), 7.10-6.90 (br s, 1H), 6.36 (br s, 1H), 4.25-3.68 (m, 6H), 2.99 (s, 3H), 2.20-2.07 (m, 2H), 1.88-1.62 (m, 7H), 1.40-1.10 (m, 3H
Compound 46	504.2 $(M+H)^+$	(DMSO-d^6) δ 9.73-9.40 (m, 1H), 8.18-7.82 (m, 5H), 7.81-7.72 (m, 1H), 7.23-7.00 (m, 2H), 3.99-3.79 (m, 2H), 3.05-2.86 (m, 3H), 2.22-2.12 (m, 1H), 1.74-1.47 (m, 7H), 1.35-1.01 (m, 3H), 0.55-0.44 (m, 2H), 0.41-0.31 (m, 2H)
Compound 48	506.0 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.35-7.91 (m, 3H), 7.90-7.80 (m, 1H), 7.77-7.63 (m, 2H), 7.20-6.92 (m, 2H), 3.97-3.65 (m, 2H), 3.06-2.81 (m, 3H), 1.75-1.59 (m, 4H), 1.58-1.40 (m, 3H), 1.35-1.04 (m, 3H), 1.02-0.87 (m, 6H)
Compound 49	516.1 $(M+H)^+$	(DMSO-d^6) δ 9.68-9.49 (brs, 1H), 8.08-8.02 (m, 3H), 7.93-7.85 (m, 1H), 7.76-7.72 (m, 1H), 7.11-6.99 (m, 2H), 4.30 (s, 1H), 3.90-3.79 (m, 2H), 3.72-3.63 (m, 1H), 3.42 (m, 1H), 2.93 (s, 3H), 1.94-1.70 (m, 4H), 1.64-1.52 (m, 12H), 1.27 (m, 1H), 1.24-1.23 (m, 1H)
Compound 50	517.0 (M+H)+	($CDCl_3$) δ 8.40-7.95 (m, 3H), 7.90-7.81 (m, 1H), 7.77-7.67 (m, 1H), 7.20-7.12 (m, 1H), 7.11-6.9 (m, 1H), 6.36-6.24 (m, 1H), 4.15-3.75 (m, 2H), 3.59-3.48 (m, 1H), 3.01-2.98 (m, 3H), 2.15-2.01 (m, 2H), 1.98-1.64 (m, 14H), 1.31-1.22 (m, 2H)
Compound 55	520.1 $(M+H)^+$	(DMSO-d^6) δ 9.67-9.51 (m, 1H), 8.10-7.87 (m, 3H), 7.78-7.70 (m, 1H), 7.23-6.99 (m, 2H), 4.15-4.02 (m, 1H), 3.94-3.77 (m, 2H), 3.02-2.86 (m, 3H), 2.79-2.64 (m, 3H), 1.77-1.47 (m, 7H), 1.34- 1.03 (m, 3H), 0.98-0.81 (m, 6H)
Compound 57	524.2 $(M+H)^+$	(DMSO-d^6) δ 9.60 (brs, 1H), 7.99 (m, 1H), 7.61 (s, 1H), 7.36 (s, 1H), 7.12 (d, J = 2.0 Hz, 2H), 7.07-7.05 (m, 1H), 4.21 (s, 2H), 2.95 (s, 3H), 2.58 (s, 3H), 1.73-1.49 (m, 6H), 1.44-1.26 (m, 4H), 1.24- 1.13 (m, 9H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 59	541.3 $(M+NH_4)^+$	(DMSO-d^6) δ 9.69-9.55 (m, 1H), 8.15-7.97 (m, 1H), 7.66-7.60 (m, 1H), 7.27-7.17 (m, 1H), 7.13 (s, 1H), 7.13 (s, 1H), 4.04 (s, 2H), 4.00 (s, 3H), 2.95 (s, 3H), 1.78-1.59 (m, 5H), 1.55-1.43 (m, 2H), 1.37-1.21 (m, 3H), 1.17 (s, 9H)
Compound 60	526.0 $(M+H)^+$	($CDCl_3$) δ 8.10-8.01 (brs, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.50 (br d, J = 3.2 Hz, 1H), 7.18 (s, 1H), 7.04-7.02 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H), 4.76 (s, 1H), 4.16 (s, 2H), 3.00 (s, 3H), 1.78-1.65 (m, 8H), 1.59 (m, 1H), 1.35 (s, 9H), 1.26 (s, 1H)
Compound 67	530.1 $(M+H)^+$	($CDCl_3$) δ 8.25-8.00 (m, 3H), 7.91 (d, J = 7.63 Hz, 1H) 7.83-7.72 (m, 1 H), 7.16-7.08 (m, 1H), 6.54-6.35 (m, 1H), 3.94-3.74 (m, 2H), 2.98-2.93 (m, 2H), 2.36-2.11 (m, 3H), 1.72-1.55 (m, 10H), 1.50-0.92 (m,5H)
Compound 70	531.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.15-7.85 (m, 4H), 7.85-7.76 (m, 1H), 7.2-6.92 (m, 2H), 3.85 (br s, 2H), 3.30 (br s, 1H), 2.94 (s, 3H), 2.00-1.89 (m, 2H), 1.78-1.70 (m, 2H), 1.70-1.47 (m, 8H), 1.34-1.05 (m, 8H)
Compound 71	532.1 $(M+H)^+$	(DMSO-d^6) δ 9.64-9.52 (m, 1H), 8.18-7.84 (m, 4H), 7.82-7.72 (m, 1H), 7.16-7.02 (m, 2H), 3.93-3.76 (m, 2H), 3.25-3.14 (m, 2H), 2.94 (s, 3H), 2.78-2.62 (m, 2H), 2.11-1.95 (m, 1H), 1.92-1.79 (m, 1H), 1.72-1.44 (m, 7H), 1.35-1.02 (m, 4H), 0.84-0.74 (m, 3H
Compound 83	536.1 $(M+H)^+$	($CDCl_3$) δ 8.36-8.07 (m, 1H), 8.06-7.90 (m, 2H), 7.88-7.77 (m, 1H), 7.74-7.60 (m, 1H), 7.22-6.90 (m, 2H), 6.69-6.38 (m, 1H), 5.31-5.02 (m, 1H), s3.85 (br d, J = 3.25 Hz, 2H), 3.69-3.48 (m, 3H), 3.42-3.21 (m, 1H), 2.99 (br s, 3H), 2.27-2.14 (m, 1H), 2.09-1.88 (m, 1H), 1.71 (br d, J = 11.01 Hz, 7H), 1.38-1.02 (m, 3H)
Compound 95	538.0 $(M+H)^+$	(DMSO-d^6) δ 9.60 (s, 1H), 8.06-7.96 (m, 1H), 7.91-7.85 (m, 1H), 7.80-7.74 (m, 3H), 7.15-7.06 (m, 2H), 3.82 (m, 2H), 2.94 (s, 3H), 1.62-1.52 (m, 8H), 1.28-1.21 (m, 2H), 1.13 (s, 9H)
Compound 96	538.1 $(M+H)^+$	($CDCl_3$) δ 8.15-8.10 (m, 1H), 7.87-7.79 (m, 1H), 7.35-7.31 (m, 1H), 7.21-7.15 (m, 2H), 7.00 (m, 1H), 6.24 (s, 1H), 4.79 (s, 1H), 3.91- 3.80 (m, 2H), 2.99 (s, 3H), 1.76-1.62 (m, 7H), 1.35-1.31 (m, 1H), 1.27 (s, 9H), 1.25 (m, 2H)
Compound 97	538.0 $(M+H)^+$	(DMSO-d^6) δ 8.08-8.03 (m, 3H), 7.66-7.59 (m, 2H), 7.15-7.11 (m, 2H), 3.70 (s, 2H), 2.99-2.94 (m, 3H), 1.64-1.61 (m, 9H), 1.26-1.22 (m, 1H), 1.13 (s, 9H)
Compound 107	548.0 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.15-7.85 (m, 4H), 7.84-7.78 (m, 1H), 7.17-7.01 (m, 2H), 3.95-3.79 (m, 3H), 3.63-3.45 (m, 4H), 2.94 (s, 3H), 2.33-2.27 (m, 1H), 1.97 (t, J = 11.13 Hz, 1H), 1.72-1.47 (m, 7H), 1.32-1.11 (m, 2H), 1.05 (d, J = 6.00 Hz, 3H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 129	544.0 $(M+H)^+$	(DMSO-d^6) δ 9.79-9.43 (m, 1H), 8.17-7.90 (m, 4H), 7.89-7.75 (m, 1H), 7.24-6.92 (m, 2H), 3.97-3.81 (m, 2H), 3.77-3.62 (m, 4H), 2.94 (s, 3H), 1.92-1.78 (m, 4H), 1.73-1.58 (m, 6H), 1.58-1.45 (m, 3H), 1.33-1.20 (m, 1H), 1.16-1.02 (m, 1H)
Compound 134	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.69 (br s, 1H), 8.03-7.96 (m, 3H), 7.84 (br s, 1H), 7.73-7.69 (m, 2H), 7.14-7.12 (m, 2H), 3.87 (s, 2H), 3.05-3.03 (m, 2H), 1.64-157 (m, 6H), 1.20-1.16 (t, J = 7.2 Hz, 3H), 1.10 (s, 9H), 0.88~0.85 (m, 2H), 0.27 (br s, 4H)
Compound 140	534.1 $(M+H)^+$	(DMSO-d^6) δ 9.68-9.49 (m, 1H), 8.10-7.92 (m, 3H), 7.89-7.77 (m, 1H), 7.77-7.62 (m, 2H), 7.39-7.31 (m, 1H), 7.16-7.02 (m, 1H), 3.88-3.72 (m, 2H), 2.95 (d, J = 3.88 Hz, 3H), 1.83-1.33 (m, 9H), 1.13-1.09 (m, 9H), 0.88-0.74 (m, 3H)
Compound 141	526.2 $(M+H)^+$	(DMSO-d^6) δ 9.52-9.67 (m, 1H), 8.08-7.85 (m, 4H), 7.79 (s, 1H), 7.51-7.45 (m, 1H), 7.32-7.18 (m, 1H), 4.16-4.06 (m, 2H), 3.98-3.80 (m, 2H), 2.93 (br s, 4H), 1.54 (br s, 11H), 1.42-1.29 (m, 3H), 1.27-1.23 (m, 3H), 1.22-0.99 (m, 2H)
Compound 144	556.2 $(M+H)^+$	(DMSO-d^6) δ 9.52-9.51 (brs, 1H), 8.03-7.97 (m, 3H), 7.83 (m, 1H), 7.83-7.61 (m, 2H), 7.11 (brs, 2H), 4.00 (s, 2H), 2.95 (s, 3H), 2.04-2.03 (m, 2H), 1.82 (m, 6 H), 1.15 (s, 9H)
Compound 145	523.1 $(M+H)^+$	(DMSO-d^6) δ 9.56 (s, 1H), 7.85-7.82 (m, 1H), 7.48 (s, 1H), 7.10 (m, 2H), 7.04-7.02 (dd, J = 8.69, 1.81 Hz, 1H), 6.91 (s, 1H), 4.09 (s, 2H), 3.77 (s, 3H), 2.93 (s, 3H), 1.68-1.62 (m, 5H), 1.59-1.49 (m, 2H), 1.31-1.25 (m, 3H), 1.16 (s, 9H)
Compound 146	485.1 $(M+H)^+$	($CDCl_3$) δ 8.48-7.92 (m, 1H), 7.50-7.46 (m, 2H), 7.39-7.32 (m, 2H), 7.14 (s, 1H), 7.09-6.88 (m, 1H), 6.44 (s, 1H), 4.02-3.82 (br s, 2H), 2.97 (m, 1H), 2.09-2.92 (m, 3H), 2.09- 2.00 (m, 2H), 1.79-1.62 (m, 14H), 1.19-1.14 (m, 2H)
Compound 147	524.1 $(M-H)^-$	(DMSO-d^6) δ 9.61 (s, 1H), 8.35 (d, J = 1.25 Hz, 1H), 7.97-7.93 (m, 2H), 7.65 (s, 1H), 7.14-7.04 (m, 2H), 4.21 (s, 2H), 2.95 (s, 3H), 1.74-1.52 (m, 8H), 1.34-1.26 (m, 2H), 1.14 (s, 9H)
Compound 148	576.1 $(M+H)^+$	(DMSO-d^6) δ 8.02-7.96 (m, 2H), 7.84-7.82 (m, 1H), 7.77-7.69 (m, 2H), 7.14-7.09 (m, 2H), 3.90 (s, 2H), 3.75-3.71 (t, J = 6.4 Hz, 2H), 3.19-3.16 (m, 2H), 1.65-1.54 (m, 6H), 1.11 (s, 9H), 1.10 (s, 1H), 0.97-0.86 (m, 2H), 0.38-0.18 (m, 4H)
Compound 149	510.1 $(M+H)^+$	(DMSO-d^6) δ 9.62 (s, 1H), 8.17 (s, 1H), 8.03-8.01 (m, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.08-7.06 (dd, J = 8.69, 2.06 Hz, 1H), 4.24 (s, 2H), 2.96 (s, 3H), 1.68-1.65 (m, 5H), 1.56-1.52 (m, 3H), 1.34-1.38 (m, 2H), 1.20 (s, 9H)
Compound 151	570.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (s, 1H), 8.06-7.0 (m, 5H), 7.13-7.11 (m, 2H), 3.91 (s, 2H), 3.72 (s, 4H), 2.94 (s, 3H), 1.85-1.83 (m, 4H), 1.68-1.55 (m, 8H), 0.88-0.85 (m, 2H), 0.28-0.23 (m, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 153	572.1 $(M+H)^+$	(DMSO-d^6) δ 9.59-9.57 (br s, 1H), 8.04-7.96 (m, 4H), 7.81-7.85 (m, 1H), 7.14 (m, 2H), 4.28-4.25 (br t, J = 7.2 Hz, 2H), 4.09 (d, J = 10.8 Hz, 2H), 3.90 (s, 2H), 3.76 (br d, J = 10.8 Hz, 2H), 2.94 (s, 3H), 2.65-2.53 (m, 2H), 1.68-1.60 (m, 6H), 0.87-0.85 (m, 2H), 0.27 (br s, 4H)
Compound 155	543.1 $(M+H)^+$	(DMSO-d^6) δ 9.66-9.57 (br s, 1H), 8.12-8.03 (m, 3H), 7.82-7.78 (m, 1H), 7.13-7.09 (m, 2H), 3.94-3.85 (m, 3H), 2.94 (s, 3H), 1.93-1.83 (m, 4H), 1.66-1.57 (m, 10H), 0.88-0.85 (m, 2H), 0.27-0.22 (br s, 4H).
Compound 157	483.4 $(M+H)^+$	(DMSO-d^6) δ 9.54 (br s, 1H), 8.03-8.00 (m, 1H), 7.51-7.42 (m, 4H), 7.10 (m, 2H), 5.24 (d, J = 4.4 Hz, 1H), 4.37 (br dd, J = 7.50, 4.50 Hz, 1H), 3.86 (br s, 2H), 2.93 (s, 3H), 2.09-2.07 (m, 1H), 1.64-1.44 (m, 13H), 1.28-1.22 (m, 5 H)
Compound 159	564.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (br s, 1H), 8.03-7.98 (m, 3H), 7.59-7.54 (m, 1H), 7.12-7.07 (m, 2H), 3.89 (s, 2H), 2.93 (s, 3H), 1.69-1.61 (m, 4H), 1.14 (s, 9H), 0.88-0.85 (m, 2H), 0.27 (br s, 4H
Compound 160	572.2 $(M+H)^+$	(DMSO-d^6) δ 9.60 (br s, 1H), 8.04-7.95 (m, 3H), 7.84 (d, J = 1.2 Hz, 1H), 7.73-7.69 (m, 2H), 7.16-7.12 (m, 2H), 3.88 (s, 2H), 3.32 (s, 1H), 1.66-1.56 (m, 6H), 1.10 (s, 9H), 0.91-0.87 (m, 6H), 0.27 (br s, 4H)
Compound 162a	570.1 $(M+H)^+$	(DMSO-d^6) δ 9.60 (s, 1H), 8.07-7.96 (m, 2H), 7.89-7.79 (m, 1H), 7.73-7.70 (m, 1H), 7.66(m, 1H), 7.12-7.06 (m, 2H), 5.98-5.70 (m, 1H), 3.89 (s, 2H), 2.95 (s, 3H), 1.92-1.83 (m, 1H), 1.77-1.60 (m, 6H), 1.10-1.05 (m, 11H
Compound 162b	570.1 $(M+H)^+$	(DMSO-d^6) δ 9.68 (br s, 1H), 8.04-8.00 (m, 2H), 7.99-7.97 (m, 1H), 7.95-7.81 (m, 2H), 7.37 (s, 1H), 7.23-7.09 (m, 1H), 6.29-5.99 (m, 1H), 3.79 (s, 2H), 2.94 (m, 3H), 1.91-1.80 (m, 3H), 1.66-1.53 (m, 6H), 1.11 (s, 9H)
Compound 163	544.2 $(M+H)^+$	(DMSO-d^6) δ 11.57-11.53 (br s, 1H), 9.58 (s, 1H), 8.04-7.61 (m, 5H), 7.59-7.11 (m, 2H), 4.45 (s, 2H), 3.95 (s, 2H), 3.45-3.37 (m, 2H), 3.14-3.13 (m, 2H), 2.94 (s, 3H), 2.49-2.32 (m, 4H), 1.66 (m, 6H), 0.89-0.87 (m, 2H), 0.28 (br s, 4H)
Compound 164	507.1 $(M+H)^+$	(DMSO-d^6) δ = 9.68 - 9.37 (m, 1H), 8.25 - 8.06 (m, 3H), 7.86-7.84 m, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.18 - 6.97 (m, 2H), 3.91-3.80 (m, 3H), 2.94 (s, 3H), 1.89 (m, 2H), 1.77 - 1.51 (m, 12H), 0.96 - 0.87 (m, 2H), 0.27 (br s, 4H)
Compound 165	509.2 $(M+H)^+$	(DMSO-d^6) δ 9.67 (bs s, 1H), 8.24-8.00 (m, 1H), 7.48-7.42 (m, 4H), 7.19-7.03 (m, 2H), 5.25 (d, J = 4.8 Hz, 1H), 4.66 (m, 1H), 3.98 (s, 2H), 2.93 (s, 3H), 2.07 (m, 1H), 1.77-1.45 (m, 12H), 1.35-1.14 (m, 2H), 0.93-0.86 (m, 2H), 0.27 (br s, 4H)
Compound 165a	509.2 $(M+H)^+$	(DMSO-d^6) δ 9.68 (br s, 1H), 8.24 (m, 1H), 7.63-7.26 (m, 4H), 7.29-6.80 (m, 2H), 5.25 (s, 1H), 4.47-4.43 (m, 1H), 3.96-3.83 (m, 2H), 2.93 (s, 3H), 2.12-2.05 (m, 1H), 1.78-1.36 (m, 12H), 1.31-1.23 (m, 2H), 0.89-0.86 (m, 2H), 0.39-0.16 (m, 4H
Compound 165b	509.3 $(M+H)^+$	(DMSO-d^6) δ 9.71 (br s, 1H), 8.22-7.85 (m, 1H), 7.52-7.42 (m, 4H), 7.11-6.90 (m, 2H), 5.26 (d, J = 4.8 Hz, 1H), 4.38-4.35 (m, 1H), 3.96 (s, 2H), 2.93 (s, 3H), 2.11-2.07 (m, 1H), 1.65-1.45 (m, 12H), 1.35-1.18 (m, 2H), 0.89-0.86 (m, 2H), 0.44-0.07 (m, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 166	455.1 $(M+H)^+$	(DMSO-d^6) δ 9.39-9.19 (brs, 1H), 7.91-7.84 (m, 3H), 7.78-7.74 (m, 1H), 6.67 (d, J = 2.0 Hz, 2H), 3.80 (s, 2H), 2.92 (m, 4H), 1.75-1.59 (m, 11H), 1.53 (m, 2H), 1.37-0.98 (m, 3H)
Compound 168	544.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.11-8.09 (m, 1H), 7.97-7.86 (m, 4H), 7.74-7.70 (m, 1H), 7.13 (m, 2H), 3.95 (s, 2H), 3.70-3.62 (m, 1H), 2.94 (m, 3H), 1.81-1.96 (m, 2H), 1.74-1.45 (m, 10H), 0.88-0.85 (m, 2H), 0.13-0.36 ppm (m, 4H)
Compound 170	546.1 $(M+H)^+$	(DMSO-d^6) δ 9.56 (brs, 1 H), 7.95 – 7.92 (m, 2 H), 7.85 (m, 1 H), 7.84 - 7.66 (m, 2 H), 7.13 (m, 2 H), 3.88 (s, 2 H), 3.11 - 3.15 (m, 1 H), 2.94 (s, 3 H), 1.65 - 1.28 (m, 6 H), 1.22 - 1.28 (m, 2 H), 0.90 - 0.86 (m, 5 H), 0.71 - 0.68 (m, 3 H), 0.27 (m, 4 H)
Compound 172	556.0 $(M+H)^+$	(DMSO-d^6) δ 9.57 (s, 1 H), 8.04 – 7.87 (m, 5 H), 7.70 - 7.79 (m, 1 H), 7.14 - 7.10 (m, 2 H), 5.57 - 5.54 (m, 2 H), 3.89 - 3.81 (m, 3 H), 2.94 (s, 3 H), 2.35-2.32 (m, 3 H), 1.99 - 2.15 (m, 2 H), 1.65-1.51 (m, 6 H), 0.87 – 0.85 (m, 2 H), 0.21 - 0.18 (m, 4 H)
Compound 174	546.0 $(M+H)^+$	(DMSO-d^6) δ 9.70-9.33 (br s, 1H), 9.01-8.45 (m, 1H), 8.10-7.91 (m, 4H), 7.64-7.83 (m, 1H), 7.14-6.97 (m, 2H), 4.36-4.58 (m, 3H), 4.13-4.33 (m, 2H), 3.73-4.00 (s, 2H), 2.94 (s, 3H), 1.81-1.49 (m, 5H), 0.99-0.79 (m, 2H), 0.39-0.05 (br s, 4H)
Compound 176	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1H), 8.11-7.85 (m, 3H), 7.80-7.78 (m, 1H), 7.75-7.71 (m, 2H), 7.10-7.18 (m, 1H), 3.98 (br s, 2H), 3.39-3.57 (m, 1H), 2.94 (s, 3H), 1.77-1.53 (m, 10H), 1.44-1.18 (m, 4H), 0.88-0.85 (m, 2H), 0.27-0.14 (m, 4H)
Compound 178	574.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (s, 1 H) 8.06 – 7.97 (m, 4 H), 7.79 - 7.94 (m, 1 H), 7.74 - 7.72 (m, 1 H), 7.13 (m, 2 H), 3.86 (s, 2 H), 3.64 - 3.73 (m, 4 H), 2.94 (s, 3 H), 2.06 - 2.16 (m, 1 H), 1.73 - 1.58 (m, 7 H) 1.19 (s, 3 H), 0.77 - 1.00 (m, 2 H) 0.27 (s, 4 H)
Compound 180	572.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (s, 1 H), 7.99 – 7.78 (m, 5 H), 7.73 - 7.69 (m, 1 H), 7.13 (m, 2 H), 3.87 (br s, 2 H), 2.94 (s, 3 H), 1.64 - 1.54 (m, 10 H), 1.48 - 1.49 (m, 1 H), 0 1.24-1.09 (m, 6 H), 0.86 (m, 2 H), 0.26-0.23 (m, 4 H)
Compound 182	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (s, 1H), 8.13-8.00 (m, 4H), 7.97-7.95 (m, 1H), 7.84 (m, 1H), 7.14-6.99 (m, 2H), 3.89 (s, 2H), 2.95 (s, 3H), 2.08 (m, 2H), 1.65-1.62 (m, 10H), 1.28 (s, 3H), 0.88-0.85 (m, 2H), 0.15-0.36 (m, 4H)
Compound 184	572.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (br s, 1 H), 8.09-7.93 (m, 3 H), 7.86 (m, 1 H), 7.74-7.70 (m, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.14-7.11 (m, 2 H), 3.88 (br s, 2 H), 3.08 (m, 1 H), 2.95 (s, 3 H), 2.21-2.09 (m, 1 H), 1.75-1.56 (m, 11 H), 1.47-1.33 (m, 1 H), 0.88-0.85 (m, 2 H), 0.78 (d, J = 6.4 Hz, 3 H), 0.26 (m, 4 H)
Compound 186	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (br s, 1 H), 8.11-7.94 (m, 3 H), 7.87 (d, J = 8.0 Hz, 2 H), 7.74-7.70 (m, 1 H), 7.13 (m, 2 H), 3.88 (s, 2 H), 2.95 (s, 3 H), 2.71-2.59 (m, 1 H), 1.76-1.48 (m, 6 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.89-0.85 (m, 2 H), 0.72 (m, 1 H), 0.21-0.39 (m, 5 H), 0.05-0.20 (m, 2 H), 0.11 (m, 1 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 188	574.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (br s, 1 H), 8.63 (m, 1 H), 7.95 - 7.94 (m, 4 H), 7.76-7.72 (m, 1 H), 7.15-7.14 (m, 2 H), 4.29 (s, 1 H), 4.05 (s, 2 H), 3.89 (s, 2 H), 2.95 (s, 3 H), 1.72-1.57 (m, 6 H), 1.19 (s, 3 H), 1.11 (s, 3 H), 0.89-0.87 (m,2 H), 0.33-0.18 (br s,4 H)
Compound 190	556.1 $(M+H)^+$	($CDCl_3$) 8.33 (m, 1H), 8.15 (m, 1H), 7.81-7.79 (m, 1H), 7.70-7.66 (t, J = 7.2 Hz, 1H), 7.21 (m, 1H), 7.05-7.10 (m, 1H), 6.62 (s, 1H), 4.83 (s, 2H), 4.82-4.77 (m, 1H), 3.93-3.88 (br s, 2H), 3.02 (s, 3H), 2.96-2.91 (m, 2H). 2.60-2.55 (m, 2H), 1.82-1.80 (m, 3H), 1.71-1.68 (m, 3H), 0.97-0.92 (m, 2H), 0.33 (s, 4H)
Compound 192	580.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 (br s, 1 H), 8.42-7.93 (m, 4 H), 7.78-7.75 (m, 1 H), 7.14-6.96 (m, 2 H), 3.96 (s, 2 H), 3.58-3.71 (m, 1 H), 2.95 (s, 3 H), 2.74-2.42 (m, 2 H), 2.46-2.34 (m, 2 H), 1.82-1.61 (m, 6 H), 0.95-0.87 (m, 2 H), 0.37 (m, 4 H)
Compound 194	574.2 $(M-H)^-$	(MeOD) 8.19-8.00 (m, 3 H), 7.82 (m, 1 H), 7.74 - 7.70 (m, 2 H), 7.21 - 7.08 (m, 2 H), 3.95 (br s, 1H), 3.71 - 3.65 (m, 1 H) 2.94 (s, 3 H) 1.84 (m, 2 H) 1.70 (m, 4 H) 1.14 - 1.11 (m, 8 H) 095 - 0.89 (m, 3 H) 0.32 (s, 4 H).
Compound 196	570.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (br s, 1 H), 8.10-7.94 (m, 4 H), 7.87 (m, 1 H), 7.76-7.72 (m, 1 H), 7.14-7.15 (m, 2 H), 5.71-5.68 (m,1 H), 5.25-5.22 (m, 1 H), 3.90 (br s, 2 H), 3.71 (br s, 1 H), 2.95 (s, 3 H), 1.87 (m, 2 H), 1.67-1.57 (m, 8 H), 1.39 (m, 2 H), 0.88-0.85 (d, J = 9.6 Hz, 2 H), 0.28-0.26 (m, 4 H)
Compound 198	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (br s, 1 H), 8.11-7.90 (m, 3 H), 7.85 (m, 1 H), 7.74-7.64 (m, 2 H), 7.14- 7.13 (m, 2 H), 3.88 (br s, 2 H), 2.98 (m, 1 H), 2.95 (s, 3 H), 1.74-1.66 (m, 6 H), 1.36- 1.28 (m, 2 H), 1.26-1.23 (m, 2 H), 0.85-0.80 (m, 2 H), 0.67-0.65 (m, 6 H), 0.28-0.26 (m, 4 H)
Compound 200	562.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (br s, 1 H), 8.11-7.95 (m, 3 H), 7.85-7.83 (m, 2 H), 7.77-7.70 (m, 1 H), 7.14 (m, 2 H), 3.90 (s, 2 H), 3.17-3.16 (m, 1 H), 3.12 (m, 1 H), 3.10 (s, 3 H), 2.95 (s, 3 H), 1.67-1.66 (m, 6 H), 0.92-0.86 (m, 5 H), 0.27 (m, 4 H)
Compound 202	560.1 $(M+H)^+$	(DMSO-d^6) δ 8.12-8.11(m, 1H),8.07-8.05 (m, 1H), 7.79 (br d, J = 7.2 Hz, 1H), 7.68-7.64 (m, 1H), 7.18 (s, 1H), 6.37 (s, 1H), 5.49 (s, 1H), 3.92-3.86 (m, 2H), 3.40 (s, 2H), 3.00 (s, 3H), 1.83-1.80 (m, 2H), 1.71-1.58 (m, 4H), 0.95-0.92 (m, 2H), 0.88-0.85 (m, 2H) 0.70-0.67 (m, 2H) 0.32 (br s, 4H)
Compound 204	562.2 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1 H), 8.18-8.16 (br d, J=7.6 Hz, 1 H), 7.96 – 7.92 (m, 4 H), 7.76-7.72 (t, J=8.0 Hz, 1 H), 7.14 - 7.08 (m, 2 H), 4.73 - 4.54 (m, 1 H), 3.88 (br s, 2 H), 3.23 - 3.27 (m, 1 H), 2.94 (s, 3 H), 2.45-2.41 (m, 2 H) 1.95 - 1.96 (m, 2 H) 1.79 - 1.50 (m, 6 H), 0.88-0.86 (m, 2 H) 0.275 (br s, 4 H)
Compound 206	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.58-9.41 (br s, 1 H) 8.58-8.53 (br s, 1 H), 8.19-7.89 (m, 4 H), 7.76 - 7.72 (m, 1 H), 7.13 (m, 2 H), 4.55 (d, J=6.0 Hz, 2 H), 4.13 (d, J=6.0 Hz, 2 H), 3.88 (br s, 2 H) 2.94 (s, 3 H) 1.66 - 1.57 (m, 6 H), 1.41 (s, 3 H), 0.88-0.75 (m, 2 H) 0.27 (br s, 4 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 208	562.1 $(M+H)^+$	(DMSO-d^6) δ 9.61 (br.s, 1 H), 8.11-7.93 (m, 3 H), 7.86 (m, 1 H), 7.73 - 7.65 (m, 2 H), 7.13-7.09 (m, 2 H), 4.60 - 4.70 (t, J = 4.8 Hz, 1 H), 3.87 (br s, 2 H), 3.29 - 3.27 (m, 1 H), 3.18 - 3.15 (m, 1 H), 2.96 (m, 1 H), 2.94 (s, 3H), 1.65 - 1.51 (m, 7 H), 1.12 - 1.29 (m, 1 H), 0.98 - 0.86 (m, 2 H), 0.69 - 0.59 (m, 3 H), 0.27 (br s, 4 H)
Compound 210	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1 H), 7.99 (s, 1 H), 7.95 (d, J = 7.8 Hz, 1 H), 7.86 (br d, J = 5.9 Hz, 1 H), 7.73 (t, J = 24.0 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 1 H), 7.03 - 7.18 (m, 2 H), 3.88 (s, 2 H), 2.98 - 3.07 (m, 1 H), 2.95 (s, 3 H), 1.50 - 1.72 (m, 7 H), 0.87 (br d, J = 11.9 Hz, 2 H), 0.74-0.81 (m, 9 H), 0.21 - 0.34 (m, 4 H)
Compound 212	530.2 $(M+H)^+$	(DMSO-d^6) δ 9.58 - 9.53 (m, 1 H), 8.07 - 8.04 (s, 1 H), 8.01 – 7.97 (m, 3 H), 7.78-7.74 (m, 1 H), 7.14 - 7.08 (m, 2 H), 3.98 (br s, 2 H), 2.94 (s, 3 H), 2.16-2.10 (m, 1 H), 1.77-1.52 (m, 6 H), 0.92-0.87 (m, 2 H), 0.42-0.55 (m, 2 H), 0.34-0.41 (m, 2 H), 0.27 (br s, 4 H)
Compound 214	574.1 $(M+H)^+$	(DMSO-d^6) δ 9.69-9.43 (br s, 1 H), 8.15-7.94 (m, 3 H), 7.84-7.79 (m, 2 H), 7.71-7.67 (m, 1 H), 7.14 (m, 1 H), 4.61 (br s, 1 H), 3.89 (br s, 2 H), 3.38-3.52 (m, 2 H), 2.94 (s, 3 H), 2.58-2.63 (m, 1 H), 1.66 (m, 6 H), 0.87-0.81 (m, 3 H), 0.27 (br s, 6 H), 0.15-0.09 (m, 2 H).
Compound 216	544.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br.s, 1 H), 8.20 (s, 1 H), 8.05 – 7.87 (m, 3 H), 7.76 - 7.72 (m, 1 H), 7.13-7.09 (m, 1 H), 7.10 (s, 1H), 3.88 (s, 2 H), 2.94 (s, 3 H), 1.46 - 1.76 (m, 6 H), 1.07 (s, 3 H), 0.89 - 0.86 (m, 2 H), 0.63-0.60 (m, 2 H), 0.41-0.38 (m, 2 H), 0.27 (br s, 4 H)
Compound 218	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (s, 1 H), 8.09-7.90 (m, 4 H), 7.66 - 7.80 (m, 1 H), 7.14-7.10 (m, 1 H), 7.15 (s, 1 H), 5.00 – 4.91 (m, 1 H), 3.89 - 3.62 (m, 3 H), 3.25 - 3.07 (m, 1 H), 2.95 (s, 3 H), 2.06 (m, 1 H), 1.83 - 2.01 (m, 2 H), 1.66 - 1.51 (m, 7 H), 0.96 - 0.87 (m, 2 H), 0.22 (br s, 4 H)
Compound 220	562.1 $(M+H)^+$	(DMSO-d^6) δ 9.60 (br s, 1 H), 8.09-7.91 (m, 3 H), 7.84 (m, 1 H), 7.75-7.62 (m, 1 H), 7.51 (s, 1 H), 7.13-7.09 (m, 2 H), 4.79 (t, J = 6.0 Hz, 1 H), 3.89 (s, 2 H), 3.21 (d, J = 5.6 Hz, 2 H), 2.94 (s, 3 H), 1.74-1.50 (m, 6 H), 0.96 - 1.08 (m, 6 H), 0.93-0.80 (m, 2 H), 0.27 (brs, 4 H)
Compound 222	574.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br.s, 1 H), 8.07 – 7.95 (m, 2 H), 7.94 – 7.88 (m, 3 H), 7.75 - 7.71 (m, 1 H) 7.14-7.11 (m, 1 H), 3.88-3.80 (br s, 2 H), 3.41 - 3.32 (m, 1 H), 3.00 (s, 3 H), 2.90 (s, 3 H), 2.27 - 2.25 (m, 2 H), 2.04-1.88 (m, 1 H), 1.66 - 1.56 (m, 8 H), 0.89 - 0.86 (d, J = 10.4 Hz, 2 H), 0.27 (br s, 4 H)
Compound 223	556.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (brs, 1H), 8.71 (s, 1H), 7.99-7.88 (m, 4H), 7.74-7.72 (m, 1H), 7.13-7.07 (m, 2H), 3.89 (s, 2H), 2.94 (s, 3H), 2.28 (s, 1H), 1.71-1.65 (m, 12H), 0.88-0.85 (m, 2H), 0.26 (br d, J = 6.50Hz, 3H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 224	594.2 $(M+H)^+$	($CDCl_3$) δ 8.02 - 8.15 (m, 3 H), 7.79 (br d, J=7.13 Hz, 1 H), 7.65 - 7.69 (m, 1 H), 7.20 (s, 1 H), 7.00 - 7.09 (m, 1 H), 6.45 (s, 1 H), 5.08 (br s, 1 H) 3.88 – 3.95 (m, 2 H), 3.00 (s, 3 H) 2.84 - 2.98 (m, 2 H) 2.55 - 2.63 (m, 2 H) 1.68 - 1.96 (m, 6 H), 1.49 (s, 3 H), 0.91-0.94 (m, 2 H), 0.32 (br s, 4 H)
Compound 225	556.1 $(M+H)^+$	(DMSO-d^6) δ 9.56 (brs, 1H), 8.07-7.93 (m, 5H), 7.77 (d, J = 7.6, 1H), 7.14-7.04 (m, 2H), 3.90 (br s, 2H), 3.26-3.30 (m, 2H), 2.94 (s, 3H), 1.76-152 (m, 6H), 0.99-1.10 (m, 1H), 0.88 (br d, J = 10.9 Hz, 2H), 0.77-0.82 (m, 1H), 0.65-0.76 (m, 4H), 0.27 (br s, 4H)
Compound 226	576.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (s, 1 H) 8.38 - 8.48 (s, 1 H) 7.94 - 8.10 (m, 2 H) 7.83 - 7.93 (m, 1 H) 7.70 - 7.80 (m, 1 H) 7.01 - 7.19 (m, 2 H) 3.80 - 3.96 (s, 2 H) 3.48 - 3.60 (m, 2 H) 2.88 - 3.00 (s, 3 H) 2.68 - 2.74 (m, 2 H) 2.11 - 2.22 (m, 1 H) 1.85 - 1.95 (m, 1 H) 1.46 - 1.78 (m, 9 H) 1.35 - 1.43 (m, 1 H) 1.12 - 1.30 (m, 1 H) 0.80 - 0.95 (m, 2 H) 0.18 - 0.34 (br s, 4 H)
Compound 227	574.1 $(M+H)^+$	(DMSO-d^6) δ 7.99 - 7.91 (m, 2 H), 7.83 (br d, J=7.70 Hz, 2H), 7.75 - 7.66 (m, 2H), 7.19 (d, J=1.83 Hz, 1 H), 7.07 (br d, J=8.19 Hz, 1 H), 3.90 (s, 2 H), 3.78 (t, J=6.60 Hz, 4 H), 3.05 (s, 2 H), 1.97 - 1.93 (m, 2 H), 1.69 - 1.48 (m, 10 H), 0.96 (br d, J=13.20 Hz, 2 H), 0.54 - 0.09 (m, 4 H)
Compound 228	600.1 $(M+H)^+$	(DMSO-d^6) δ 8.04-7.94 (m, 4H), 7.84-7.80 (m, 1H), 7.14-7.10 (m, 2H), 3.91 (ms, 2H), 3.78-3.72 (m, 6H), 3.24-3.18 (m, 2H), 1.87-1.83 (m, 4 H), 1.68-1.55 (m, 8H), 0.87-0.83 (m, 2H), 0.28-0.23 (m, 4H)
Compound 229	573.1 $(M+H)^+$	(DMSO-d^6) δ 9.52 - 9.65 (m,1 H), 7.94 - 8.16 (m, 4 H), 7.76 - 7.86 (m, 1 H), 7.04 - 7.18 (m, 2 H), 4.95 (m, 1 H), 3.81 - 3.95 (m, 3 H), 3.73 (br t, J=6.32 Hz, 2 H), 3.18 (br t, J=6.44 Hz, 2 H), 1.77 - 1.92 (m, 4 H), 1.50 - 1.72 (m, 10 H), 0.88 (br d, J=9.26 Hz, 2 H), 0.28 (br s, 4 H)
Compound 230	610.1 $(M+H)^+$	(DMSO-d^6) δ 8.51 - 8.22 (m, 1 H), 8.22 - 7.84 (m, 4 H), 7.82 - 7.68 (m, 1 H), 7.24 – 6.96 (m, 2 H), 3.97 - 3.81 (m, 2 H), 3.79 - 3.70 (m, 2 H), 3.68 - 3.59 (m, 1 H), 3.23 - 3.13 (m, 2 H), 2.80 - 2.64 (m, 2 H), 2.38 - 2.29 (m, 2 H), 1.78 - 1.46 (m, 6 H), 0.97 - 0.77 (m, 2 H), 0.37 - 0.12 (m, 4 H)
Compound 231	534.2 $(M+H)^+$	(DMSO-d^6) δ 9.58 (s, 1 H) 8.36 (s, 1 H) 7.81 - 7.91 (m, 2 H) 7.01 - 7.15 (m, 2 H) 4.02 (s, 2 H) 2.94 (s, 3 H) 1.52 - 1.67 (m, 7 H) 1.22 - 1.30 (m, 3 H) 1.19 (s, 9 H)
Compound 233	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (s, 1H), 8.27-8.44 (m, 1H), 7.71-8.12 (m, 4H), 7.64-7.80 (m, 1H), 6.92-7.23(m, 2H), 4.69 (br d, J = 1.6 Hz, 1H), 4.55 (br s, 1H), 4.23-4.39 (m, 1H), 3.77-4.00(m, 2H), 2.95 (s,3H), 2.17-2.34 (m, 2H), 1.84-2.02 (m, 1H), 1.46-1.75 (m, 7H), 0.76-0.98 (m, 2H), 0.15-0.38 (m, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 235	570.1 $(M+H)^+$	(DMSO-d^6) δ 8.09 (br s, 1H), 8.04 (d, J = 7.88 Hz, 1H), 7.79 (br d, J = 7.63 Hz, 1H), 7.71-7.63 (m, 1H), 7.21 (s, 2H), 6.28 (br s, 1H), 5.67 (ddt, J = 9.82, 3.60, 1.67, 1.67 Hz, 1H), 5.56-5.48 (m, 1H), 4.59 (d, J = 8.25 Hz, 1H), 4.03-3.78 (m, 2H), 3.65-3.50 (m, 1H), 3.00 (s, 3H), 2.32-2.20 (m, 1H), 2.09 (br d, J = 2.38 Hz, 2H), 1.93-1.63 (m, 8H), 1.26 (s, 1H), 1.02-0.77 (m, 3H), 0.32 (br s, 4H)
Compound 237	592.1 $(M+H)^+$	(DMSO-d^6) δ 8.15 - 8.65 (br s, 1H), 7.95-8.00 (m, 2H), 7.83 (d, J = 8.0 Hz 3H), 7.66-7.70 (m, 1H), 7.20 (s, 1H), 7.00 (m, 1H), 6.27 (s, 1H), 3.88-3.90 (m, 2H), 3.67 (s ,4H), 3.00 (s, 3H), 2.29 (d, J = 11.6 Hz, 2H), 1.80 - 1.82 (m, 3H), 1.71 (m, 3H), 0.92 – 0.4 (m, 2H), 3.19 (s , 4H)
(R)-Compound 239	562.1 $(M+H)^+$	(DMSO-d^6) δ 8.15 - 8.30 (br s, 1H), 7.98-8.02 (m, 2H), 7.83 (d, J = 7.2 Hz, 1H), 7.67-7.71 (m, 1H), 7.19 (s, 1H), 7.10 (m, 1H), 6.45 (s, 1H), 5.10-5.23 (d, J = 53.2 Hz, 2H), 3.89 (m, 2H), 3.59-3.63 (m , 3H), 3.31-3.32 (m, 1H), 2.15-2.25 (m, 1H), 1.98 (m, 2H), 1.71 (m, 2H), 0.91 – 0.93 (m, 2H), 0.31 (s , 4H)
(S)-Compound 239	562.1 $(M+H)^+$	($CDCl_3$) δ 8.12-8.34 (m, 1H), 7.97-8.09 (m, 2H), 7.81-7.88 (m, 1H), 7.67-7.74 (m, 1H), 7.18-7.25 (m, 1H), 6.96-7.15 (m, 1H), 6.25-6.40 (m, 1H), 5.01-5.35 (m, 1H), 3.75-4.17 (m, 2H), 3.59-3.66 (m, 2H), 3.47-3.58 (m, 1H), 3.28-3.39 (m, 1H), 2.98-3.04 (m, 3H), 2.16-2.27 (m, 1H), 1.97 (br s, 1H), 1.86-1.95 (m, 1H), 1.77-1.85 (m, 2H), 1.65-1.76 (m, 3H), 0.88-1.00 (m, 2H), 0.24-0.42 (br s, 4H
Compound 240	532.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (s, 1 H) 7.83 - 8.11 (m, 3 H) 7.75 - 7.82 (m, 1 H) 6.91 - 7.21 (m, 2 H) 3.76 - 4.00 (s, 2 H) 2.79 - 3.06 (m, 7 H) 1.61 - 1.43(m, 13 H) 1.03 - 1.30 (m, 4 H)
Compound 241	518.1 $(M+H)^+$	(DMSO-d^6) δ 9.59 (1 H, br s)) 7.81 - 8.40 (m, 4 H) 7.72 - 7.80 (m, 1 H) 6.78 - 7.25 (m, 2 H) 3.85 (s, 2 H) 3.19 (br s, 4 H) 2.80 - 3.03 (m, 3 H) 1.41 - 1.90 (m, 11 H) 0.93 - 1.38 (m, 3 H)
Compound 243	504.0 $(M+H)^+$	(DMSO-d^6) δ 9.61 (s, 1H), 8.00 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 7.72 -7.66 (m, 1H), 7.65 (s, 1H), 7.16 (d, J = 2.0 Hz, 2H), 5.72 (s, 2H), 3.93 (s, 2H), 2.94 (s, 3H), 2.60 (s, 4H), 1.09 (s, 9H)
Compound 245	558.2 $(M+H)^+$	(DMSO-d^6) δ 9.49 - 9.56 (m, 1 H), 7.91-7.98 (m, 3 H), 7.73 - 7.74 (m, 1 H), 6.99 - 7.12 (m, 2 H), 3.88 - 3.90 (br s, 2 H), 3.65 - 3.80 (m, 2 H), 2.91 (s, 3 H), 1.93 - 2.08 (m, 2 H), 1.56 - 1.75 (m, 6 H), 1.33 (s, 6 H), 0.85 - 0.90 (m, 2 H), 0.18 - 0.35 (m, 4 H)
Compound 247	562.1 $(M+H)^+$	(DMSO-d^6) δ 8.12-8.34 (m, 1H), 7.97-8.09 (m, 2H), 7.81-7.88 (m, 1H), 7.67-7.74 (m, 1H), 7.18-7.25 (m, 1H), 6.96-7.15 (m, 1H), 6.25-6.40 (m, 1H), 5.01-5.35 (m, 1H), 3.75-4.17 (m, 2H), 3.59-3.66 (m, 2H), 3.47-3.58 (m, 1H), 3.28-3.39 (m, 1H), 2.98-3.04 (m, 3H), 2.16-2.27 (m, 1H), 1.97 (br s, 1H), 1.86-1.95 (m, 1H), 1.77-1.85 (m, 2H), 1.65-1.76 (m, 3H), 0.88-1.00 (m, 2H), 0.24-0.42 (br s, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 249	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (s, 1 H) 7.87 - 8.18 (m, 4 H) 7.75 - 7.82 (m, 1 H) 7.14 (d, J=2.00 Hz, 2 H) 3.90 (br s, 2 H) 3.41 (dd, J=9.82, 7.19 Hz, 1 H) 3.30 (br s, 1 H) 3.16 - 3.26 (m, 1 H) 2.95 (s, 3 H) 2.72 (dd, J=9.88, 7.50 Hz, 1 H) 1.99 - 2.09 (m, 1 H) 1.87 (td, J=11.73, 6.69 Hz, 1 H) 1.46 - 1.76 (m, 6 H) 1.23 - 1.35 (m, 1 H) 0.88 (br d, J=11.76 Hz, 2 H) 0.80 (d, J=6.63 Hz, 3 H) 0.28 (br d, J=5.63 Hz, 4 H)
Compound 250	517.1 $(M+H)^+$	(DMSO-d^6) δ 8.22 - 7.93 (m, 3H), 7.91 (m, 1H), 7.86 - 7.74 (m, 3H), 3.96 (s, 2H), 3.40 (s ,4H), 2.99 - 2.82 (m, 4H), 1.76 - 1.60 (m, 6H), 1.54 (s, 5H), 1.38 (d, J = 4.0 Hz, 2H), 1.33 - 1.09 (m, 3H)
Compound 252	520.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (br s, 1 H), 7.92 - 8.04 (m, 2 H), 7.82 (br d, J=6.85 Hz, 1 H), 7.63 - 7.74 (m, 2 H), 7.01 - 7.16 (m, 2 H), 3.77 - 3.91 (m, 2 H), 2.94 (s, 3 H), 1.85 - 1.99 (m, 2 H), 1.62 - 1.84 (m, 2 H), 1.30 - 1.42 (m, 2 H), 1.20 - 1.27 (m, 2 H), 1.11 (s, 9 H), 0.92 - 1.04 (m, 3 H), 0.81 - 0.90 (m, 1 H).
Compound 254	556.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 - 9.63 (br s, 1 H), 7.89 - 8.11 (m, 3 H), 7.75 - 7.83 (m, 1 H), 7.04 - 7.18 (m, 2 H), 3.86 - 3.97 (s, 2 H), 3.42 (br d, J=9.26 Hz, 2 H), 3.11 - 3.21 (s, 2 H), 2.90 - 2.98 (s, 3 H), 1.57 - 1.74 (m, 6 H), 1.45 - 1.54 (m, 2 H), 0.81 - 0.96 (m, 2 H), 0.46 - 0.56 (m, 1 H), 0.19 - 0.37 (m, 4 H), -0.24 - 0.14 (m, 1 H).
Compound 255	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 - 9.63 (s, 1 H), 7.93 - 8.12 (m, 4 H), 7.79 - 7.88 (m, 1 H), 7.13 (s, 2 H), 5.64 (s, 1 H), 3.92 (br s, 2 H), 3.50 - 3.66 (m, 4 H), 2.94 (s, 3 H), 1.68 (s, 6 H), 1.16 (s, 3 H), 0.80 - 0.95 (m, 2 H), 0.27 (br s, 4 H).
Compound 257	566.0 $(M+H)^+$	(DMSO-d^6) δ 9.57 (br s, 1 H) 8.13 - 8.02 (m, 3 H) 7.83 (t, J = 7.60, 1 H) 7.11 (d, J=1.60 Hz, 2 H) 4.32 (t, J=12.80 Hz, 4 H) 3.83 - 3.82 (m, 2 H) 2.92 (s, 3 H) 1.67 - 1.61 (m, 6 H) 0.84 - 0.80 (m, 2 H) 0.26 - 0.22 (m, 4 H)
Compound 258	542.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1 H), 8.20-7.94 (m, 4 H), 7.89 - 7.81 (m, 1 H), 7.14 (s, 2 H), 4.95 (s, 2H), 4.41 (br s, 4 H), 4.00 -3.82 (m, 2H), 2.94 (s, 3 H), 1.77-1.49(m, 6H), 0.97-0.80(m, 2 H), 0.38-0.19 (m, 4 H)
Compound 260	544.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (br s , 1 H), 8.14 - 7.91 (m, 4 H), 7.86 - 7.82 (m, 1 H), 7.13 (J = 2.0 Hz, br d, 2 H), 3.92 - 3.86 (m, 4 H), 3.29 - 3.26 (m, 2 H), 2.94 (s, 3 H), 2.52 - 2.51 (m, 1 H), 1.68 (br s , 6 H), 0.86 (J = 6.8 Hz, br d, 5 H), 0.27 - 0.24 (m, 4 H)
Compound 261	558.7 $(M+H)^+$	(DMSO-d^6) δ 9.43 - 9.95 (br s, 1H), 8.08 - 8.18 (m, 1H), 7.81 – 8.00 (m, 3H), 7.66 - 7.78 (m, 1H), 7.05 - 7.20 (m, 2H), 3.81 - 3.95 (s, 2H), 3.57 - 3.75 (m, 1H), 3.00 - 3.11 (m, 2H), 1.83 - 1.94 (m, 2H), 1.43 - 1.76 (m, 10H), 1.15 - 1.22 (m, 3H), 0.82 - 0.91 (m, 2H), 0.19 - 0.33 (m, 4H)
Compound 262	552.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 - 9.74 (br s, 1 H) 8.40 (s, 1 H) 7.69 - 8.19 (m, 3 H) 6.94 - 7.24 (m, 2 H) 4.06 (s, 2 H) 2.89 (s, 3 H) 1.69-1.76 (m, 6 H) 1.19 (s, 9 H) 0.89-0.90 (m, 2 H) 0.24 (s, 4 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 264	555.1 $(M+H)^+$	(DMSO-d^6) δ 9.57 (br s, 1 H) 9.28 (br s, 1 H) 8.03 – 7.97 (m, 4 H) 7.82 - 7.78 (m, 1 H) 7.14 - 7.12 (m, 2 H) 3.91 (br s, 2 H) 2.95 (s, 3 H) 1.65 (br s, 6 H) 1.44 - 1.35 (m, 4 H) 0.83 (br s, 2 H) 0.25 (br s, 4 H)
Compound 266	559.2 $(M+H)^+$	(CD_3OD) δ 9.60 (brs, 1 H) 7.94 - 8.03 (m, 2 H) 7.83 (m, 1 H) 7.69 - 7.73 (m, 1 H) 7.57 (m, 1 H) 6.98 - 7.23 (m, 2 H) 3.88 (s, 2 H) 2.94 (s, 3 H) 1.57 - 1.65 (m, 6 H) 1.36 - 1.50 (m, 2 H) 1.04 (s, H) 0.85 - 0.88 (m, 2 H) 0.71 - 0.74 (m, 3 H) 0.27 (m, 4 H)
Compound 268	552.1 $(M+H)^+$	(DMSO-d^6) δ 9.60 (br s, 1H), 8.36 (s, 1H), 7.87-8.14 (m, 2H), 7.55-7.80 (m, 1H), 7.01-7.27 (m, 2H), 4.27 (s, 2H), 2.96 (s, 3H), 1.62-1.92 (m, 6H), 1.17 (s, 9H), 0.86-1.02 (m, 2H), 0.31 ppm (br s, 4H)
Compound 269	566.1 $(M+H)^+$	(DMSO-d^6) δ 9.69 (br s, 1H), 8.35 (s, 1H), 7.96 (m, 2H), 7.65 (s, 1H), 7.01-7.24 (m, 2H), 4.19-4.38 (m, 2H), 3.05 (q, 2H), 1.62-1.89 (m, 6H), 1.07-1.29 (m, 12H), 0.92 (br d, J = 13.0 Hz, 2H), 0.31 (br s, 4H)
Compound 270	527.1 $(M+H)^+$	(DMSO-d^6) δ 9.64 - 9.54 (m, 1H), 8.20 - 8.00 (m, 1H), 7.92 - 7.80 (m, 2H), 7.78 - 7.66 (m, 2H), 7.19 - 7.07 (m, 2H), 3.99 - 3.79 (s, 2H), 2.97 - 2.91 (s, 3H), 1.94 - 1.75 (m, 4H), 1.72 - 1.64 (m, 4H), 1.61 - 1.49 (m, 6H), 1.44 - 1.36 (m, 1H), 0.92 - 0.83 (m, 2H), 0.32 - 0.21 (m, 4H)
Compound 272	600.0 $(M+H)^+$	(DMSO-d^6) δ 9.81 - 9.58 (m, 1 H), 8.57 (s, 1 H), 8.11 – 7.82 (m, 2 H), 7.24 - 7.01 (m, 2 H), 4.58 - 4.31 (s, 2 H), 3.86 - 3.71 (m, 6 H), 3.14 – 2.99 (m, 2 H), 2.16 – 1.99 (m, 2H), 1.96 - 1.84 (m,8 H), 1.67 - 1.61 (m, 2 H), 1.30 - 1.13 (m, 3 H)
Compound 274	582.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1 H) 8.38 (s, 1 H) 8.08 – 7.94 (m, 1 H) 7.93 - 7.80 (m, 2 H) 7.18 - 7.01 (m, 2 H) 4.93 (br d, J=2.00 Hz, 1 H) 4.07 (s, 2 H) 3.73 (br d, J=2.00 Hz, 2 H) 3.19 (t, J=6.75 Hz , 2 H) 1.78 - 1.58 (m, 6 H) 1.20 (s, 9 H) 0.89 (br d, J=10.51 Hz, 2 H) 0.29 (s, 4 H)
Compound 275	566.1 $(M+H)^+$	(DMSO-d^6) δ 9.66 (br s,1 H), 8.37 (s, 1 H), 8.07 (m, 1 H), 7.92 - 7.82 (m, 2 H), 7.13 (d, J=1.97 Hz, 2 H), 4.06 (s, 2 H), 3.03 (m, 2 H), 1.80 - 1.58 (m, 6 H), 1.21 - 1.15 (m, 12 H), 0.88 (br d, J=10.74 Hz, 2 H), 0.29 (s, 4 H)
Compound 277	562.0 $(M+H)^+$	(DMSO-d^6) δ 9.59 (s, 1H), 8.41 (s, 1H), 8.19 - 7.95 (m, 1H), 7.93 - 7.82 (m, 2H), 7.18 - 7.01 (m, 2H), 4.18 (s, 2H), 2.96 (s, 3H), 2.14 - 1.73 (m, 8H), 1.20 (s, 9H)
Compound 279	576.1 $(M+H)^+$	(DMSO-d^6) δ 9.58 (br s, 1 H), 8.56 (s, 1 H), 8.03 (br s, 2 H), 7.18 - 7.04 (m, 2 H), 4.07 (s, 2 H), 3.82 (s, 4 H), 2.95 (s, 3 H), 1.99 - 1.89 (m, 4 H), 1.68 (br s, 8 H), 0.88 (br d, J=5.63 Hz, 2 H), 0.36 - 0.21 (m, 4 H)
Compound 281	600.0 $(M+H)^+$	(DMSO-d^6) δ 9.67 - 9.49 (m, 1H), 8.65 - 8.52 (m, 1H), 8.14 - 7.91 (m, 2H), 7.21 - 7.01 (m, 2H), 4.20 - 4.05 (m, 2H), 3.22 - 3.11 (m, 4H), 2.96 - 2.82 (m, 3H), 2.22 - 2.06 (m, 4H), 1.80 - 1.59 (m, 6H), 0.93 - 0.82 (m, 2H), 0.41 - 0.20 (m, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 283	578.0 $(M+H)^+$	(DMSO-d^6) δ 9.69 - 9.51 (m, 1H), 8.56 (br s, 1H,), 8.18 - 8.01 (m, 2H), 7.19 - 7.00 (m, 2H), 4.31 (t, J = 7.4 Hz, 2H,), 4.18 (d, J = 11.0 Hz, 2H,), 4.06 (s, 2H, s), 3.85 (d, J = 10.9 Hz, 2H,), 2.94 (s, 3H), 2.72 (br t, J = 7.4 Hz, 2H), 1.85 - 1.60 (m, 6H), 0.96 - 0.82 (m, 2H), 0.28 (s, 4H)
Compound 284	524.0 $(M+H)^+$	(DMSO-d^6) δ 9.61 - 9.52 (m, 1H), 8.50 - 8.22 (m, 2H), 8.12 - 7.73 (m, 2H), 7.16 - 6.90 (m, 2H), 4.11 - 3.92 (m, 2H), 3.81 - 3.66 (m, 1H), 3.00 - 2.87 (m, 3H), 2.08 - 1.93 (m, 2H), 1.87 - 1.74 (m, 2H), 1.68 - 1.46 (m, 10H), 1.36 - 1.12 (m, 3H)
Compound 285	572.2 $(M+H)^+$	(DMSO-d^6) δ 9.59 (s, 1 H) 8.15 – 7.91 (m, 3 H) 7.90 - 7.79 (m, 2 H) 7.77 - 7.70 (m, 1 H) 7.14 (m, 2 H) 3.89 (s, 2 H) 3.64 - 3.43 (m, 1 H) 2.95 (s, 3 H) 2.05 – 1.91 (m, 1 H) 1.84 - 1.45 (m, 9 H) 1.38 - 1.05 (m, 2 H) 0.99 - 0.79 (m, 6 H) 0.27 (br d, J=9.13 Hz, 4 H)
Compound 287	542.1 $(M+H)^+$	(DMSO-d^6) δ 9.60 - 9.54 (m, 1 H) 8.11 - 8.01 (m, 3 H) 7.93 - 7.84 (m, 1 H) 7.78 - 7.71 (m, 1 H) 7.15 - 7.11 (m, 2 H) 4.30 - 4.26 (s, 1 H) 3.96 - 3.83 (s, 2 H) 3.73 - 3.62 (m, 1 H) 2.99 - 2.90 (s, 3 H) 1.95 - 1.83 (m, 2 H) 1.74 - 1.63 (m, 6 H) 1.62 - 1.46 (m, 6 H) 0.96 - 0.80 (m, 2 H) 0.34 - 0.20 (m, 4 H)
Compound 289	556.0 $(M+H)^+$	(DMSO-d^6) δ 9.59 (s, 1H), 8.36 (br s, 1H), 8.12 - 7.94 (m, 1H), 7.94 - 7.77 (m, 2H), 7.12 (d, J = 1.8 Hz, 1H), 7.10 - 6.96 (m, 1H), 5.28 - 4.60 (m, 1H), 4.01 (s, 2H), 3.73 (t, J = 6.7 Hz, 2H), 3.18 (t, J = 6.7 Hz, 2H), 1.65 (br d, J = 11.7 Hz, 5H), 1.58 - 1.44 (m, 2H), 1.33 - 1.23 (m, 3H), 1.19 (s, 9H)
Compound 291	550.0 $(M+H)^+$	(DMSO-d^6) δ 9.71 - 9.45 (m, 1 H), 8.44 - 8.28 (m, 2 H), 7.85 (br s, 2 H), 7.17 - 7.02 (m, 2 H), 4.06 (s, 2 H), 3.76 (br s, 1 H), 2.94 (s, 3 H), 2.08 – 1.96 (m, 2 H), 1.91 - 1.48 (m, 11 H), 0.88 (br d, J=8.38 Hz, 2 H), 0.29 (br s, 4 H)
Compound 292	631.2 $(M+H)^+$	(DMSO-d^6) δ 8.20 – 7.97 (m, 3 H), 7.89 - 7.76 (m, 1 H), 7.75 - 7.62 (m, 1 H), 7.25 - 7.02 (m, 2 H), 4.06 – 3.84 (m, 2 H), 3.27 - 3.17 (m, 2 H), 3.15 – 2.96 (m, 2 H), 2.05 – 1.80 (m, 7 H), 1.78 - 1.50 (m, 4 H), 1.33 - 1.11 (m, 9 H), 1.06 – 0.82 (m, 2 H), 0.47 - 0.09 (m, 4 H)
Compound 293	594.1 $(M+H)^+$	(DMSO-d^6) δ 9.86 - 9.44 (m, 1 H), 8.55 - 8.22 (m, 1 H), 8.11 - 7.86 (m, 4 H), 7.80 - 7.69 (m, 1 H), 7.20 - 7.01 (m, 2 H), 3.97 - 3.78 (m, 2 H), 3.70 - 3.55 (m, 1 H), 3.10 – 2.97 (m, 2 H), 2.80 - 2.67 (m, 2 H), 2.43 - 2.35 (m, 2 H), 1.76 - 1.49 (m, 6 H), 1.27 - 1.10 (m, 3 H), 0.97 - 0.76 (m, 2 H), 0.37 - 0.14 (m, 4 H)
Compound 295	532.1 $(M+H)^+$	(DMSO-d^6) δ 9.62 (br s, 1 H), 8.08 – 7.92 (m, 3 H), 7.80 (br d, J=6.63 Hz, 1 H), 7.74 - 7.63 (m, 2 H), 7.10 (d, J=1.75 Hz, 2 H), 5.34 (br s, 1 H), 3.86 - 3.75 (m, 1 H), 3.74 - 3.61 (m, 1 H), 2.94 (s, 3 H), 2.22 - 2.04 (m, 2 H), 2.02 – 1.89 (m, 2 H), 1.87 - 1.75 (m, 1 H), 1.72 - 1.52 (m, 4 H), 1.09 (s, 9 H)
Compound 297	576.1 $(M+H)^+$	(DMSO-d^6) δ 9.65 - 9.46 (m, 1 H) 8.03 – 7.93 (m, 1 H) 7.87 (br d, J=7.50 Hz, 1 H) 7.37 - 7.28 (m, 1 H) 7.25 - 7.18 (m, 1 H) 7.15 - 7.10 (m, 1 H) 7.04 (br d, J=8.88 Hz, 1 H) 4.00 (s, 3 H) 3.93 (s, 2 H) 2.98 - 2.89 (m, 3 H) 1.74 - 1.56 (m, 6 H) 1.10 (s, 9 H) 0.93 - 0.82 (m, 2 H) 0.36 - 0.20 (m, 4 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 298	562.1 $(M+H)^+$	(DMSO-d^6) δ 11.64 – 10.86 (m, 1 H) 9.64 - 9.45 (m, 1 H) 7.99 - 7.82 (m, 1 H) 7.74 - 7.54 (m, 1 H) 7.23 – 6.81 (m, 4 H) 4.03 – 3.85 (s, 2 H) 3.03 – 2.86 (s, 3 H) 1.75 - 1.56 (m, 6 H) 1.13 (s, 9 H) 0.97 - 0.81 (m, 2 H) 0.37 - 0.16 (m, 4 H)
Compound 299	536.1 $(M+H)^+$	(DMSO-d^6) δ 9.71 - 9.10 (m, 1 H) 8.43 - 8.31 (m, 1 H) 8.13-7.95 (m, 1 H) 7.47 - 7.28 (m, 1 H) 7.23 – 6.99 (m, 3 H) 4.40 - 4.17 (s, 2 H) 3.03 – 2.86 (s, 3 H) 1.99 - 1.78 (m, 2 H) 1.75 - 1.56 (m, 4 H) 1.26 - 1.13 (s, 9 H) 0.99 - 0.82 (m, 2 H) 0.42 - 0.17 (s, 4 H)
Compound 301	515.1 $(M+H)^+$	(DMSO-d^6) δ 9.08 – 8.37 (m, 1 H) 8.02 – 7.90 (m, 1 H) 7.29 - 7.20 (m, 1 H) 7.14 – 6.99 (m, 2 H) 5.73 - 5.64 (m, 1 H) 4.65 - 4.53 (m, 1 H) 4.13 – 3.97 (m, 2 H) 2.96 - 2.90 (m, 3 H) 2.19 - 2.09 (m, 1 H) 1.86 - 1.37 (m, 14 H) 0.95 - 0.84 (m, 2 H) 0.34 - 0.23 (m, 4 H)
Compound 302	596.0 $(M+H)^+$	(DMSO-d^6) δ 9.66 - 9.49 (m, 1 H, m) 8.14 – 7.92(m, 2 H) 7.42 (d, J=8.55 Hz, 1 H) 7.17 – 6.93 (m, 2 H) 4.57 - 4.33 (m, 4 H) 4.09 - 4.00 (m, 5 H) 2.93 (s, 3 H) 1.76 - 1.53 (m, 6 H) 0.95 - 0.78 (m, 2 H) 0.36 - 0.17 (m, 4 H)
Compound 303	582.0 $(M+H)^+$	(DMSO-d^6) δ 11.64 - 11.90 (m, 1 H) 9.43 - 9.61 (m, 1 H) 7.69 - 7.95 (m, 2 H) 6.93 - 7.18 (m, 3 H) 4.43 (t, J=12.88 Hz, 4 H) 3.95 (s, 2 H) 2.93 (s, 3 H) 1.55 - 1.76 (m, 6 H) 0.76 - 1.01 (m, 2 H) 0.28 (s, 4 H)
Compound 305	509.3 $(M+H)^+$	(DMSO-d^6) δ 9.62 (s, 1H), 8.19 - 7.87 (m, 1H), 7.55 - 7.39 (m, 4H), 7.16 - 6.94 (m, 2H), 5.18 (d, J = 4.3 Hz, 1H), 4.56 - 4.45 (m, 1H), 3.96 - 3.84 (m, 2H), 2.94 (s, 3H), 2.35 - 2.20 (m, 1H), 1.97 - 1.47 (m, 14H), 0.89 (br d, J = 11.3 Hz, 2H), 0.27 (br d, J = 5.5 Hz, 4H)
Compound 306	529.1 $(M+H)^+$	(DMSO-d^6) δ 9.56 (br s, 1H), 8.22 - 7.92 (m, 1H), 7.83 - 7.57 (m, 4H), 7.19 - 6.95 (m, 2H), 3.89 (br s, 2H), 2.94 (s, 3H), 2.86 - 2.71 (m, 1H), 1.79 - 1.45 (m, 14H), 0.89 (br d, J = 12.0 Hz, 2H), 0.28 (br s, 4H)
Compound 309	564.1 $(M+H)^+$	(DMSO-d^6) δ 9.70 - 9.33 (m, 1H), 8.08 - 8.03 (m, 1H), 7.99 (br d, J = 7.8 Hz, 1H), 7.91 - 7.78 (m, 1H), 7.76 - 7.67 (m, 2H), 7.32 - 7.17 (m, 1H), 3.92 (br s, 2H), 3.07 - 2.91 (m, 3H), 1.82 - 1.47 (m, 6H), 1.19 - 1.03 (m, 9H), 0.93 - 0.75 (m, 2H), 0.37 - 0.15 (m, 4H)
Compound 310	564.1 $(M+H)^+$	(DMSO-d^6) δ 9.81 - 9.25 (m, 1 H), 8.09 - 8.02 (m, 1 H), 8.02 – 7.95 (m, 1 H), 7.90 - 7.80 (m, 1 H), 7.76 - 7.62 (m, 2 H), 7.32 - 7.11 (m, 1 H), 4.03 – 3.86 (s, 2 H), 3.02 – 2.89 (s, 3 H), 2.05 – 1.95 (m, 2 H), 1.82 - 1.49 (m, 4 H), 1.11 (s, 9 H), 0.89 - 0.70 (m, 2 H), 0.33 - 0.14 (m, 4 H)
Compound 311	586.1 $(M+H)^+$	($CDCl_3$) δ 8.16 (br s, 1 H) 7.89 (br d, J=7.88 Hz, 1 H) 7.21 (s, 1 H) 7.17 (d, J=8.63 Hz, 1 H) 7.10 – 6.86 (m, 1 H) 6.53 - 6.42 (m, 1 H) 5.62 (br d, J=3.25 Hz, 1 H) 4.09 (s, 3 H) 3.99 (br s, 2 H) 2.99 (s, 3 H) 2.33 (s, 1 H) 1.91 - 1.64 (m, 12 H) 0.92 (br d, J=11.51 Hz, 2 H) 0.31 (s, 4 H)
Compound 312	495.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 (br s, 1 H,) 8.24 – 7.41 (m, 5 H) 7.11 – 6.80 (m, 2 H) 5.26 (d, J=4.50 Hz, 1 H) 4.49 (dd, J=6.88, 4.75 Hz, 1

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
		H) 3.89 (br s, 2 H) 2.93 (s, 3 H) 2.61 - 2.78 (m, 1 H) 2.32 - 1.74 (m, 4 H, m) 1.71 – 1.65 (m, 8 H) 0.91 – 0.88 (m, 2 H) 0.28 (br s, 4 H)
Compound 313	495.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 (br s, 1 H,) 8.24 – 7.41 (m, 5 H) 7.11 – 6.80 (m, 2 H) 5.26 (d, J=4.50 Hz, 1 H) 4.49 (dd, J=6.88, 4.75 Hz, 1 H) 3.89 (br s, 2 H) 2.93 (s, 3 H) 2.61 - 2.78 (m, 1 H) 2.32 - 1.74 (m, 4 H, m) 1.71 – 1.65 (m, 8 H) 0.91 – 0.88 (m, 2 H) 0.28 (br s, 4 H)
Compound 314	546.1 $(M+H)^+$	(DMSO-d^6) δ 9.55 (br s, 1 H), 7.59 - 7.41 (m, 4 H), 7.13 (d, J=1.88 Hz, 2 H), 5.40 (d, J=4.50 Hz, 1 H), 4.69 - 4.60 (m, 1 H), 3.89 (br s, 2 H), 3.66 - 3.49 (m, 4 H), 2.94 (s, 3 H), 2.75 (m, 2 H), 1.73 - 1.54 (m, 6 H), 0.95 - 0.84 (m, 2 H), 0.28 (br s, 4 H)
Compound 315	574.1 $(M+H)^+$	(DMSO-d^6) δ 8.46 (br d, J=1.59 Hz, 1 H) 7.38 - 7.62 (m, 5 H) 7.17 (d, J=2.20 Hz, 1 H) 7.03 (m, 1 H) 4.98 (br s, 1 H) 4.79 (m, 1 H) 3.90 (s, 2 H) 2.90 - 2.96 (m, 3 H) 2.65 – 2.56 (m, 6 H)1.83 - 1.99 (m, 4 H) 1.56 - 1.80 (m, 6 H) 0.92 - 1.04 (m, 2 H) 0.24 - 0.38 (m, 4 H)
Compound 316	510.6 $(M+H)^+$	(DMSO-d^6) δ 9.64 (br d, J=5.26 Hz, 1H), 8.69 - 8.57 (d, 1H), 8.11 – 7.98 (d, 1H), 7.66 - 7.54 (s, 1H), 7.45 (m, 1H), 7.16 (m, 2H), 5.46 (d, 1H), 4.57 - 4.46 (t, 1H), 3.75 (m, 2H), 2.95 (s, 3H), 1.70 - 1.36 (m, 15H), 0.91 - 0.80 (m, 2H), 0.32 - 0.21 (m, 4H)
Compound 317	510.3 $(M+H)^+$	(DMSO-d^6) δ 9.56 (s, 1 H), 8.14 (d, J=8.38 Hz, 1 H), 8.01 – 7.93 (m, 1 H), 7.74 - 7.66 (m, 1 H), 7.62 (d, J=7.63 Hz, 1 H), 7.18 - 7.04 (m, 2 H), 5.45 (d, J=5.00 Hz, 1 H), 4.53 - 4.44 (m, 1 H), 4.35 (d, J=11.2 Hz, 1 H), 4.12 (d, J=11.6 Hz, 1 H), 2.95 (s, 3 H), 2.43 - 2.35 (m, 1 H), 1.74 - 1.39 (m, 14 H), 0.95 - 0.79 (m, 2 H), 0.36 - 0.21 (m, 4 H)
Compound 318	521.2 $(M+H)^+$	(DMSO-d^6) δ 9.66 - 9.46 (m, 1 H), 8.15 – 7.90 (m, 1 H), 7.78 - 7.62 (m, 3 H), 7.54 - 7.38 (m, 2 H), 6.38 - 7.97 (m, 2 H), 4.01 – 3.83 (s, 2 H), 3.20-3.07 (s, 4 H), 3.00 – 2.87 (m, 3 H), 1.83 - 1.43 (m, 12 H), 0.98 - 0.80 (m, 2 H), 0.38 - 0.14 (m, 4 H)
Compound 319	510.1 $(M+H)^+$	(DMSO-d^6) δ 9.60 (s, 1H), 8.58 (s, 1H), 8.05 (s, 2H), 7.37 (s, 1H), 7.12 (d, J = 2.1 Hz, 1H), 7.06 (brd, J = 8.5 Hz, 1H), 4.09 (s, 2H), 2.95 (s, 3H), 1.65 (br d, J = 10.5 Hz, 5H), 1.54 (br t, J = 11.4 Hz, 2H), 1.45 - 1.23 (m, 3H), 1.18 (s, 9H).
Compound 320	586.1 $(M+H)^+$	(DMSO-d^6) δ 9.78 - 9.56 (m, 1H), 8.15 – 7.91 (m, 4H), 7.87 - 7.77 (m, 1H), 7.21 – 6.97 (m, 2H), 4.26 (br t, J = 7.4 Hz, 2H), 4.09 (br d, J = 10.5 Hz, 2H), 3.89 (br s, 2H), 3.79 - 3.68 (m, 2H), 3.12- 3.00 (m, 2H), 2.71 - 2.60 (m, 2H), 1.78 - 1.51 (m, 6H), 1.27 - 1.14 (m, 3H), 0.86 (br d, J = 4.5 Hz, 2H), 0.39 - 0.14 (m, 4H)
Compound 321	560.1 $(M+H)^+$	(DMSO-d^6) δ 9.69 - 9.57 (m, 1 H) 8.14 - 8.00 (m, 1 H) 7.58 - 7.51 (m, 1 H) 7.50 - 7.43 (m, 1 H) 7.21 - 7.02 (m, 2 H) 4.51 - 4.24 (m, 2 H) 3.98 - 3.79 (m, 4 H) 3.00 - 2.92 (m, 3 H) 2.01 - 1.91 (m, 4 H) 1.90 - 1.78 (m, 2 H) 1.75 (br d, J=2.88 Hz, 6 H) 0.97 - 0.88 (m, 2 H) 0.43 - 0.21 (m, 4 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 322	565.0 $(M+H)^+$	(DMSO-d^6) δ 9.68 - 9.41 (m, 1 H) 8.23 - 7.94 (m, 4 H) 7.88 - 7.76 (m, 1 H) 7.21 - 7.03 (m, 2 H) 4.35 - 4.17 (m, 1 H) 4.01 – 3.78 (m, 2 H) 3.12 – 2.86 (m, 7 H) 1.85 - 1.44 (m, 6 H) 1.04 – 0.75 (m, 2 H) 0.42 - 0.11 (m, 4 H)
Compound 323		(DMSO-d^6) δ 8.08 – 7.94 (m, 2 H) 7.89 - 7.78 (m, 1 H) 7.76 - 7.69 (m, 1 H) 7.69 - 7.62 (m, 1 H) 7.54 - 7.45 (m, 1 H) 7.45 - 7.30 (m, 1 H) 4.69 (s, 1 H) 4.01 – 3.87 (m, 2 H) 3.30 (s, 1 H) 2.29 - 2.15 (m, 2 H) 2.05 – 1.88 (m, 6 H) 1.13 - 1.06 (m, 9 H)
Compound 324	532.1 $(M+H)^+$	(DMSO-d^6) δ 9.61 (br s, 1 H) 8.12 – 7.92 (m, 2 H) 7.90 - 7.76 (m, 1 H) 7.75 - 7.64 (m, 2 H) 7.18 - 7.03 (m, 1 H) 5.35 (br d, J=10.08 Hz, 1 H) 4.77 - 4.64 (m, 1 H) 4.03 – 3.65 (m, 2 H) 2.95 (s, 3 H) 2.31 – 1.75 (m, 6 H) 1.67 - 1.53 (m, 2 H) 1.13 - 1.07 (m, 9 H)
Compound 325		(DMSO-d^6) δ 8.45 – 7.95 (m, 4H), 7.90 - 7.74 (m, 1H), 7.57 - 7.26 (m, 2H), 3.91 (br s, 2H), 3.60 - 3.45 (m, 1H), 1.84 - 1.53 (m, 6H), 1.25 - 1.13 (m, 6H), 0.94 - 0.73 (m, 2H), 0.26 (br s, 4H)
Compound 326	517.1 $(M+H)^+$	(DMSO-d^6) δ 9.74 - 9.46 (m, 1H), 8.19 – 7.93 (m, 4H), 7.82 (t, J = 7.8 Hz, 1H), 7.26 – 6.96 (m, 2H), 4.10 – 3.81 (m, 2H), 3.61 - 3.43 (m, 1H), 2.94 (s, 3H), 1.82 - 1.47 (m, 6H), 1.29 - 1.04 (m, 6H), 0.97 - 0.78 (m, 2H), 0.27 (br s, 4H)
Compound 327	570.0 $(M+H)^+$	(DMSO-d^6) δ 9.69 (br s, 1H), 8.23 – 7.93 (m, 3H), 7.91 - 7.79 (m, 1H), 7.76 - 7.59 (m, 2H), 7.24 - 7.01 (m, 2H), 4.12 – 3.89 (m, 2H), 3.07 (q, J = 7.0 Hz, 2H), 2.04 (br s, 2H), 1.82 (br d, J = 11.9 Hz, 6H), 1.27 - 1.16 (m, 3H), 1.13 (s, 9H)
Compound 329	552.2 $(M+H)^+$	(CD_3OD) δ 8.41 - 7.98 (m, 3 H) 7.66 - 7.88 (m, 2 H) 7.03 - 7.34 (m, 2 H) 3.83 - 4.09 (m, 2 H) 2.95 (s, 3 H) 1.99 - 2.15 (m, 2 H) 1.73 - 1.96 (m, 3 H) 1.44 - 1.70 (m, 4 H) 1.30 - 1.39 (m, 2 H) 1.17 - 1.25 (m, 9 H)
Compound 330	549.3 $(M+H)^+$	(DMSO-d^6) δ 9.53 - 9.62 (m, 1 H) 8.55 - 8.67 (m, 1 H) 7.94 - 8.16 (m, 2 H) 7.00 - 7.18 (m, 2 H) 4.05 - 4.11 (m, 2 H) 3.87 - 3.98 (m, 1 H) 2.90 - 2.98 (m, 3 H) 1.90 - 1.99 (m, 4 H) 1.51 - 1.82 (m, 12 H) 0.25 - 0.34 (m, 4 H)
Compound 331	523.2 $(M+H)^+$	($CDCl_3$) δ 9.73 - 9.43 (m, 1H), 8.30 – 7.83 (m, 1H), 7.75 - 7.53 (m, 2H), 7.51 - 7.31 (m, 2H), 7.23 – 6.88 (m, 2H), 4.87 (s, 1H), 4.07 – 3.77 (m, 2H), 2.93 (s, 3H), 2.29 - 2.15 (m, 1H), 1.78 - 1.33 (m, 15H), 1.31 - 1.01 (m, 2H), 0.98 - 0.80 (m, 2H), 0.42 - 0.13 (m, 4H)
Compound 332	497.3 $(M+H)^+$	(DMSO-d^6) δ 8.11 – 7.90 (m, 3 H) 7.87 - 7.79 (m, 1 H) 7.75 - 7.67 (m, 2 H) 7.29 (s, 2 H) 5.14 (br d, J=2.25 Hz, 1 H) 4.71 (br d, J=3.13 Hz, 1 H) 3.88 (br d, J=8.76 Hz, 2 H) 1.83 - 1.54 (m, 6 H) 1.35 - 1.25 (m, 3 H) 1.11 (s, 9 H) 0.92 - 0.77 (m, 2 H) 0.33 - 0.19 (m, 4 H)
Compound 333a	584.1 $(M+H)^+$	(DMSO-d^6) δ 9.77 - 9.61 (m, 1 H) 8.10 – 7.92 (m, 3 H) 7.82 (br s, 3 H) 7.19 - 7.03 (m, 2 H) 6.05 – 5.04 (m, 1 H) 3.92 - 3.75 (m, 2 H) 3.11 – 2.97 (m, 2 H) 2.01 – 1.55 (m, 7 H) 1.25 (br s, 14 H)
Compound 333b	584.1 $(M+H)^+$	(DMSO-d^6) δ 9.71 - 9.59 (m, 1 H) 8.08 – 7.91 (m, 3 H) 7.87 - 7.63 (m, 3 H) 7.42 - 7.35 (m, 1 H) 7.20 - 7.01 (m, 1 H) 6.28 –

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
		5.96 (m, 1 H) 3.82 - 3.74 (m, 1 H) 3.08 - 3.00 (m, 2 H) 1.96 - 1.77 (m, 2 H) 1.97 - 1.49 (m, 9 H) 1.25 - 1.06 (m, 12 H)
Compound 335	543.1 $(M+H)^+$	(DMSO-d^6) δ 9.65 - 9.52 (m, 1 H), 8.17 – 7.92 (m, 4 H), 7.84 - 7.75 (m, 1 H), 7.20 - 7.04 (m, 2 H), 4.00 – 3.79 (m, 2 H), 3.60 - 3.49 (m, 2 H), 3.01 – 2.88 (m, 3 H), 1.94 - 1.46 (m, 13 H), 0.95 - 0.79 (m, 2 H), 0.26 (br d, J=8.76 Hz, 4 H)
Compound 336a	580.1 $(M+H)^+$	(DMSO-d^6) δ 9.71 - 9.53 (m, 1 H) 8.81 - 8.69 (m, 1 H) 8.10 – 7.67(m, 5 H) 7.17 – 6.99 (m, 2 H) 6.03 – 5.65 (m, 1 H) 3.92 - 3.73 (m, 2 H) 2.97 - 2.93 (m, 3 H) 2.26 (s, 1 H) 1.79 - 1.60 (m, 13 H) 1.12 – 0.91 (m, 2 H)
Compound 336b	580.1 $(M+H)^+$	(DMSO-d^6) δ 9.67 - 9.42 (m, 1 H) 8.83 - 8.64 (m, 1 H) 8.15 – 7.65 (m, 5 H) 7.40 - 7.34 (m, 1 H) 7.18 - 7.00 (m, 1 H) 6.33 – 5.97 (m, 1 H) 3.88 - 3.72 (m, 2 H) 2.97 - 2.93 (m, 3 H) 2.30 - 2.29 (m, 1 H) 1.85 - 1.53 (m, 15 H)
Compound 337	574.1 $(M+H)^+$	(DMSO-d^6) δ 9.65 - 9.50 (m, 1 H) 9.15 - 9.00 (m, 1 H) 8.05 - 7.95 (m, 2 H) 7.60 (dd, J=9.88, 8.63 Hz, 1 H) 7.19 - 7.00 (m, 2 H) 3.91 (br s, 2 H) 2.94 (s, 3 H) 2.29 (s, 1 H) 1.75 (s, 6 H) 1.71 - 1.54 (m, 6 H) 0.92 - 0.80 (m, 2 H) 0.26 (br d, J=6.75 Hz, 4 H)
Compound 338	551.1 $(M+H)^+$	(DMSO-d^6) δ 8.13 - 7.95 (m, 2 H), 7.90 - 7.79 (m, 1 H), 7.76 - 7.64 (m, 2 H), 7.45 - 7.26 (m, 2 H), 6.87 - 6.74 (m, 1 H), 5.22 - 5.08 (s, 1 H), 4.01 - 3.82 (s, 2 H), 1.84 - 1.49 (m, 6 H), 1.19 - 1.03 (m, 9 H), 0.93 - 0.79 (m, 2 H), 0.38 - 0.16 (m, 4 H)
Compound 339	518.1 $(M+H)^+$	(DMSO-d^6) δ 9.62 - 9.52 (m, 1H), 8.16 - 7.93 (m, 1H), 7.71 - 7.50 (m, 4H), 7.18 - 7.03 (m, 2H), 4.31 - 4.22 (m, 1H), 3.96 - 3.84 (m, 2H), 3.35 (s, 1H), 2.99 - 2.91 (m, 3H), 2.46 - 2.31 (m, 1H), 1.81 - 1.74 (m, 1H), 1.65 (br s, 6H), 1.60 - 1.39 (m, 5H), 1.32 - 1.20 (m, 1H), 0.94 - 0.82 (m, 2H), 0.37 - 0.19 (m, 4H)
Compound 340	578.1 $(M+H)^+$	(DMSO-d^6) δ 9.72 - 9.60 (m, 1 H), 8.11 – 7.88 (m, 3 H), 7.62 - 7.50 (m, 1 H), 7.18 – 6.99 (m, 2 H), 3.97 - 3.80 (s, 2 H), 3.11 – 2.97 (s, 2 H), 1.75 - 1.50 (m, 6 H), 1.25 - 1.08 (m, 12 H), 0.93 - 0.79 (m, 2 H), 0.37 - 0.18 (m, 4 H)
Compound 341	558.1 $(M+H)^+$	(DMSO-d^6) δ 9.86 - 9.10 (m, 1 H) 8.54 -7.75 (m, 1 H) 7.56 - 7.42 (m, 4 H) 7.21 – 6.80 (m, 2 H) 3.99 - 3.85 (m, 2 H) 3.83 - 3.54 (m, 1 H) 3.50 - 3.38 (m, 2 H) 2.95 - 2.92 (m, 3 H) 1.95 - 1.86 (m, 4 H) 1.77 - 1.49 (m, 8 H) 1.39 - 1.33 (m, 3 H) 0.92 - 0.82 (m, 2 H) 0.32 - 0.23 (m, 4 H)
Compound 342	545.1 $(M+H)^+$	(DMSO-d^6) δ 9.66 - 9.54 (m, 1H), 8.20 - 8.09 (m, 1H), 8.04 - 7.93 (m, 1H), 7.73 (br d, J = 7.6 Hz, 1H), 7.65 - 7.53 (m, 1H), 7.20 - 7.03 (m, 2H), 4.27 - 4.16 (m, 2H), 3.79 - 3.72 (m, 2H), 3.02 - 2.86 (s, 3H), 2.69 - 2.55 (m, 4H), 2.05 - 1.91 (m, 4H), 1.75 - 1.57 (m, 6H), 0.95 - 0.85 (m, 2H), 0.39 - 0.19 (m, 4H)
Compound 343	560.1 $(M+H)^+$	(CD_3OD) δ 8.18 (d, J=8.63 Hz, 1 H) 7.68 (s, 1 H) 7.26 - 7.12 (m, 2 H) 4.28 - 4.05 (m, 4 H) 3.12 – 2.91 (m, 7 H) 2.67 (s, 3 H) 2.25 - 2.06 (m, 4 H) 1.92 - 1.64 (m, 6 H) 0.95 (br d, J=12.76 Hz, 2 H) 0.42 - 0.27 (m, 4 H)
Compound 345	516.2 $(M+H)^+$	(CD_3OD) δ δ 8.07 (m, 1H), 7.56-7.53 (m, 4H), 7.20-7.10 (m, 2H), 4.03-3.90(m, 4H), 3.82-3.72 (m, 4H), 2.92 (s, 3H), 1.85-1.61 (m, 6 H), 0.97-0.94 (m, 2H), 0.26 (brs, 4H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 346	496.1 $(M+H)^+$	(DMSO-d^6) δ 9.83 (s, 1H), 8.03-8.00 (br s, 1H), 7.50-7.43 (m, 4H), 7.12-6.97 (m, 2H), 4.01 (s, 2H), 3.71-3.90(m, 2H), 3.02-2.97 (m, 1H), 2.93 (s, 3), 2.81 (m, 1 H), 2.22-2.19 (m, 2H), 1.65 (m, 6H), 0.94-0.88 (m, 2H), 0.27 (br s, 4H)
Compound 347	494.1 $(M+H)^+$	(DMSO-d^6) δ 9.54 - 9.48 (m, 1 H) 7.20 - 7.10 (m, 2 H) 7.07 – 6.94 (m, 1 H) 6.72 - 6.62 (m, 3 H) 5.88 - 5.81 (m, 1 H) 3.93 - 3.86 (m, 2 H) 3.76 - 3.66 (m, 1 H) 2.94 - 2.91 (m, 3 H) 1.96 - 1.86 (m, 2 H) 1.73 - 1.59 (m, 8 H) 1.58 - 1.51 (m, 2 H) 1.48 - 1.39 (m, 2 H) 0.99 - 0.84 (m, 2 H) 0.32 - 0.24 (m, 4 H)
Compound 348	508.1 $(M+H)^+$	(DMSO-d^6) δ 9.29 – 8.82 (s, 1 H), 7.65 - 7.44 (s, 1 H), 7.31 - 7.24 (m, 1 H), 7.18 - 7.13 (m, 1 H), 7.02 – 6.99 (m, 1 H), 6.97 - 6.90 (m, 2 H), 6.80 - 6.74 (m, 1 H), 4.26 - 4.16 (m, 1 H), 3.94 - 3.87 (s, 2 H), 2.94 - 2.91 (s, 3 H), 2.80 - 2.76 (s, 3 H), 1.89 - 1.79 (m, 2 H), 1.75 - 1.55 (m, 12 H), 1.02 – 0.94 (m, 2 H), 0.35 - 0.25 (m, 4 H)
Compound 349	530.1 $(M+H)^+$	(DMSO-d^6) δ 9.26 (s, 1 H), 7.56 - 7.45 (m, 5 H), 7.17 (d, J=2.20 Hz, 1 H), 7.03 (dd, J=8.50, 1.77 Hz, 1 H), 3.90 (s, 2 H), 3.74 (s, 2 H), 2.94 (s, 3 H), 2.93 - 2.89 (m, 2 H), 2.81 - 2.75 (m, 2 H), 2.31 - 2.21 (m, 2 H), 1.75 - 1.61 (m, 6 H), 0.97 (br d, J=13.33 Hz, 2 H), 0.32 - 0.26 (m, 4 H)
Compound 351	531.1 $(M+H)^+$	(DMSO-d^6) δ 9.35-9.17 (m, 1H), 7.61-7.39 (m, 5H), 7.17 (d, J = 2.1 Hz, 1H), 7.06-6.96 (m, 1H), 5.48-5.35 (m, 1H), 4.70-4.57 (m, 1H), 3.97-3.82 (m, 2H), 2.93 (s, 3H), 2.45-2.33 (m, 3H), 1.80-1.55 (m, 6H), 0.97 (br d, J = 13.3 Hz, 2H), 0.43-0.23 (m, 4H)
Compound 352	499.1 $(M+H)^+$	(DMSO-d^6) δ 9.63 - 9.48 (m, 1 H) 8.02 (br d, J=7.13 Hz, 1 H) 7.23 (d, J=3.38 Hz, 1 H) 7.14 - 7.10 (m, 1 H) 7.06 (dd, J=8.76, 2.00 Hz, 1 H) 6.48 (d, J=3.38 Hz, 1 H) 5.51 (d, J=5.25 Hz, 1 H) 4.48 - 4.35 (m, 1 H) 4.35 - 4.23 (m, 2 H) 2.94 (s, 3 H) 2.35 - 2.25 (m, 1 H) 1.88 - 1.68 (m, 7 H) 1.61 - 1.19 (m, 7 H) 0.92 (br d, J=13.26 Hz, 2 H) 0.32 (s, 4 H)
Compound 353		(DMSO-d^6) δ 11.68 (s, 1 H) 9.55 (br s, 1 H) 8.11 – 7.76 (m, 3 H) 7.70-7.55 (m, 1 H) 7.20-6.97 (m, 2 H) 3.91 (br s, 2 H) 3.84 - 3.72 (m, 1 H) 3.32 (s, 2 H) 2.93 (s, 3 H) 2.58-2.55 (m, 1 H) 2.14 – 1.90 (m, 4 H) 1.71-1.60 (br s, 6 H), 1.55 (br s, 3 H) 0.95-0.80 (m, 2 H) 0.27 (br s, 4 H)
Compound 354	509.2 $(M+H)^+$	(DMSO-d^6) δ 9.53 (s, 1 H) 8.0 (br m, 1 H) 7.58 - 7.30 (m, 4 H) 7.20-6.87 (m, 2 H) 5.32 (d, J=4.0 Hz, 1H) 4.47 (d, J=3.6 Hz, 1 H) 3.89 (br s, 2 H) 2.93 (s, 3 H) 2.30-2.18 (m, 2 H) 1.93 - 1.78 (m, 1 H) 1.75 - 1.25 (m, 9 H) 0.95 (s, 3H) 0.85-0.75 (m, 2 H) 0.28 (br s, 4 H)
Compound 355	546.1 $(M+H)^+$	(DMSO-d^6) δ 9.50 - 9.11 (m, 1 H) 7.70 - 7.39 (m, 4 H) 7.27 - 7.22 (m, 1 H) 7.18 - 7.15 (m, 1 H) 7.07 - 7.01 (m, 1 H) 3.95 - 3.84 (m, 2 H) 2.97 - 2.91 (m, 3 H) 1.79 - 1.61 (m, 6 H) 1.34 - 1.30 (m, 9 H) 1.02 – 0.91 (m, 2 H) 0.37 - 0.21 (m, 4 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 356	594.0 $(M+H)^+$	(DMSO-d^6) δ 9.69 - 9.35 (m, 1 H) 8.13 – 7.90 (m, 3 H) 7.83 - 7.73 (m, 1 H) 7.20 - 7.05 (m, 2 H) 4.02 – 3.80 (m, 3 H) 3.00-2.90 (m, 3 H) 2.83 - 2.63 (m, 7 H) 1.78 - 1.48 (m, 6 H) 0.96 - 0.80 (m, 2 H) 0.42 - 0.11 (m, 4 H)
Compound 357	511.3 $(M+H)^+$	(DMSO-d^6) δ 9.58 - 9.50 (m, 1 H) 8.11 – 7.91 (m, 1 H) 7.54 - 7.39 (m, 4 H) 7.17 – 6.98 (m, 2 H) 5.09 (d, J=4.63 Hz, 1 H) 4.72 (m, 1 H) 3.89 (br s, 2 H) 2.97 - 2.90 (m, 3 H) 1.73 - 1.41 (m, 8 H) 0.94 (s, 9 H) 0.91 - 0.84 (m, 2 H) 0.32 - 0.21 (m, 4 H)
Compound 358	542.1 $(M+H)^+$	(DMSO-d^6) δ 9.53 (brs 1H), 8.06-7.99 (m, 1H), 7.53-7.44 (m, 4H), 7.15 (s, 1H), 7.12-7.04 (m, 1H), 3.96 (s, 2H), 3.89 (s, 2H), 3.03-2.96 (m, 2H), 2.85-2.80 (m, 2H), 2.33-2.30 (m, 2 H), 1.78-1.54 (m, 6H), 0.96-0.88 (m, 2H), 0.38-0.28 (m, 4H)
Compound 359	576.1 $(M+H)^+$	(DMSO-d^6) δ 9.79 - 9.47 (m, 1 H) 8.18 – 7.95 (m, 2 H) 7.88 - 7.78 (m, 1 H) 7.76 - 7.63 (m, 1 H) 7.57 - 7.40 (m, 1 H) 7.22 - 6.99 (m, 2 H) 4.87 - 4.61 (m, 1 H) 4.05 – 3.77 (m, 2 H) 3.29 - 3.14 (m, 2 H) 3.11 – 2.94 (m, 2 H) 1.96 - 1.45 (m, 6 H) 1.29 - 1.14 (m, 3 H) 1.12 – 0.96 (m, 6 H) 0.95 - 0.81 (m, 2 H) 0.47 - 0.07 (m, 4 H)
Compound 361a	588.1 $(M+H)^+$	(DMSO-d^6) δ 9.64 (s, 1 H) 8.13 - 8.02 (m, 1 H) 7.98 (d, J=8 Hz, 1 H) 7.82 (d, J=6 Hz, 1 H) 7.75 - 7.70 (m, 1 H) 7.67 (s, 1 H) 7.13 (d, J=2 Hz, 2 H) 3.86 (s, 2 H) 2.95 (s, 3 H) 2.45 (d, J=1.2 Hz, 1 H) 1.90 - 1.61 (m, 6 H) 1.22 - 1.02 (m, 11 H)
Compound 361b	588.1 $(M+H)^+$	(DMSO-d^6) δ 9.68 (s, 1 H) 8.06 – 7.92 (m, 2 H) 7.83 (d, J=6.8 Hz, 1 H) 7.74 - 7.64 (m, 2 H) 7.37 (d, J=1.8 Hz, 1 H) 7.25 - 7.00 (m, 1 H) 3.78 (s, 2 H) 2.95 (s, 3 H) 2.46 - 2.29 (m, 1 H) 1.89 - 1.52 (m, 8 H) 1.11 (s, 9 H)
Compound 362	541.2 $(M+H)^+$	(DMSO-d^6) δ 9.19 (s, 1 H) 7.95 - 7.84 (m, 2 H) 7.80 - 7.50 (m, 3 H) 7.20 - 7.15 (m, 1 H) 7.10 – 6.98 (m, 1 H) 3.99 - 3.85 (m, 2 H) 3.06 - 3.01 (m, 1 H) 2.98 - 2.90 (m, 3 H) 2.23 – 1.99 (m, 3 H) 1.91 - 1.49 (m, 14 H) 1.01 – 0.90 (m, 2 H) 0.36 - 0.23 (m, 4 H)
Compound 364	515.1 $(M+H)^+$	(DMSO-d^6) δ 9.52 (br s, 1 H) 7.94 (br d, J=5.38 Hz, 1 H) 7.73 (s, 1 H) 7.59 (s, 1 H) 7.13 (d, J=2.00 Hz, 1 H) 7.06 (dd, J=8.63, 2.13 Hz, 1 H) 5.23 (d, J=5.13 Hz, 1 H) 4.42 (dd, J=7.19, 5.32 Hz, 1 H) 4.26 (s, 2 H) 2.94 (s, 3 H) 2.24 - 2.09 (m, 1 H) 1.88 - 1.63 (m, 7 H) 1.60 - 1.36 (m, 6 H) 1.34 - 1.17 (m, 1 H) 0.93 (br d, J=12.13 Hz, 2 H) 0.32 (s, 4 H)
Compound 365	568.3 $(M+H)^+$	(DMSO-d^6) δ 9.92 - 9.74 (m, 1 H) 8.09 – 7.93 (m, 2 H) 7.83 (br d, J=4.75 Hz, 1 H) 7.75 - 7.63 (m, 2 H) 7.16 - 7.05 (m, 2 H) 4.80 (t, J=5.19 Hz, 1 H) 4.69 (t, J=5.19 Hz, 1 H) 3.88 (br s, 2 H) 3.58 - 3.43 (m, 2 H) 1.72 - 1.49 (m, 6 H) 1.11 (s, 9 H) 0.88 (br d, J=11.26 Hz, 2 H) 0.27 (br s, 4 H)
Compound 367	513.3 $(M+H)^+$	(DMSO-d^6) δ 9.62 (s, 1 H) 8.01 (br d, J=8.50 Hz, 1 H) 7.22 (d, J=3.50 Hz, 1 H) 7.14 (d, J=2.13 Hz, 1 H) 7.06 (m, 1 H) 6.48 (d, J=3.38 Hz, 1 H) 5.50 (d, J=5.50 Hz, 1 H) 4.41 (m, 1 H) 4.36 - 4.25 (m, 2 H) 3.04 (m, 2 H) 2.37 - 2.24 (m, 1 H) 1.90 - 1.62 (m, 7 H) 1.62 - 1.42 (m, 6 H) 1.38 - 1.26 (m, 1 H) 1.19 (t, J=7.38 Hz, 3 H) 0.93 (br d, J=13.26 Hz, 2 H) 0.32 (s, 4 H)

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 368	529.2 $(M+H)^+$	(DMSO-d^6) δ 9.63 - 9.47 (m, 1 H) 8.01 (br d, J=9.38 Hz, 1 H) 7.23 (d, J=3.50 Hz, 1 H) 7.14 (d, J=2.25 Hz, 1 H) 7.06 (m, 1 H) 6.48 (d, J=3.38 Hz, 1 H) 5.50 (d, J=5.50 Hz, 1 H) 4.92 (br t, J=7.13 Hz, 1 H) 4.41 (m, 1 H) 4.31 (d, J=2.25 Hz, 2 H) 3.74 (br t, J=6.07 Hz, 2 H) 3.19 (t, J=6.75 Hz, 2 H) 1.92 - 1.45 (m, 13 H) 1.39 - 1.21 (m, 1 H) 1.01 – 0.85 (m, 2 H) 0.33 (s, 4 H)
Compound 369	521.0 $(M+H)^+$	(DMSO-d^6) δ 9.54 (br d, J=3.25 Hz, 1 H) 8.06 – 7.97 (1 H, m) 7.25 (d, J=3.38 Hz, 1 H) 7.13 (d, J=2.13 Hz, 1 H) 7.06 (m,1 H) 6.53 (d, J=3.63 Hz, 1 H) 5.90 (d, J=5.75 Hz, 1 H) 4.70 - 4.61 (m, 1 H) 4.29 (s, 2 H,) 2.94 (s, 3 H) 2.54 - 2.64 (m, 5 H) 1.81 - 1.96 (m, 2 H) 1.76 - 1.62 (m, 4 H) 0.93 (br d, J=13.76 Hz, 2 H) 0.32 (s, 4 H)
Compound 370		(DMSO-d^6) δ 8.15 – 7.92 (m, 1 H) 7.51 - 7.46 (m, 1 H) 7.43 - 7.35 (m, 1 H) 7.31 - 7.25 (m, 1 H) 6.58 - 6.33 (m, 1 H) 5.65 - 5.40 (m, 1 H) 4.35 - 4.32 (m, 2 H) 2.04 – 1.73 (m, 5 H) 1.70 - 1.33 (m, 3 H) 0.94 (s, 9 H) 0.38 - 0.24 (m, 4 H)
Compound 371	517.3 $(M+H)^+$	(DMSO-d^6) δ 9.70 - 9.42 (m, 1 H) 8.15 – 7.94 (m, 1 H) 7.31 - 7.18 (m, 1 H) 7.16 - 7.10 (m, 1 H) 7.08 – 6.97 (m, 1 H) 6.52 - 6.39 (m, 1 H) 5.58 - 5.45 (m, 1 H) 5.03 – 4.81 (m, 1 H) 4.38 - 4.24 (m, 3 H) 3.83 - 3.63 (m, 2 H) 3.24 - 3.11 (m, 2 H) 1.93 - 1.77 (m, 2 H) 1.76 - 1.58 (m, 4 H) 0.98 - 0.91 (m, 11 H) 0.39 - 0.25 (m, 4 H)
Compound 372	501.1 $(M+H)^+$	(DMSO-d^6) δ 9.62 (s, 1H), 8.03 (br d, J = 8.6 Hz, 1H), 7.31-6.91 (m, 3H), 6.47 (d, J = 3.4 Hz, 1H), 5.51 (d, J = 4.9 Hz, 1H), 4.38-4.22 (m, 3H), 3.13-2.98 (m, 2H), 1.93-1.57 (m, 6H), 1.19 (t, J = 7.3 Hz, 3H), 1.06-0.86 (m, 11H), 0.32 (s, 4H)
Compound 373	487.3 $(M+H)^+$	9.55 (s, 1 H) 8.05 (br d, J=8.58 Hz, 1 H) 7.31 - 7.20 (m, 1 H) 7.15 - 7.00 (m, 2 H) 6.47 (d, J=3.46 Hz, 1 H) 5.52 (d, J=4.89 Hz, 1 H) 4.39 - 4.24 (m, 3 H) 2.94 (s, 3 H) 1.93 - 1.58 (m, 6 H) 1.00 – 0.83 (m, 11 H) 0.38 - 0.26 (m, 4 H)

Biological Assays

Inhibition of KIF18A microtubule-dependent ATPase activity:

[0288] Test compounds were plated in a 3x dilution scheme in a 384-well plate. Assay buffer: 80 mM PIPES (pH 6.9), 1 mM $MgCl_2$, 75 mM KCl, 1 mM EGTA, 1 mM DTT, 0.01% BSA, 0.005% Tween-20, 1 μM Taxol in H_2O. To 50 nL of compound in DMSO was added 2.5 μL of enzyme mix [4 nM hKIF18A (1-374) in assay buffer]. After incubation at room temperature for 30 min, 2.5 μL of microtubule mix was added [0.2 mg/mL pre-formed microtubules, 2.0 mM ATP in assay buffer], the plate was centrifuged for 30 s and then incubated at 28 °C for 60 min. 5 μL of Promega® ADP-Glo Max R1 was added, the plate was centrifuged for 30s, and the mixture incubated for 4 h at room temperature. 10 μL of Promega® ADP-Glo Max R2 was added, the plate centrifuged for 30 s, and incubated for 60

min at room temperature. Luminescence was measured with an Envision plate reader, and %Inhibition was calculated for each well as: ([max – min] – [test – min])/[max – min]. IC_{50} values were calculated from concentration vs. % Inhibition data via a four-parameter variable slope model.

[0289] Table 9 indicates that compounds as provided herein are potent inhibitors of KIF18a. As a comparison, the data for AMG650 (2-{6-azaspiro[2.5]octan-6-yl}-N-[2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl]-4-(2-hydroxyethanesulfonamido)benzamide) is 17 nM.

Binding kinetics to KIF18a-microtubule complex

[0290] Compound binding kinetics parameters (k_{on} and k_{off}) were determined by the method of global progress curve analysis (GPCA). KIF18A (0.25 nM) was incubated for up to 24 hr with serially diluted compound in the assay buffer containing 80mM PIPES, pH 6.9, 1 mM ATP, 0.1 mg/ml preformed microtubule from porcine brain (Cytoskeleton), 1 mM $MgCl_2$, 1μM Taxol, 75 mM KCl, 1 mM EGTA, 1 mM DTT, 0.01% BSA and 0.005% Tween-20. ADP product levels were determined by the Promega® ADP-Glo assay. The time/dose-dependent progress curves were then globally fit to a Michaelis-Menten kinetics model with 1-step slow binding inhibition to derive both on-rate k_{on} and off-rate k_{off} values (Zhang, R., Wong, K. (2017): "High performance enzyme kinetics of turnover, activation and inhibition for translational drug discovery", *Expert Opinion on Drug Discovery*, 2017 Jan;12(1):17-37. doi: 10.1080/17460441.2017.1245721).

[0291] Results from the binding kinetics assay are summarized in Table 10. The data in Table 10 indicate that compounds as provided herein can achieve sub-nanomolar potency with small off-rates, or very long dissociation half-life ($ln(2)/k_{off}$). As a comparison, the data for AMG650 (2-{6-azaspiro[2.5]octan-6-yl}-N-[2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl]-4-(2-hydroxyethanesulfonamido)benzamide) are: $k_{on} = 0.059\ nM^{-1}h^{-1}$; $k_{off} = 0.21\ h^{-1}$, dissociation $t_{1/2} = 4.1$ h; $K_I = 3.4$ nM.

Cell Viability of KIF18a-sensitive cell lines

[0292] Cell lines were seeded as follows 24 hours before compound treatment: HCC15 (Korean Cell Line Bank) 600 cell/well, 95 μL of RPMI-1640 media supplemented with 100 units/mL penicillin, 100 units/mL streptomycin and 10% FBS; NIH:OVCAR-3

(ATCC), 1000 cell/well, 95 µL of RPMI-1640 media supplemented with 100 units/mL penicillin, 100 units/mL streptomycin, 0.01 mg/mL bovine insulin, and 20% FBS; JIMT-1 (Addexbio) 1000 cell/well, 95 µL of DMEM media supplemented with 100 units/mL penicillin, 100 units/mL streptomycin, and 10% FBS.

[0293] Test compounds were added to cells in a 20x dilution scheme by adding 5 µL of serially diluted compound to the plate, and the treated cells were incubated for an additional 7 days in a 37 °C, 5% CO_2 incubator. DMSO was used as the negative control (0% effect), and wells omitting cells were used as the positive control (100% effect). The cells were incubated for seven days, and cell viability determined via the Promega Cell Titre-Glo® Assay kit. Luminescence units were converted to ATP concentrations via an ATP standard curve (10 point, 2-fold dilution from 5 uM). %Inhibition was calculated for each well as: ([max – min] – [test – min])/[max – min]. IC_{50} values were calculated from concentration vs. %Inhibition data via a four-parameter variable slope model. Results from the biological assay are summarized in Table 10.

[0294] Table 11 indicates that compounds as provided herein potently inhibit cell growth or induce cell killing for KIF18a-senstive cancer cell lines. As a comparison, the data for AMG650 (2-{6-azaspiro[2.5]octan-6-yl}-N-[2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl]-4-(2-hydroxyethanesulfonamido)benzamide) are: HCC-15, 0.066 µM; JIMT-1 0.13 µM; NIH: OVCAR3 0.10 µM.

Table 9. Summary of biochemical assay data

Compound	IC_{50} (μM)
Compound 1	1.6
Compound 3	1.6
Compound 4	0.36
Compound 6	0.58
Compound 8	0.94
Compound 9	1.0
Compound 10	0.27
Compound 15	0.78 (n=1) 0.74 (n=2)
Compound 18	0.079
Compound 19	0.032
Compound 20	0.013
Compound 21	0.019
Compound 22	0.011 (n=3) 0.0094 (n=10)
Compound 23	0.023
Compound 24	0.010
Compound 24a	0.011
Compound 24b	0.014
Compound 25	0.12
Compound 26	0.067
Compound 27	0.083
Compound 28	0.010
Compound 29	0.022
Compound 30	0.18
Compound 31	0.039
Compound 32	0.078
Compound 42	1.3
Compound 43	0.089
Compound 45	0.27
Compound 46	0.12
Compound 48	0.10
Compound 49	0.13
Compound 50	0.072
Compound 55	0.14
Compound 57	1.1
Compound 59	1.0
Compound 60	1.2
Compound 67	0.46

Compound	IC_{50} (μM)
Compound 70	0.030
Compound 71	0.086
Compound 83	0.13
Compound 95	0.17
Compound 96	0.10
Compound 97	0.85
Compound 107	0.47
Compound 129	0.045
Compound 134	0.016
Compound 140	0.013
Compound 141	1.1
Compound 144	0.051
Compound 145	0.29
Compound 146	0.19
Compound 147	0.043
Compound 148	0.012
Compound 149	0.078
Compound 151	0.0068
Compound 153	0.018
Compound 155	0.0074
Compound 157	0.058
Compound 159	0.019
Compound 160	0.020
Compound 162a	0.015
Compound 162b	0.037
Compound 163	0.020
Compound 164	0.12
Compound 165	0.015
Compound 165a	0.0088
Compound 165b	0.010
Compound 166	1.1
Compound 168	0.0055
Compound 170	0.015
Compound 172	0.0055
Compound 174	0.056
Compound 176	0.0056
Compound 178	0.017
Compound 180	0.011

Compound	IC_{50} (μM)
Compound 182	0.0073
Compound 184	0.033
Compound 186	0.012
Compound 188	0.075
Compound 190	0.0048
Compound 192	0.010
Compound 194	0.050
Compound 196	0.010
Compound 198	0.026
Compound 200	0.072
Compound 202	0.053
Compound 204	0.013
Compound 206	0.027
Compound 208	0.064
Compound 210	0.016
Compound 212	0.012
Compound 214	0.08
Compound 216	0.0093
Compound 218	0.10
Compound 220	0.025
Compound 222	0.10
Compound 223	0.0067
Compound 224	0.023
Compound 225	0.0075
Compound 226	0.013
Compound 227	0.0072
Compound 228	0.0046
Compound 229	0.0062
Compound 230	0.014
Compound 231	0.0087
Compound 233	0.012
Compound 235	0.022
Compound 237	0.011
(R)-Compound 239	0.0093
(S)-Compound 239	0.015
Compound 240	0.040
Compound 241	0.18
Compound 243	0.14

Compound	IC_{50} (μM)
Compound 245	0.034
Compound 247	0.021
Compound 249	0.0090
(R)-Compound 249	0.011
(S)-Compound 249	0.016
Compound 250	0.67
Compound 252	0.034
Compound 254	0.010
Compound 255	0.063
Compound 257	0.0083
Compound 258	0.014
Compound 260	0.012
Compound 261	0.0093
Compound 262	0.0059
Compound 264	0.035
Compound 266	0.016
Compound 268	0.077
Compound 269	0.079
Compound 270	0.110
Compound 272	0.038
Compound 274	0.0060
Compound 275	0.0080
Compound 277	0.041
Compound 279	0.0063
Compound 281	0.013
Compound 283	0.018
Compound 284	0.026
Compound 285	0.011
Compound 287	0.017
Compound 287a	0.034
Compound 287b	0.012
Compound 289	0.017
Compound 291	0.0058
Compound 292	0.022
Compound 293	0.017
Compound 295	0.038
Compound 297	0.017
Compound 298	0.0084

Compound	IC_{50} (μM)
Compound 299	0.014
Compound 300	0.031
Compound 301	0.021
Compound 302	0.019
Compound 303	0.0082
Compound 305	0.0089
Compound 305a	0.0081
Compound 305b	0.0068
Compound 306	0.033
Compound 309	0.0065
Compound 310	0.0066
Compound 311	0.0052
Compound 313	0.020
Compound 313a	0.019
Compound 313b	0.015
Compound 314	0.028
Compound 315	0.053
Compound 316	0.018
Compound 316a	0.021
Compound 316b	0.016
Compound 317	0.011
Compound 317a	0.011
Compound 317b	0.010
Compound 318	0.93
Compound 319	1.2
Compound 320	0.018
Compound 321	0.0063
Compound 322	0.021
Compound 324	0.021
Compound 326	0.050
Compound 327	0.044
Compound 329	0.072
Compound 330	0.012
Compound 331	0.035
Compound 332	0.15
Compound 333a	0.018
Compound 333b	0.033
Compound 335	0.0093

Compound	IC_{50} (μM)
Compound 336a	0.0085
Compound 336b	0.017
Compound 337	0.0088
Compound 338	0.049
Compound 338a	0.048
Compound 338b	0.083
Compound 339	0.024
Compound 340	0.018
Compound 341	0.025
Compound 341a	0.030
Compound 341b	0.024
Compound 342	0.020
Compound 343	0.81
Compound 345	0.058
Compound 346	0.31
Compound 347	0.28
Compound 348	0.19
Compound 349	0.045
Compound 351	0.0088
Compound 351a	0.0087
Compound 351b	0.012
Compound 352	0.0050
Compound 352a	0.0040
Compound 352b	0.0033
Compound 354	0.014
Compound 355	0.025
Compound 356	0.051
Compound 357	0.011
Compound 358	0.028
Compound 359	0.016
Compound 361a	0.015
Compound 361b	0.10
Compound 362	0.035
Compound 364	0.0051
Compound 365	0.013
Compound 367a	0.0039
Compound 367b	0.0048
Compound 368a	0.0030

Compound	IC_{50} (μM)
Compound 368b	0.0035
Compound 369	0.0071
Compound 371a	0.030
Compound 371b	0.040
Compound 372a	0.037
Compound 372b	0.035

Compound	IC_{50} (μM)
Compound 373a	0.20
Compound 373b	0.17
Compound 1'	2.6
Compound 2'	0.92

Table 10. Summary of kinetic assay data

Compound	k_{on} ($nM^{-1}h^{-1}$)[a]	k_{off} (h^{-1})[b]	disc. $t_{1/2}$ (h)[c]	K_I (nM)[d]
Compound 19	0.051	0.096	7.2	1.8
Compound 22	0.038	0.018	38	0.55
Compound 24b	0.052	0.015	45	0.29
Compound 24a	0.080	0.043	16	0.54
Compound 70	0.036	0.23	3.0	6.5
Compound 129	0.044	0.28	2.5	6.3
Compound 134	0.054	0.018	40	0.34
Compound 140a	0.047	0.024	29	0.50
Compound 140b	0.058	0.080	8.7	1.4
Compound 144	0.015	0.14	5.2	9.3
Compound 148	0.049	0.014	48	0.29
Compound 151	0.096	0.011	61	0.12
Compound 155	0.11	0.11	6.5	2.0
Compound 159	0.026	0.022	32	0.83
Compound 160	0.038	0.021	33	0.54
Compound 162a	0.029	0.055	13	1.9
Compound 165a	0.043	0.18	3.8	4.2
Compound 165b	0.043	0.17	4.2	3.9
Compound 182	0.11	0.029	24	0.26
Compound 192	0.052	0.033	21	0.64
Compound 229	0.061	0.018	39	0.29
Compound 223	0.023	0.088	7.9	0.26
Compound 237	0.082	0.036	19	0.44
(R)-Compound 239	0.060	0.086	8.1	1.4
Compound 257	0.066	0.067	10	0.96
Compound 262	0.032	0.103	6.7	0.31
Compound 269	0.020	0.080	8.7	4.0
Compound 297	0.037	0.014	49	0.38
Compound 298	0.071	0.027	26	0.38
Compound 305a	0.35	1.3	0.56	3.5
Compound 305b	0.38	1.4	0.49	3.7
Compound 317a	0.033	0.33	2.1	10
Compound 317b	0.059	0.35	2.0	5.9
Compound 320	0.027	0.015	45	0.57
Compound 322	0.037	0.12	5.7	3.3

Compound	k_{on} ($nM^{-1}h^{-1}$)[a]	k_{off} (h^{-1})[b]	disc. $t_{1/2}$ (h)[c]	K_I (nM)[d]
Compound 333a	0.028	0.013	53	0.47
Compound 333b	0.014	0.011	63	0.77
Compound 351a	0.070	0.41	1.7	5.8
Compound 352a	0.10	0.38	1.8	3.7
Compound 352b	0.080	0.25	2.8	3.1

[0295] a) on-rate from binding kinetics assay. b) off-rate from binding kinetics assay. c) dissociation half-life $\ln(2)/k_{off}$. d) K_I determined from binding kinetic assay k_{off}/k_{on}

Table 11: Summary of cellular assay data

Compound	HCC-15 IC_{50} (μM)	JIMT-1 IC_{50} (μM)	NIH-OVCAR3 IC_{50} (μM)
Compound 4	2.1		
Compound 10	2.2		
Compound 18	0.16		
Compound 19	0.092		
Compound 20	0.025		
Compound 21	0.055		
Compound 22	0.011	0.0078	0.0097
Compound 24	0.023		
Compound 24a	0.26		
Compound 24b	0.032		
Compound 26	0.069		
Compound 27	0.14		
Compound 28	0.024		
Compound 29	0.33		
Compound 30	3.5	2.3	1.43
Compound 43	0.49		
Compound 70	0.59		
Compound 134	0.0051	0.0040	0.0051
Compound 140	0.038		
Compound 140a	0.010		
Compound 140b	0.045		
Compound 148	0.036		
Compound 151	0.013		
Compound 153	0.044		
Compound 157	0.60	0.44	0.72
Compound 159	0.021	0.015	0.022
Compound 160	0.0075	0.0054	0.0080

Compound	HCC-15 IC_{50} (μM)	JIMT-1 IC_{50} (μM)	NIH-OVCAR3 IC_{50} (μM)
Compound 163	0.14	0.12	0.19
Compound 165a	0.068	0.045	0.059
Compound 165b	0.046	0.038	0.057
Compound 168	0.028		
Compound 172	0.032		
Compound 182	0.015		
Compound 192	0.51	0.50	0.41
Compound 223	0.021	0.015	0.020
Compound 229	0.011	0.011	0.013
Compound 257	0.021	0.012	0.021
Compound 287b	0.097	0.064	0.033
Compound 297	0.011	0.0098	0.010
Compound 305a	0.074	0.052	0.090
Compound 305b	0.060	0.040	0.069
Compound 309	0.012	0.0094	0.012
Compound 310	0.011	0.0079	0.0091
Compound 320	0.021	0.014	0.020
Compound 322	0.043	0.032	0.040
Compound 333a	0.022	0.024	0.017
Compound 352a	0.034	0.040	0.045
Compound 352b	0.019	0.019	0.027
Compound 355	0.094	0.12	0.11
Compound 2'	2.6		

Assessment of *in vivo* Activity

[0296] OVCAR-3 (ATCC) tumor cells were maintained in *vitro* in RPMI-1640 medium supplemented with 20% fetal bovine serum, 0.01 mg/mL bovine insulin and 1% Anti-Anti at 37ºC in an atmosphere of 5% CO_2 in air. HCC15 (DSMZ) tumor cells were maintained *in vitro* in RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% Anti-Anti at 37ºC in an atmosphere of 5% CO_2 in air.

[0297] The tumor cells were sub-cultured twice weekly. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[0298] Tumor cells (10×10^6) in 0.2 mL of PBS mixed with Matrigel (50:50) were inoculated subcutaneously on the right flank of each mouse. When the average tumor volume reached 110-175 mm^3, animals were randomized into groups of 10 and treatment started.

OVCAR-3 cells were implanted in Balb/C nude mice, and HCC15 cell were implanted in SCID Beige mice.

[0299] Compounds were dosed once or twice a day (12h) orally. Tumor Growth Inhibition (TGI) was calculated using the formula: TGI (%) = [1-(T_N-T_0)/ (V_N-V_0)] ×100; T_N is the average tumor volume of a treatment group at the indicated timepoint, T_0 is the average tumor volume of the treatment group on treatment day 0, V_N is the average tumor volume of the vehicle control group at the indicated timepoint, and V_0 is the average tumor volume of the vehicle group on treatment day 0. P value was calculated based on tumor size by One-Way ANOVA with GraphPad Prism 9.4.0 compared with the vehicle group, respectively. **** indicates $p<0.0001$.

[0300] The tumor volume of vehicle- and compound-treated mice as a function of time after start of treatment and the results of treatments with selected compounds on SCID Beige mice or nude mice implanted with HCC15 or OVCAR-3 are shown in Figures 1A-1E. The TGI calculated for treatments with selected compounds are showin in Table 12.

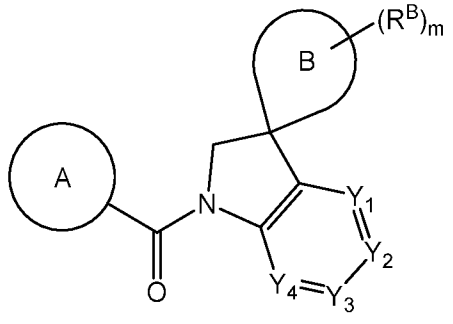
Table 12

Compound	Model	Subfigure	Dose	TGI
Compound 22	HCC15	1A	10 mg/kg BID PO	30 ± 15%
Compound 22	HCC15	1A	30 mg/kg BID PO	72 ± 6%
Compound 22	HCC15	1A	60 mg/kg BID PO	82 ± 9%
Compound 22	OVCAR3	1B	10 mg/kg QD PO	24 ± 26%
Compound 22	OVCAR3	1B	30 mg/kg QD PO	72 ± 17%
Compound 22	OVCAR3	1B	60 mg/kg QD PO	82 ± 10%
Compound 134	HCC15	1C	10 mg/kg BID PO	61 ± 10%
Compound 134	HCC15	1C	30 mg/kg BID PO	89 ± 7%
Compound 134	HCC15	1C	60 mg/kg BID PO	94 ± 5%
Compound 134	OVCAR3	1D	10 mg/kg BID PO	60 ± 17%
Compound 134	OVCAR3	1D	30 mg/kg BID PO	111 ± 1%
Compound 134	OVCAR3	1D	60 mg/kg BID PO	112 ± 1%
Compound 134	OVCAR3	1E	30 mg/kg QD PO	104 ± 7%
Compound 134	OVCAR3	1E	60 mg/kg QD PO	109 ± 2%
Compound 134	OVCAR3	1R	30 mg/kg BID PO	110 ± 1%

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

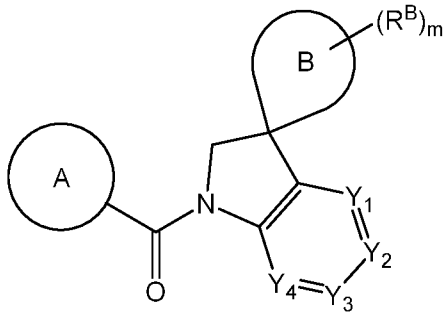
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

2. A compound of Formula (I-2):



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, -

$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

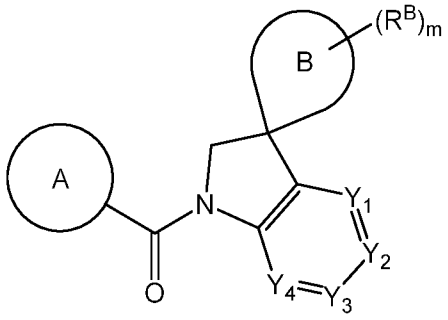
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

3. A compound of Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

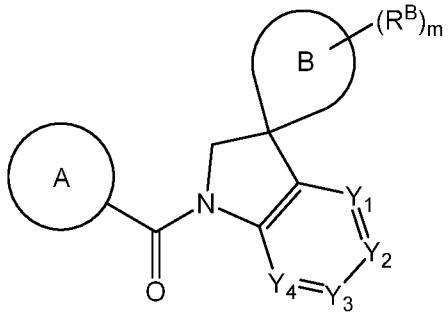
wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the compound is not 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; or salt of any of the foregoing.

5. A compound of Formula (I-3):



(I-3),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C_{3-7} cycloalkyl;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

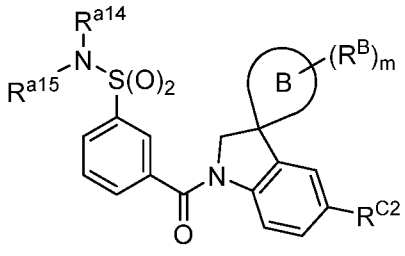
R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted C_{6-14} aryl.

7. The compound of any one of the claims 1-6, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted phenyl.

8. A compound of Formula (Ia1):



(Ia1),

or a pharmaceutically acceptable salt thereof, wherein:

R^{a14} and R^{a15} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

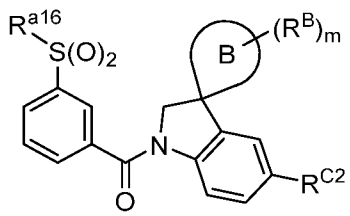
R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; and R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

10. The compound of claim 8 or claim 9, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is $-NR^{c5}S(O)_2R^{c6}$, and R^{c5} and R^{c6} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

11. A compound of Formula (Ia2):



(Ia2),

or a pharmaceutically acceptable salt thereof, wherein:

R^{a16} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents

independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), =$CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

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

R^{C2} is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH, and R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

13. The compound of claim 11 or claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is -$NR^{c5}S(O)_2R^{c6}$, and R^{c5} and R^{c6} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

14. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted 5- to 10-membered heteroaryl.

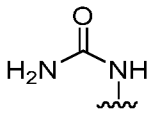
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted.

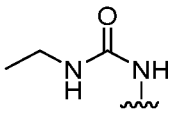
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein R^{a1} is hydrogen or C_{1-6} alkyl; R^{a2} and R^{a3} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a4} is hydrogen or C_{1-6} alkyl; R^{a5} is hydrogen or C_{1-6} alkyl; R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl; R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a10} is C_{3-10} cycloalkyl; R^{a11} is C_{3-10} cycloalkyl; R^{a12} is hydrogen or C_{1-6} alkyl; R^{a13} is C_{3-10} cycloalkyl; R^{a16} is C_{3-10} cycloalkyl or 3- to 12-membered heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo; R^{a17} and R^{a18} are each independently hydrogen or C_{1-6} alkyl; R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a21} is C_{3-10} cycloalkyl; and R^{a22} is C_{3-10} cycloalkyl.

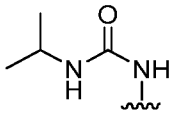
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one or more C_{1-6} alkyl.

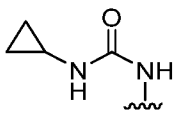
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^{a14} is hydrogen and R^{a15} is *tert*-butyl.

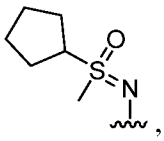
19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein ring A is substituted with one or more substituents independently selected from the

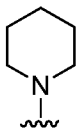


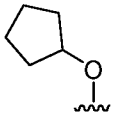


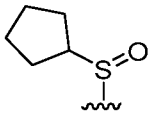


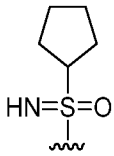


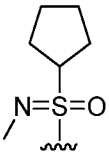


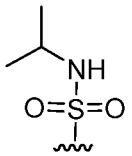


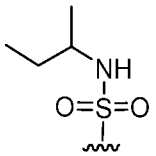


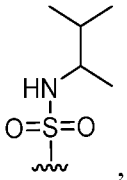


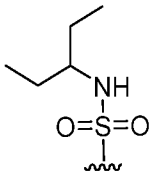


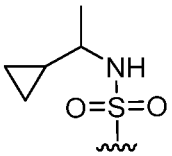


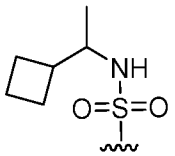


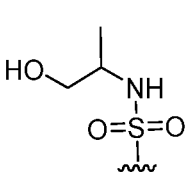


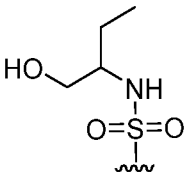


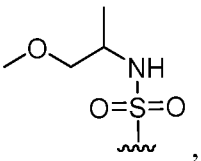


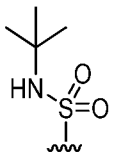


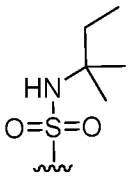


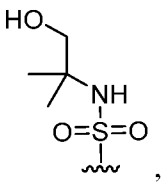


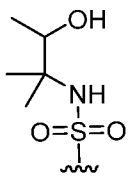


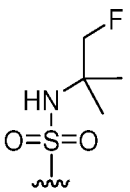


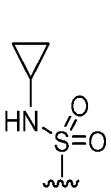


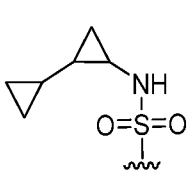


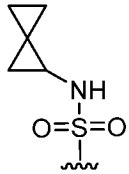


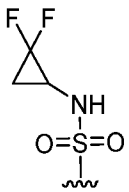


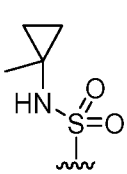


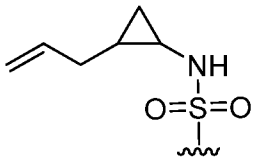


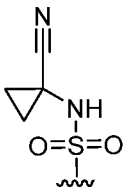


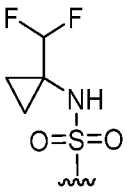


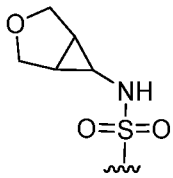


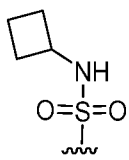


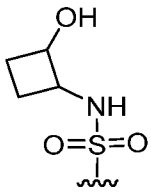


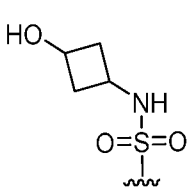


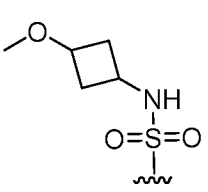


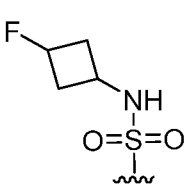


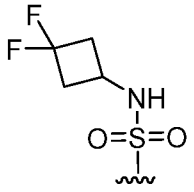


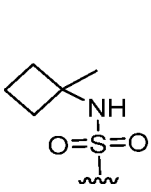












group consisting of fluoro, chloro, -OH, methyl, amino, , ,

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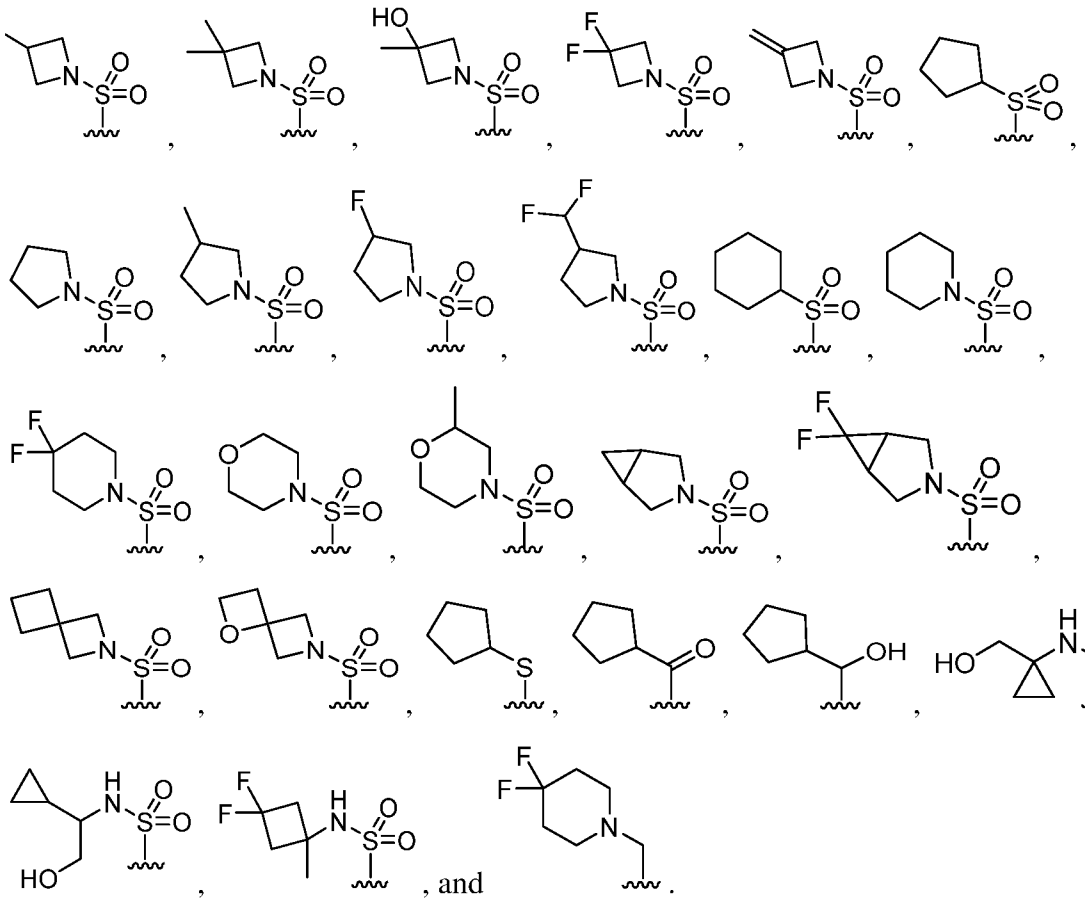
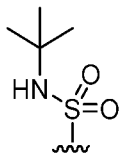
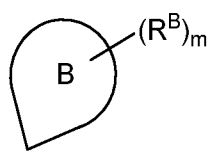


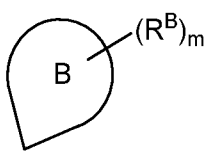
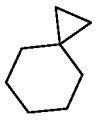
20. The compound of any one of claims 1-13 and 16-19, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl substituted with  .

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein ring B is  , wherein * denotes the point of attachment to the rest of Formula (I).

24. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is , or wherein * denotes the point of attachment to the rest of Formula (I).

25. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is  .

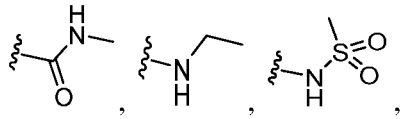
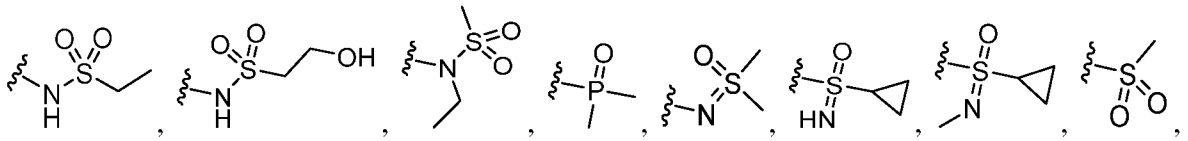
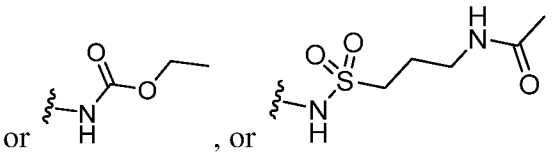
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

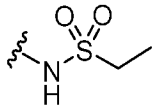
27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

28. The compound of claim 26 or claim 27, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each hydrogen.

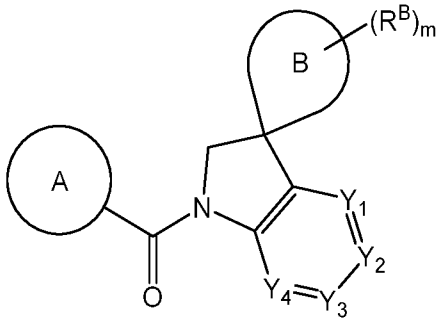
29. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

30. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

31. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, -CH_2OH, bromo, -NO_2,  ,  , or  .

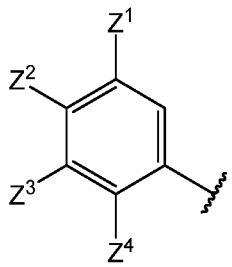
32. The compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is  .

33. A compound of Formula (II):


(II),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is

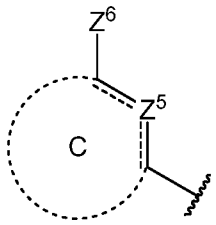
(i)  , wherein Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, -$NR^{a4}C(O)OR^{a5}$, -$NR^{a6}R^{a7}$, -

$N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl,

provided that

(1) when Z^4 is hydrogen, then at least one of Z^1 and Z^3 is R^D; and

(2) when Z^4 is R^D, then Z^1 is R^D, or

(ii) 

, wherein

 is a single bond or a double bond,

Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl;

Z^6 is $-NR^{a26}C(O)NR^{a27}R^{a28}$, $-NR^{a29}C(O)OR^{a30}$, $-N=S(O)R^{a31}R^{a32}$, $-S(O)R^{a33}$, $-S(O)(NR^{a34})R^{a35}$, $-S(O)_2NR^{a36}R^{a37}$, $-S(O)_2R^{a38}$, $-SR^{a39}$, 3- to 10-membered heterocycloalkyl, $-C(O)R^{a40}$, or $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo, and

ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl;

R^{a4}-R^{a40} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the

group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo or C_{1-6} alkyl optionally substituted with one or more halo; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together to form a $=CR^{1a3}R^{1a4}$ group, wherein R^{1a3} and R^{1a4} are each independently hydrogen or C_{1-6} alkyl;

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

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

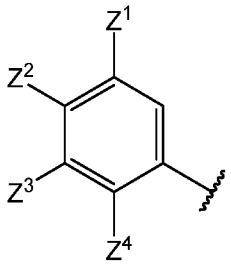
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

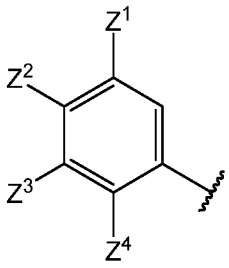
R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, - $NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, -O-$S(O)_2R^{c19}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and -OH, and

R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -O(C_{1-6} alkyl), - NHC(O)(C_{1-6} alkyl), and -OH;

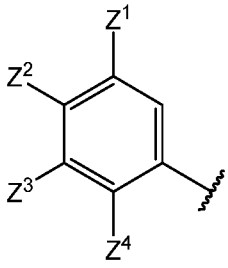
provided that

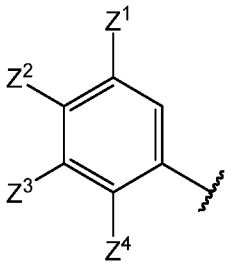


(1) when ring B is unsubstituted cyclopentyl, then ring A is , wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) substituted with one or more halo,



(2) when ring B is unsubstituted cyclohexyl and ring A is , then at least one of R^{C1}-R^{C4} is R^F, and

(3) when ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4 R^B, then ring A is  , wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) optionally substituted with one or more halo.

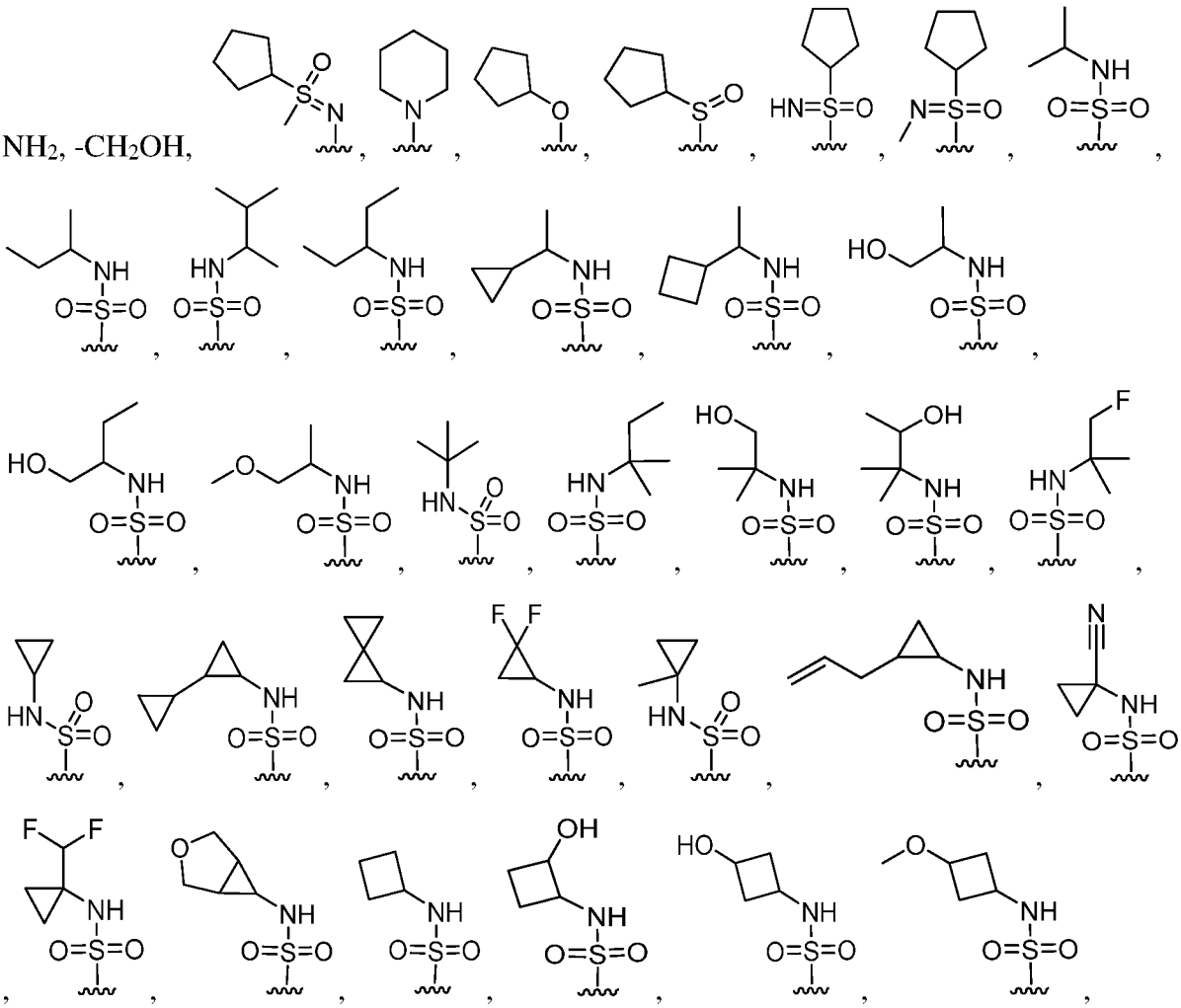
34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein ring A is  .

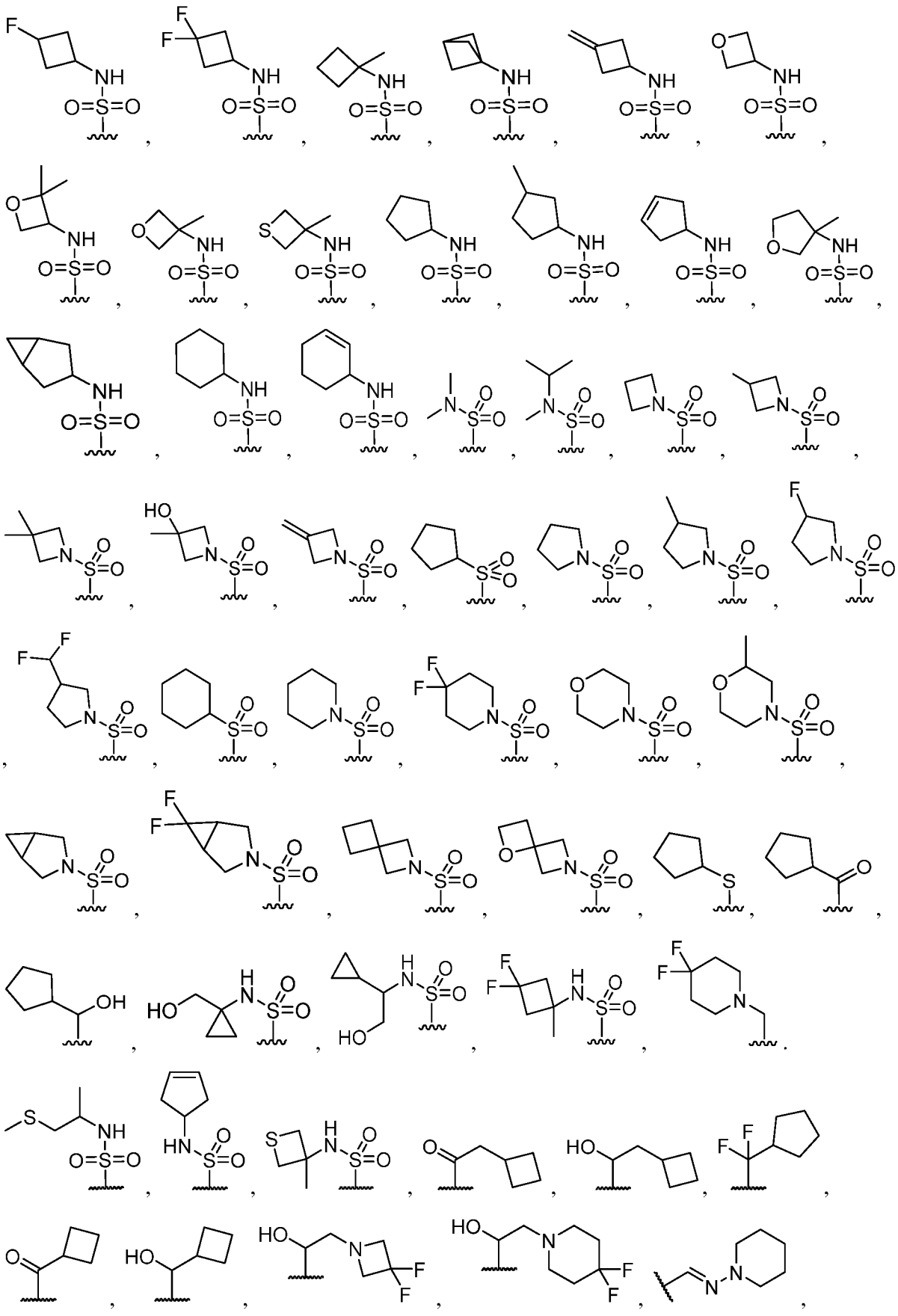
35. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein Z^4 is hydrogen, and at least one of Z^1 and Z^3 is R^D, wherein R^D is halo, -OH, -$NR^{a4}C(O)OR^{a5}$, -$NR^{a6}R^{a7}$, -$N{=}S(O)R^{a8}R^{a9}$, -OR^{a10}, -$S(O)R^{a11}$, -$S(O)(NR^{a12})R^{a13}$, -$S(O)_2NR^{a14}R^{a15}$, -$S(O)_2R^{a16}$, -$(CR^{a17}R^{a18})_{0\text{-}1}C(O)NR^{a19}R^{a20}$, -$SR^{a21}$, -$C(O)R^{a22}$, -$P(O)(R^{a23})(R^{a24})$, -$C{=}NR^{a25}$, or $C_{1\text{-}6}$ alkyl

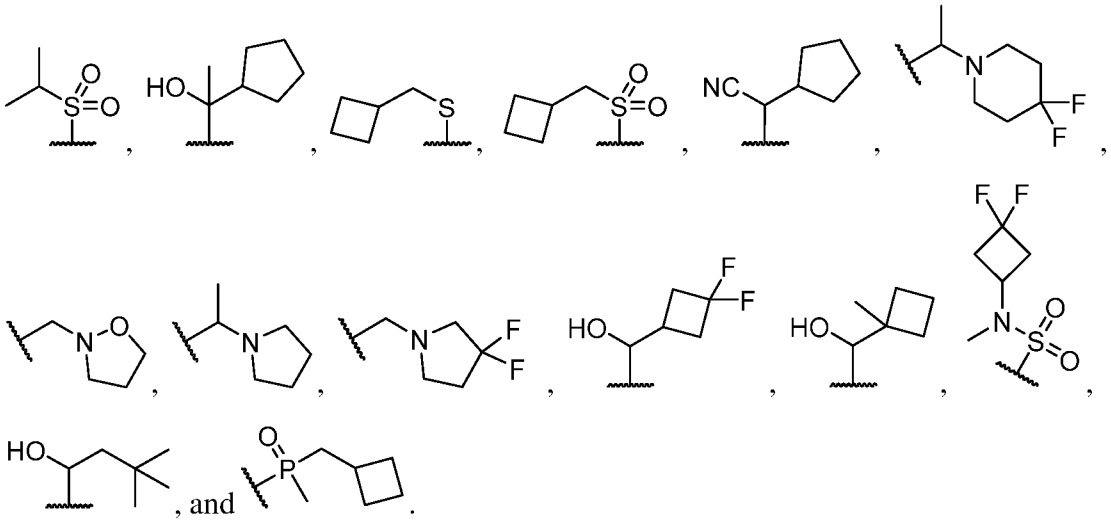
substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl.

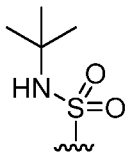
36. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein Z^4 is R^D and Z^1 is R^D, wherein R^D is independently halo, -OH, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl.

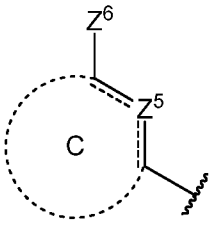
37. The compound of any one of claims 33-36, or a pharmaceutically acceptable salt thereof, wherein one or more of Z^1-Z^4 is selected from the group consisting of fluoro, chloro, -OH, -NH_2, -CH_2OH,

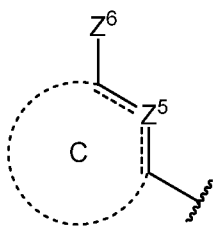






38. The compound of any one of claims 33-37, or a pharmaceutically acceptable salt thereof, wherein one of Z^1-Z^4 is  .

39. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein ring A is  and ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl.

40. The compound of claim 33 or claim 39, or a pharmaceutically acceptable salt thereof, wherein ring A is  and ring C is 5- to 6-membered heteroaryl optionally

substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl.

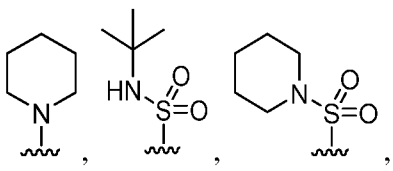
41. The compound of claim 39 or claim 40, or a pharmaceutically acceptable salt thereof, wherein ring C is pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, or oxazolyl, each optionally substituted.

42. The compound of any one of claims 39-41, or a pharmaceutically acceptable salt thereof, wherein the one or more R^E substituents are independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl.

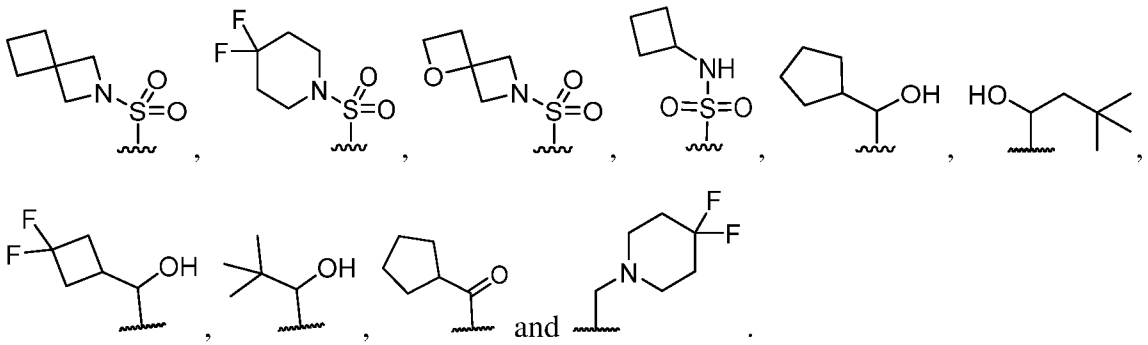
43. The compound of claim 42, or a pharmaceutically acceptable salt thereof, wherein the one or more R^E substituent is methyl.

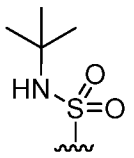
44. The compound of claim 39 or claim 40, or a pharmaceutically acceptable salt thereof, wherein two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl.

45. The compound of any one of claims 39-44, or a pharmaceutically acceptable salt thereof, wherein Z^6 is $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo.

46. The compound of any one of claims 39-44, or a pharmaceutically acceptable salt thereof, wherein Z^6 is selected from the group consisting of 

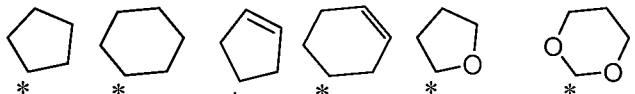
,

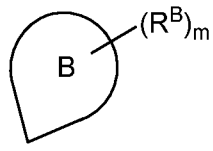
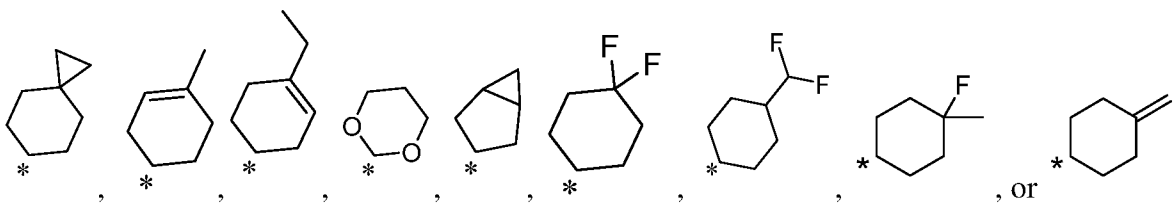


47. The compound of claim 46, wherein Z^6 is  .

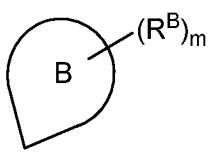
48. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

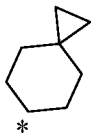
49. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

50. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein ring B is  , wherein * denotes the point of attachment to the rest of Formula (II).

51. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein  of Formula (II) is  , wherein * denotes the point of attachment to the rest of Formula (II).

52. The compound of claim 51, or a pharmaceutically acceptable salt thereof, wherein



of Formula (II) is  .

53. The compound of any one of claims 33-52, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

54. The compound of claim 53, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

55. The compound of claim 54, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each hydrogen.

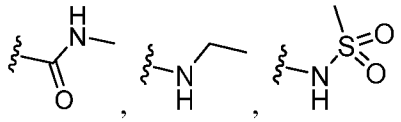
56. The compound of any one of claims 33-52, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

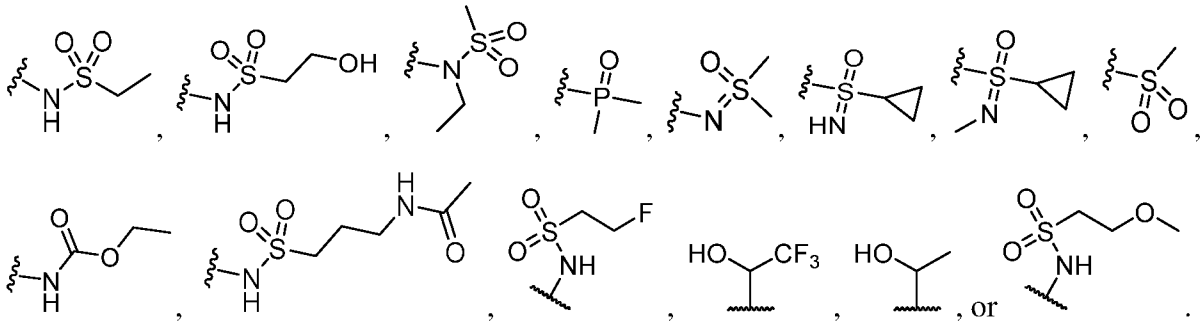
57. The compound of any one of claims 33-52, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

58. The compound of claim 53 or claim 57, or a pharmaceutically acceptable salt thereof, wherein R^{C1} is halo.

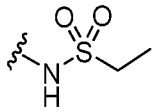
59. The compound of any one of claims 53, 56, or 57, or a pharmaceutically acceptable salt thereof, wherein R^{C3} is halo.

60. The compound of any one of claims 53, 56, or 57, or a pharmaceutically acceptable salt thereof, wherein R^{C4} is halo or $-NH_2$.

61. The compound of any one of claims 33-56, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, $-CH_2OH$, fluro, bromo, $-NO_2$,  .



62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is



63. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds of **Table 1**.

64. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds of **Table 2**.

65. A pharmaceutical composition comprising a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

66. A method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65.

67. A method of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65.

68. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65.

69. The method of claim 68, wherein the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

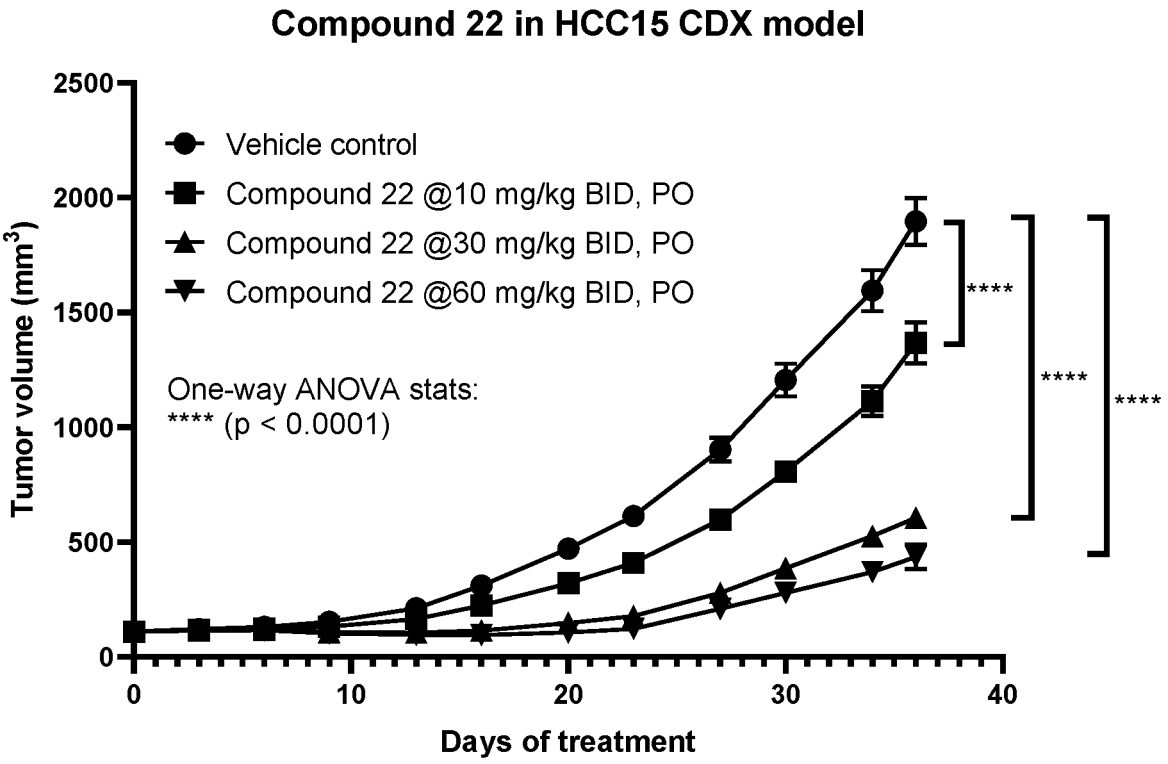

Compound 22 in HCC15 CDX model
Vehicle control
Compound 22 @10 mg/kg BID, PO
Compound 22 @30 mg/kg BID, PO
Compound 22 @60 mg/kg BID, PO
One-way ANOVA stats:
**** (p < 0.0001)
****
****
****
Tumor volume (mm3)
2500
2000
1500
1000
500
0
0
10
20
30
40
Days of treatment

Figure 1A

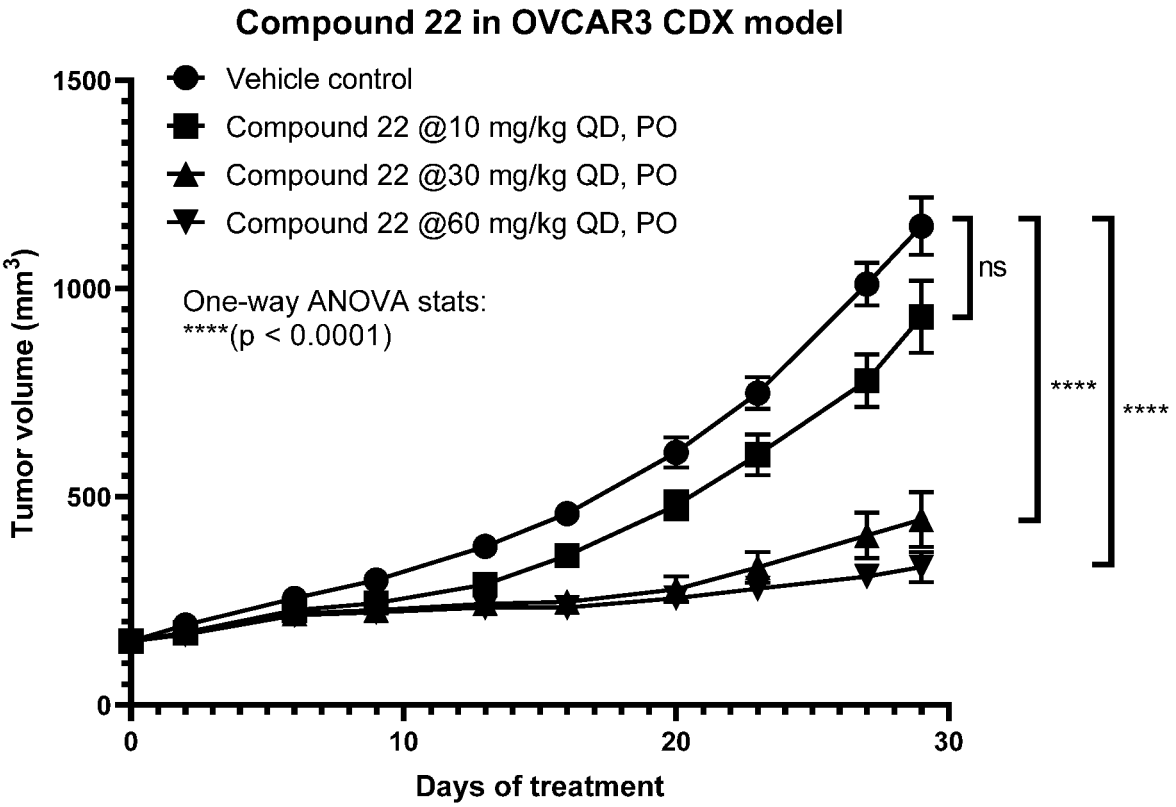

Compound 22 in OVCAR3 CDX model
Vehicle control
Compound 22 @10 mg/kg QD, PO
Compound 22 @30 mg/kg QD, PO
Compound 22 @60 mg/kg QD, PO
One-way ANOVA stats:
****(p < 0.0001)
ns
****
****
Tumor volume (mm3)
1500
1000
500
0
0
10
20
30
Days of treatment

Figure 1B

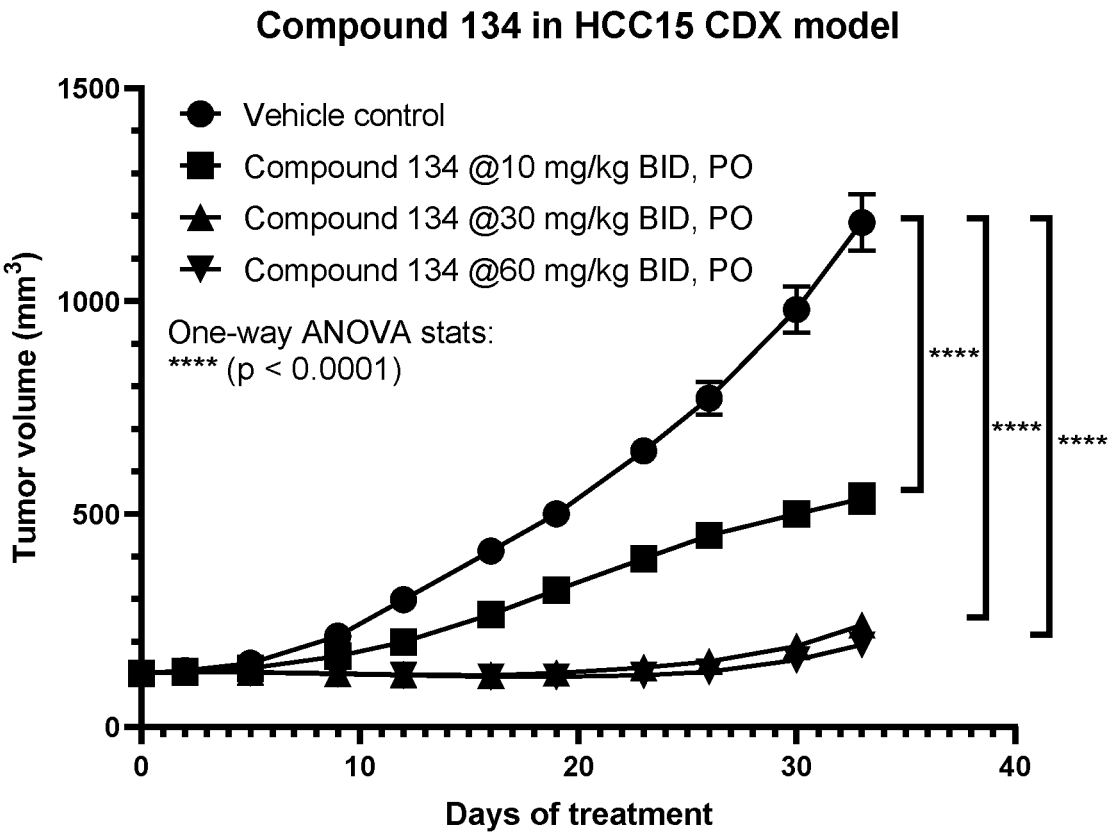

Compound 134 in HCC15 CDX model
Vehicle control
Compound 134 @10 mg/kg BID, PO
Compound 134 @30 mg/kg BID, PO
Compound 134 @60 mg/kg BID, PO
One-way ANOVA stats:
**** (p < 0.0001)
****
****
****
Tumor volume (mm3)
1500
1000
500
0
0
10
20
30
40
Days of treatment

Figure 1C

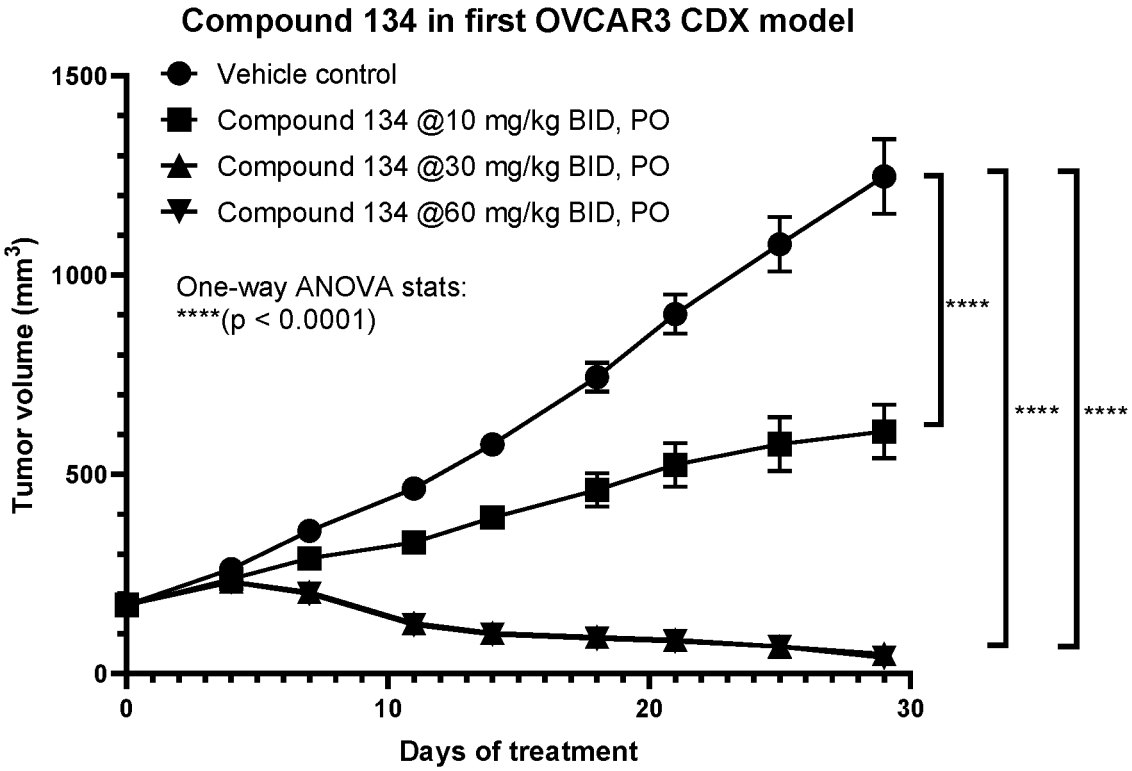

Compound 134 in first OVCAR3 CDX model
Vehicle control
Compound 134 @10 mg/kg BID, PO
Compound 134 @30 mg/kg BID, PO
Compound 134 @60 mg/kg BID, PO
One-way ANOVA stats:
****(p < 0.0001)
Tumor volume (mm3)
1500
1000
500
0
0
10
20
30
Days of treatment
****
****
****

Figure 1D

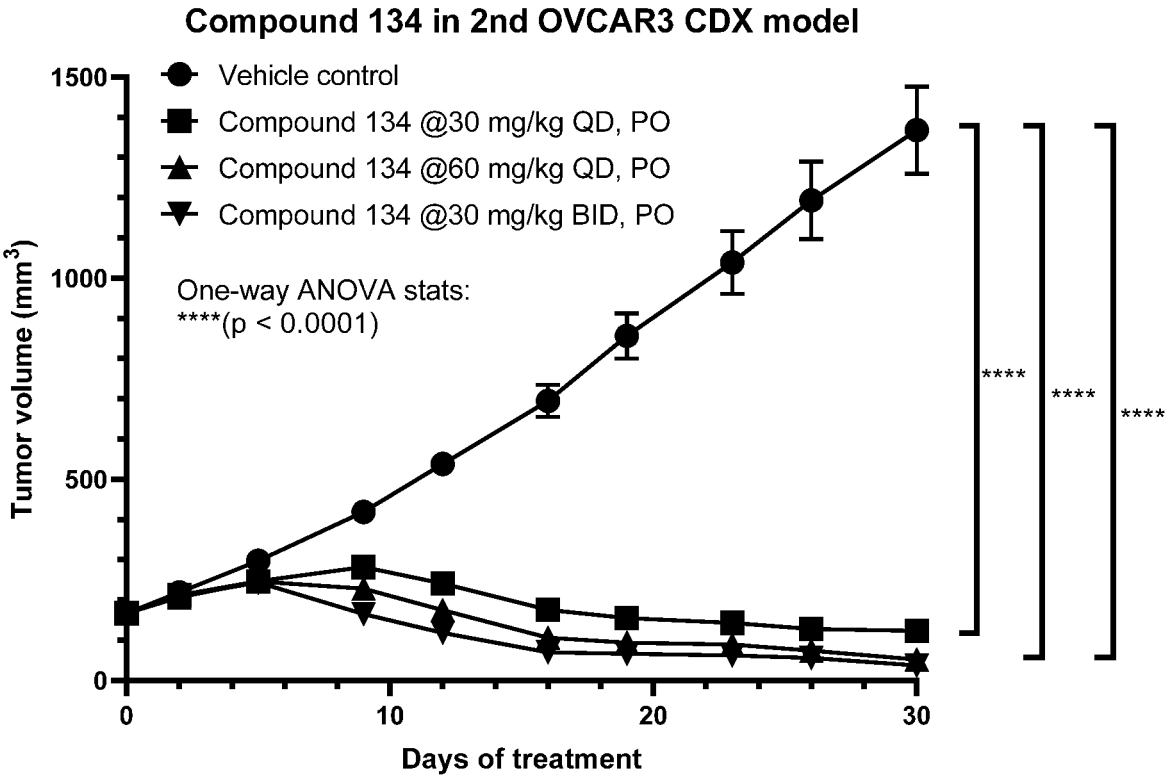

Compound 134 in 2nd OVCAR3 CDX model
Vehicle control
Compound 134 @30 mg/kg QD, PO
Compound 134 @60 mg/kg QD, PO
Compound 134 @30 mg/kg BID, PO
One-way ANOVA stats:
****(p < 0.0001)
Tumor volume (mm3)
1500
1000
500
0
0
10
20
30
Days of treatment
****
****
****

Figure 1E